THE DETECTION AND TREATMENT OF ALCOHOL DEPENDENCE

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University of Edinburgh

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CONTENTS

Statement of Originality

I confirm that I was the originator of the idea, principal investigator, and principal and final author for all the studies presented in this collection, with the exception of those for which I have attributed the contribution of collaborators.

None of the work has been previously submitted as part of a thesis to this or any other university.

Each study (with the exception of the Cost-Effectiveness Study) has been published in a peer reviewed journal, and thus subjected to review by external referees appointed by the editor of the respective journal.

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ABSTRACT

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The cohesiveness of the proposed syndrome of alcohol dependence, and the evolution of symptoms over time, was validated in a clinical sample. In healthy individuals and in clinical samples, biological markers showed early signs of the syndrome in healthy men. A comparison of Lothian general population data with Edinburgh hospital admission data showed that heavier alcohol consumption predicted admission to a general hospital bed. Analysis of national centrally collected data showed that the burden on Scottish hospitals due to alcohol problems rose in the last 40 years.

A randomized controlled trial showed the value of intervening at an early stage in the career of a problem drinker.

To treat more severe alcohol dependence, withdrawal symptoms must be controlled. When randomly allocated to either a longer-acting or a shorter-acting benzodiazepine, the former showed an advantage.

To help prevent relapse, 'extended' treatment emerged as only very marginally more effective than one session of firm advice to the patient to abstain. The medications disulfiram and naltrexone, if compliance was enhanced, were found to reduce relapse. Acamprosate appeared to be effective too, when results from many studies were pooled. A selective serotonin re-uptake inhibitor (SSRI), fluvoxamine, was associated with increased likelihood of relapse in early-onset alcohol dependence, a surprising finding, which speculatively might be mediated through increased impulsivity in some patients. Analysis of data on treatment of depression in the General Practice Research Database confirmed other emerging concerns regarding the safety of the SSRI group of drugs in young people.

Abstinence was accompanied by improvement in brain magnetic resonance parameters and cognitive testing.

Analysis of outcomes in placebo-controlled treatment studies for alcohol dependence, set alongside the costs to the Health Service of treating the complications of alcohol dependence, showed that the costs of failure to help patients attain abstinence are much greater than the costs of providing effective treatments.

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SYNOPSIS

The numbering refers to the Table of Publications

The syndrome of alcohol dependence I commenced this contribution to research on alcohol dependence in 1976. At that time, there was debate about how alcohol consumption and 'alcohol problems' were related, and the part played by some putative psychobiological process meriting the term 'syndrome' or even 'disease'. Having attempted to distill items of proven reliability, I tested the cohesiveness of the components of the proposed syndrome of alcohol dependence, and their evolution in time, in a clinical sample (1, 2, 3). I also studied the interaction of these symptoms with self-reported consumption, and problems, in non-clinical samples where heavy drinkers were to be found – namely brewery and distillery manual workers and (at the other end of the socioeconomic spectrum) members of the Institute of Directors and Chamber of Commerce.

The concept of a dependence syndrome could be justified in terms of a dominant single factor, with elements forming a scale of severity. Early features were indicators of impaired control of drinking and growing tolerance e.g. 'needing more than companions'; later features were those of physiological withdrawal such as morning tremor and relief drinking.

Early detection The survey of working men sponsored by the Medical Research Council (1977-9) was my opportunity to refine ways of obtaining self-report and objective data about alcohol consumption patterns and problems, and examine reliability (4, 6). The experience of measuring these parameters in mainly healthy men, alerted me to the possibility of early intervention, to detect and treat a condition which was, at least potentially, reversible. (Having trained in psychiatry and neurology, it was clear to me that we were seeing many illnesses which, at least with present knowledge, were not reversible!).

I tested various emerging biological markers, and developed a brief questionnaire, to aid in early detection. Tests were carried out in healthy populations of working men and in clinical samples. Mean cell volume of the red blood cell was more likely to be raised in smokers, and in frequent drinkers ('tipplers') rather than episodic drinkers: two novel findings. But only two-thirds of heavy drinkers (over 4 pints of beer per day or equivalent) had an elevation of either MCV or gamma-glutamyl transferase (GGT) (6). I investigated the accuracy of an amino-acid anomaly (whose analysis proved too complex to introduce more widely) (7) and that of serum ferritin (8). However, the use of carbohydrate deficient transferrin (CDT) as a marker of excessive drinking was being developed by commercial interests. Its widening use led me to wonder whether the slightly different time-frame of its response to drinking alcohol, as well as its apparent freedom from confounding by drug therapies, would make it a useful clinical tool in advance detection of when an alcoholic patient in treatment had a relapse. We discovered that CDT might 'herald' relapse to drinking – in the sense that sometimes the CDT would rise above the abstinent baseline level - before the patient declared a relapse which later he/she would admit, or be clinically evident in terms of deterioration in health, liver

enzymes or social circumstances. The CDT test can be helpful is this way, although there is still some 'noise', or unreliability, around this test (9, 10).

In the general medical wards, comparison of hospital case records with results of screening interview by a nurse showed that routine admission procedures underestimated consumption, adverse consequences and dependence. Laboratory markers were not sufficient to be used as a screening test on their own (12) The dependence syndrome was by no means a universal feature of men admitted to medical wards with alcohol related problems. (13) This has subsequently been noted, sometimes with surprise, in studies of patients admitted to hospital with alcoholic liver cirrhosis. It was also found when we studied 100 case records of patients who had received a liver transplant for alcoholic liver disease (although a diagnosis of alcohol dependence pre-transplant turned out to be a predictor of relapse to harmful drinking during the follow-up years) (39).

Early intervention We compared the drinking patterns of patients admitted to medical wards to those of the general population documented in a drinking survey conducted in the Lothians at the same period. As might be expected, the risk of admission for liver disease was increased 8-fold in those drinking over 50 units (400gm ethanol) per week, and three fold for upper gastrointestinal disorders, respiratory disorders and myocardial infarction, compared light drinkers. (14)
Thus, medical wards were able to provide a sample in which to test, in a randomized controlled trial, the value of intervening at an early stage in the career of a problem drinker (This study was funded by the Scottish Health Department). We tested an intervention by a nurse: a non-judgmental dialogue of the concerning the *pros* and *cons* of the patient's drinking (in his/her view), and a discussion aimed at helping the patient modify some social behaviours and some beliefs and attitudes. The one-year follow-up was conducted by another nurse who was blind to the original treatment group, and who obtained in many cases a serum specimen to test for markers of heavy drinking. We concluded that the nurse's intervention, while the patient had been in a medical ward, had tweaked some patients into changing their drinking to a less harmful pattern, beyond what may have been effected by the medical service' s and physician's input (i.e. beyond what had been achieved in the 'no intervention' control).
The resulting paper (BMJ, 1985) (19) affirmed a role for specially trained nurses in the general hospital. The design and method were replicated in several large trials in primary care in UK and by the World Health Organization. The Edinburgh Royal Infirmary alcohol liaison nurse service developed after two further feasibility studies in the 1990s funded by the Scottish NHS, and a further prevalence survey, this time in the orthopedic service (15). The study is still influencing the development of services for alcohol problems in acute general hospitals in a number of countries.
I studied the data-bases held by several of the *Centres d'Hygiène Alimentaire.* These health centres had been instituted in France in the 1960's to assess and treat drink-drive offenders, and workers referred through managers and occupational physicians due to alcohol-related work problems (20). I was able to show that these centres tended to see people at an early stage of their drinking problem (compared to the psychiatric and general hospital services), and recorded some good outcomes with fairly minimal medical

and nursing intervention - minimal, that is, compared to the 6-12 week residential programmes being offered widely in the Western countries in the 1970's.

Other Prevalence Studies

- **General**

I reviewed UK data on prevalence of alcohol problems and dependence in 1982, which in 2007 is of course out-of date, but nevertheless shows the principles and limitations in this area of study(11).

The demand in **primary care** for management of alcohol problems needed to be quantified. Locally, we experimented with an inexpensive method of estimating the demand in one primary care locality using a combination of data already held on practice records, interviews with key people in the community (not only health workers), hospital discharge by address of the patients and other local area statistics which were already available on alcohol-related problems (17).

Hospital discharge data, though a more precise measure, will almost always underestimate the total population prevalence of a condition. However, because trends in our own clinical work load suggested a rising prevalence, I examined trends in the **Scottish NHS hospital data base.** This showed that there was, indeed, a striking rise in alcohol-related disorders throughout Scotland (18). Sadly the trend noted in 1997 has continued to date.

- Special groups

Throughout the 1950's - 1970's analysis of morbidity by occupation groupings, alcohol problems were seen to occur among the **medical profession** more commonly than would be expected by chance. It had been hoped, however, that just as happened with smoking and lung cancer in the 1950's-1960's, doctors in the UK might show an example to the population and reduce their incidence of alcohol-related illness. The data collected by Scottish psychiatric hospitals allowed an analysis of discharge data by diagnosis and by occupation. We found that although there was indeed still an excess of doctors compared to other Social Class 1 groups, this might be accounted for by a cohort of heavy drinkers over the age of 45(16). Perhaps the trend of an excess in the medical profession would disappear. A possible avenue for this change might be a greater willingness by the profession itself to identify earlier, and manage more successfully doctors with impending alcohol problems.

The treatment of doctors, with psychiatric or addiction illnesses, had not always been well conducted. I was asked to make a distillation of the literature, and therapists' experience, on how to assist doctors, including those whose professional practice was deemed impaired. (42) It is important for clinicians to realize that doctors might evade admitting their problems; objective and constructive approaches are necessary ingredients of successful therapy, including objective monitoring of the drinking and drugs use, and work performance.

Management of Harmful Drinking and Alcohol Dependence in Primary Care

Evidence of the value of early intervention for alcohol problems led to a successful bid to the commissioning committee of SIGN (Scottish Intercollegiate Guidelines Network) to fund a systematic review of the detection and management of alcohol problems in

primary care. I brought together a team which I chaired, with technical support from SIGN. I oversaw the review and the grading of evidence, leading to Guidelines for The Management of Harmful Drinking and Alcohol Dependence in Primary Care. This was peer reviewed, and the final product was published by SIGN www.sign.ac.uk/pdf/sign74.pdf) As well as being distributed by NHS Scotland, the document has served as a model for a number of other national alcohol guidelines. (41)

Treatments for alcohol dependence

Managing alcohol withdrawal: This step in the treatment of alcohol dependence seldom presented major clinical problems, if cases were promptly identified and protocols were followed. Benzodiazepines seemed safe and effective. However, there were concerns that benzodiazepines with a long half-life might accumulate and impair cognitive recovery, and thus retard the patient's learning and practising the skills for sobriety. We tested a short-acting versus a long-acting benzodiazepine. However, we found no major differences in cognitive functioning, and since the only seizure occurred with the shorter acting lorazepam, it remains our practice today to use one of the longer acting compounds (25).

Treatment for alcohol problems: Preventing relapse

The more severely dependent drinkers seemed to require more than one brief motivating dialogue. We conducted another randomized controlled study funded by the Scottish Health Department to investigate the efficacy of the treatments that the NHS services typically provided at that time (1980's) – in-patient detoxification and group work, and/or the opportunity for regular out-patient supportive counselling and an invitation to join an out-patient support group. However, compared to just one session of firm advice to the patient to abstain, 'extended' treatment emerged as marginally more effective only in terms of reduction of social problems. (One caveat in interpreting that result was that, for ethical reasons, a safety net was in place in which patients' families were being seen monthly by a worker gathering outcome data. This could have had a therapeutic effect on the family and thereby influenced the problem drinker) (27).

This study obtained follow-up data at 2 years on over 80% of the sample. Our early intervention study quoted above had follow-up data at 1 year on 85%. Other studies being published in the field had lower follow-up rates, and the effect of this on the value of the study required attention, to know best how to deal, in the analysis, with loss of data. For example, should all those lost to follow-up be regarded as failures? In fact, published work giving baseline data and other information on those harder to follow-up seemed to support such a view (4).

It was important to look for other treatments. Disulfiram (**'Antabuse')** had been in use for over 20 years, but there was only limited evidence of its efficacy, and no trials had been conducted in the UK.

The literature revealed that the only studies showing efficacy had set up a supervision system to help ensure that the patient was seen to swallow the medication. This was needed in any further test of the medication. I also decided that the correct test of the drug must be 'single blind' i.e. where the clinician and patients knew whether or not the patient was taking an active deterrent tablet, because *knowing* you are on this drug is part

of the treatment. The research assessor was kept blind to the treatment allocation. This study showed that, in patients who were prepared to volunteer for a trial of disulfiram, those allocated to disulfiram supervised by a partner, an employer or by the clinic, drank much less than patients taking supervised Vitamin C. (Vitamin C tablets were chosen as the 'control' because it is one of the vitamins which has been shown to be deficient in many alcoholic patients, and thus we could ethically advise subjects that taking a Vitamin C tablet regularly might help their recovery)(28). The paper led to a renewed interest by centres in Finland, India and Germany to conduct trials into the use of supervised disulfiram. This has been accompanied by a wider and more effective use of the drug by clinicians in the UK and a number of other countries.
Recently, we have looked further at the issue of compliance with this drug, by testing the efficiency of a breath analyzer (invented by a collaborating chemist) to detect metabolites of disulfiram (30).
Unwanted effects of disulfiram including neuropathy, and liver damage, have long been a concern of the use of disulfiram. I conducted a literature search to attempt to quantify the risks (29).
More recent pharmacotherapies By 1980, animal models had revealed certain neuronal pathways and receptor sites which were implicated in liking for alcohol (i.e. exhibiting preference for ethanol over sucrose solution), alcohol-seeking behaviour, and emergence of signs and behaviours resembling human alcohol dependence.

Animal research had shown that animals with reduced cerebral **serotonin receptor** transmission drank more alcohol. The first SSRI (selective serotonin enhancing drug) licensed for human use in the UK was fluvoxamine. I approached the manufacturer for assistance to test this as a method of reducing relapse over one year in alcohol dependent patients, including depressed and non-depressed subjects. An overall negative result proved to be due mainly to a subgroup (defined *a priori* as 'early onset' and characterized by novelty-seeking and impulsivity) who consumed more alcohol, not less, when randomized to this medication (34). Later, a similar result was found by US research teams for two other SSRIs. It is clinically an important finding, because of the widespread use of SSRIs in primary care today.

This same pattern was found in USA with fluoxetine, and with sertraline. The SSRIs have proven helpful in freeing patients from inhibiting obsessional anxiety. But some alcoholics do not benefit from 'freeing' from their inhibitions. Rather, they need to improve their self-control!

We can speculate that this might be related to an increase in impulsivity due to SSRI treatment. This possibility has since emerged in another area. I contributed to the conception, design and interpretation of two epidemiological studies into another potential unwanted effect of SSRIs, related to impulsivity, namely deliberate self-harm.

We examined whether the risk of deliberate self-harm was greater when an SSRI had been prescribed compared to when a tricyclic, or other type of antidepressant, had been prescribed for depression. The general practice research data-base study showed that although there was no greater risk demonstrable of completed suicide, there was indeed a

greater risk of non-fatal self-harm associated with the SSRIs in those aged 18 and under (35). (One manufacturer subsequently admitted that the previously analyzed data showed an increase risk up to the age of 25.)

Another opportunity to gather insight into the connection between SSRIs and self-harm was to compare the prescription of antidepressants in the Edinburgh area according to the Lothian prescribing data base, and the frequency of admission for self-poisoning to the Edinburgh Royal Infirmary. This did not reveal an excess of admissions related to the SSRIs but did highlight an excess with two other antidepressants, venlafaxine and mirtazapine (36). (As discussed in the paper, confounding by severity of depression could have accounted for the excess related to these medications, since they tended at the time of the study to be prescribed as second –line after failure to respond to an SSRI.)

These and related studies will hopefully increase the caution with which antidepressant drugs are prescribed, including in alcohol dependent people.

Animals consuming ethanol, or being exposed to ethanol vapour for long periods, develop withdrawal symptoms when ethanol is withdrawn. In a number of laboratory models, the animals have been observed to return quite rapidly to consumption of alcohol, once it is made available again. In the 1980's a compound was described which reduced the animals' rapid return to ethanol-seeking behaviour during the withdrawal period. This appeared to be due to partial inhibition of an over-sensitive **GABA (gamma amino butyric acid) -glutamate receptor system.** The drug was not addictive itself. I contacted the firm and requested that we conduct a multicentre study in the UK to test whether this drug helped to prevent rapid return to drinking. The company was already mounting a series of controlled studies in other European countries. Our UK study did not show a statistically significant advantage of acamprosate over placebo in terms of abstinence (32). However, because of the 13 positive studies that were conducted elsewhere in mid- and south- Europe, I remained interested, and I suggested to the manufacturers a *post hoc* analysis to test whether the drug could help patients limit their drinking once they started. The combined multi-site data base was large enough to permit such an analysis. A small effect in the predicted direction was found, as well as a confirmation in the meta-analysis of its effectiveness in sustaining complete abstinence (33).

A third neural receptor system implicated in alcohol dependence concerns what is thought to underlie the rewarding, positive, experience of alcohol particularly for some genetically predisposed people – the **endogenous opioid transmitter system**. Previous trials of medications in alcohol dependent patients conducted by ourselves and many others had shown how, without supervision, compliance with medication was poor. In our protocol for the study of the opioid antagonist, naltrexone, I included *a priori* that we should look at naltrexone efficacy separately in compliant and non-compliant patients. In the event, the drug was only shown to reduce relapse in the compliant sub-group. (31) In conjunction with a Finnish pharmaceutical company, I was the lead clinician in planning

and conducting a multicentre UK study of another opioid antagonist, nalmefene, recruiting and treating patients largely in primary care. A trend emerged favouring nalmefene over placebo in preventing relapse (in preparation, not cited in publications listed below; two Finnish studies have found more convincing evidence of efficacy, whereas a study in USA, reported at scientific meetings, found a high recovery rate in the placebo group too, and failed to show an advantage of nalmefene over placebo).

Brain damage in alcohol dependence, and treatment

It is a tautology to state that alcohol dependent patients repeat their mistakes. It is the hallmark of the syndrome. Our aim in treatment is to prevent relapse and, if it occurs, to help minimize adverse consequences for the drinker and family.

The dimensions of cognitive impairment were fairly well delineated by 1980-90. However, the installation in the 1980s in the Edinburgh Royal Infirmary of one of the first magnetic coils to measure resonance of water components in body tissues including brain provided an opportunity to find anatomical and physiological markers of these cognitive deficits. Magnetic resonance imaging (MRI), as it came to be called, showed that nearly half of our patients had abnormalities compared to controls. (21, 22, 23) The extent of these was related (though weakly) to impairment in flexibility of thinking and planning as well as, in more deteriorated patients, in the ability to learn new material (24). (This was one of the first to use MRI to study brain damage in alcoholics. The paper is the lead citation in a 2005 *New England Journal of Medicine* review paper on cognition and alcohol by Stampfer *et al.*, Vol 352:245) This clearly was relevant to treatment, which till then depended mainly on discussion of how the patient might change thinking and behaviour, and learn new ways of coping with problems, and social cues to drinking. If learning was impaired till the brain recovered (if it was going to recover), which might require months of abstinence, these treatments would have limitations. Abstinence was indeed shown to be associated with improvement in MRI and cognitive testing.

The growing pool of research into cognitive impairment in heavy drinkers has influenced psychological treatment programmes. We have lowered our expectation of how rapidly patients can change engrained attitudes and patterns of behaviour, and amplified the role of pharmacotherapies, particularly in the early months of abstinence.

A tool for clinical services to measure outcome of treatment for alcohol dependence

From my experience of rating scales for alcohol dependence and problems, I developed a brief tool for clinic use to measure outcome. This 11 item scale, the Alcohol Related Problems Questionnaire (ARPQ), administered at follow-up was a proxy for both the patient's previous 6 month's scores on quality of life and the utilization of health service resources in that period. (26) The costing of health service usage proved an important exercise and was a forerunner of the national exercise undertaken later (see below).

Cost effectiveness of treatments for alcohol dependence

There is skepticism about the value to society of offering treatment for alcohol dependence. This is perhaps due to the visibility of those patients who repeatedly relapse and deteriorate in their physical health and social functioning. We followed a sample of patients treated at our service to see how costs continued to accrue for those patients who

relapsed – and we examined costs of helping those who succeeded in remaining abstinent. (38)
An extended approach to this was studied in the coming years. In the 1990's, the Scottish Executive created the Health Technology Board Scotland (HTBS), tasked with evaluating the efficacy, and cost effectiveness, of treatments offered by NHS Scotland. I helped prepare a proposal, that the Board should examine the cost effectiveness of treatments to prevent relapse in alcohol dependence.
A systematic review was conducted of published studies, and also included unpublished studies where these were discovered and the raw data could be obtained. A review to assess scientific quality was conducted. Studies using behavioral measures and in which the family and/or significant others were involved in the treatment, were grouped together (e.g. behavioral marital therapy; community reinforcement therapy) . The following treatments were found to be effective in quality studies: Psychosocial treatments: relapse prevention/ coping skills training, motivational interviewing, behavioral family therapy/ community reinforcement therapy; Pharmacotherapy: acamprosate, naltrexone, and supervised disulfiram. Meta-analysis was conducted to give a composite outcome effect size for each treatment.
The cost of providing a course of each treatment was calculated.
Also, the cost to NHS Scotland of *failed* treatment was calculated, based on the known rates of medical complications which ensue in the drinking alcohol dependent individual, and the costs to NHS Scotland of treating these complications (e.g. the cost of managing alcoholic liver disease, alcohol-related trauma, alcohol chronic pancreatitis etc., including GP consultation and hospital admission costs).
In the health-economic model used, the assumption was made that cases who recovered (went without a relapse for the study duration) remained well after that treatment, which permitted an estimate of the cost advantages over time of that treatment compared to our previous standard outcome (from early UK studies) of a 15% recovery rate. Table 1 summarizes the surprising estimates obtained, and published in the Health Technology Assessment Report (38). For the effective psychosocial treatments, there is actually a negative cost i.e. a cost saving overall arising because while only some patients recover completely, others offered the treatments improve and reduce their use of health service resources.
The review also found evidence that helping patients to link with Alcoholics Anonymous was an effective part of treatment, and noted that AA groups placed no financial burden on the Health Service. Although I have not conducted research, other than literature reviews, of the AA method, its value to hundreds of our patients over these 30 years has been immense.

A complex treatment sometimes needed to save the life of an alcohol dependent patient is **liver transplant**. In a project with colleagues in the liver transplant service in Sydney, Australia, I assessed outcomes over up to 17 years in 100 patients who had received a liver transplant for alcoholic cirrhosis. Relapse after a costly procedure as transplantation generates much concern. This project revealed that relapse was related to baseline severity of dependence and psychiatric illness (39). The implication is that monitoring and treatment by psychiatric or alcohol services might prevent some relapses to harmful drinking in transplant patients.

CONCLUSIONS

During the period of this research, Scotland saw an increase in the prevalence of alcohol dependence. The research submitted for this thesis does not attend to the causes of that change. Cultural and economic changes have probably been the main contributing factors. However, there have been advances in the recognition of people who develop alcohol dependence, and in how they can be helped.

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TABLE 1

Costs, calculated over 20 years, for 1000 patients with alcohol dependence offered specific effective treatments, compared with 'standard' support (Health Technology Board of Scotland, 2003) (negative cost = health cost saving) (In this Thesis, see published paper No. 38)

www.docs.scottishmedicines.org/ docs/pdf/Alcohol%20Report.pdf

	Additional recovered patients	Cost per additional recovery	Deaths avoided	Cost per death avoided
Pharmacological Therapies				
Acamprosate	84	£36	62	£61
Naltrexone	55	£3,252	40	£5,421
Psychosocial Therapies				
Coping Skills Training	122	-£3,196	89	-£5,365
Motivational interviewing	99	-£3,083	73	-£5,158
Behavioural family therapy; community reinforcement approach	105	-£2,696	77	-£4,516

TABLE 2 List of candidate's peer-reviewed publications of original research on the theme of the Thesis.

		CANDIDATE'S CONTRIBUTION
	VALIDITY OF A SYNDROME OF ALCOHOL DEPENDENCE	
1	Chick J. and Duffy J. (1979) Application to the alcohol dependence syndrome of a method for determining the sequential development of symptoms. *Psychological Medicine,* 9, 313 -9	Conceived project and design; gathered the data; co-author devised and conducted analysis
2	Chick J (1980) Alcohol dependence : Methodological issues in its measurement; reliability of the criteria *British J Addiction* **75,** 175-186	Sole author (supervisor N. Kreitman)
3	Chick J (1980) Is there a unidimensional alcohol dependence syndrome? *British J Addiction* 75, 265-280 Reprinted in *Annual Review of Addictions Research and Treatment,* 1991, pp 297-308	Sole author (supervisor N. Kreitman)
	METHODOLOGY IN ALCOHOL RESEARCH	
4	Chick J, Kreitman N, Plant M. (1981) Saving face? Survey respondents who claim their last week's drinking was atypical *Drug Alcohol Dependence* 7, 265-72	Chief data manager and writer; conjoint design
5	Chick, J (1995) Alcoholism treatment evaluation: the drop out dilemma *Alcoholism* 31, , 79-86	Sole author (a review with methodological without new original data)

	DETECTION and PREVALENCE	
6	Chick J, Kreitman N, Plant M. (1981) Mean cell volume and gamma glutamyl transpeptidase as markers of drinking in working men, *Lancet* I, 1249-51	Conceived study with NK; Chief data manager and writer MP involved in survey method.
7	Chick J, Longstaff M, Kreitman N, Plant M, Thatcher D, Waite J. (1982) Plasma alpha-amino butyric acid: leucine ratio and alcohol consumption in working men and in alcoholics. *J Studies Alcohol*, 43, 583-7	Conceived, conducted and wrote study. ML, DT and JW analyzed blood samples
8	Chick J, Plant M, Pikkarainen J, (1987) Serum ferritin as a marker of alcohol consumption in working men *Alcohol and Alcoholism* 22, 75-7	Conceived, conducted and wrote paper. JP analyzed blood samples
9	Mitchell C, Simpson D, Chick J (1997) Carbohydrate deficient transferrin in detecting relapse in alcohol dependence *Drug and Alcohol Dependence* **48** 97-103	Conceived, designed and analyzed, CM collected most data, DS did lab analyses
10	Limin SM, Harvie DR, Chick J, Simpson D (1999) Limitations of CDT and GGT in detecting relapses in patients attending an alcohol problems clinic. *Scottish Medical Journal,* **44** 140-143	Conceived, designed and supervised data gathering, wrote paper
11	Chick J. (1982) Epidemiology of alcohol use and its hazards *British Medical Bulletin* , 38, 3-8	Review paper, sole author
12	Lloyd G, Chick, J, Crombie E (1982) Screening for problem drinkers among medical inpatients. *Drug and Alcohol Dependence, 10, 355-9*	Conceived, designed jointly with GL, and executed by JC GL and EC . GL was main author
13	Lloyd G, Chick, J, Crombie E. Anderson S. (1986) Problem drinkers in medical wards: consumption patterns and disabilities in newly identified male cases. *British Journal of Addiction* 81, 789-795	Conceived, designed jointly with GL, and executed by JC GL SA and EC . GL was main author
14	Chick J, Duffy J, Lloyd G, Ritson B. (1986) Medical admissions among men: The risk among drinkers. *Lancet* ii 1380-3	Conceived and conducted study. GL conjoint in medical data; BR provided general population data

15	Chick J, Rund D, Gilbert M-A (1991) Orthopaedic trauma in men: the relative risk among drinkers and the prevalence of problem drinking in male orthopaedic admissions *Annals of the Royal College of Surgeons of England,* **73**, 311-315	Designed instruments, analyzed and wrote study. Conceived jointly with DR, M-A G collected data.
16	Harrison D, Chick J (1994) Trends in alcoholism among male doctors in Scotland *Addiction* **89** 1613-1617	Joint conception, DH collected and analysed data ; supervised by JC
17	Murray SA, Perry B, Chick J (1996) Mental Health, alcohol and drugs: constructing a neighbourhood profile. *Primary Care Psychiatry* **2**: 217-243	Joint conception and write up. Data collected by BP and SAM
18	Chick J (1997) Evidence suggesting increasing health damage in Scotland related to alcohol *Health Bulletin* **55** 134-9	Conceived, executed and written by JC
	EARLY INTERVENTION	
19	Chick J, Lloyd G, Crombie E (1985) Counselling problem drinkers in medical wards : a controlled study *British Medical Journal* 290, 965-7	Conceived, designed jointly with G L, and executed by JC GL and EC . JC performed the analysis, and was main author. Funded by Scottish Office.
20	Chick J (1984) Secondary prevention of alcoholism in the Centres d'Hygiene Alimentaire, *British J Addiction* 79, 221-5	JC conceived, executed the project and wrote the paper; funded by Council of Europe

	COGNITIVE IMPAIRMENT	
21	Smith MA. Chick J, Kean DM, Douglas R, Singer A, Kendell RE and Best J. (1985) Brain water in chronic alcoholic patients measured by magnetic resonance imaging. *Lancet*, i, 1273-4	Contributed to design, analysis and writing
22	Smith MA, Chick J, Mander A, Douglas R and Best J (1988) Brain hydration during alcohol withdrawal measured by magnetic resonance imaging *Drug and Alcohol Dependence* 21, 25-8	Contributed to design, analysis and writing
23	Mander AJ, Young A, Chick J, Best JJK (1989) The relationship between cerebral atrophy and T1 in alcoholics: an MRI study *Drug and Alcohol Dependence* 24, 57-9	Contributed to design, analysis and writing
24	Chick J, Smith M, Engleman H, Kean D, Best J.(1989) Magnetic resonance imaging of the brain in alcoholics, lifetime alcohol consumption, cerebral atrophy and cognitive deficits *Alcoholism: Clin. Exp. Res* **13.** 512-8.	Designed and conducted the study, with MRI data collected by MS and DK, and analysis assisted by HE. Wrote paper.

	ALCOHOL WITHDRAWAL	
25	Ritson B, Chick J (1986) Comparison of two benzodiazepines in the treatment of alcohol withdrawal: effects on symptoms and cognitive recovery. *Drug Alcohol Dependence* 18, 329-334	Conceived study and obtained funds. Joint design, conduct and writing of the paper.

	AN OUTCOME TOOL FOR CLINICAL USE	
26	Patience D, Buxton M, Chick J, Hewlett H, McKenna M and Ritson B (1997) The SECCAT Survey: II: The Alcohol Related Problems Questionnaire as a proxy for resource costs and quality of life in alcoholism treatment *Alcohol and Alcoholism,* **32** 79-84	Project jointly conceived, conducted, analyzed and written up. (ARPQ devised by JC)

	PREVENTION OF RELAPSE	
27	Chick J, Ritson B, Connaughton J, Stewart A. (1988) Advice versus extended treatment for alcoholism: a controlled study. *British Journal of Addiction* 83, **159-170** Reprinted in Annual Review of Addiction Research and Treatment, 1991, (pp 297-308) Pergamon Press, New York	Conceived and designed study jointly with BR. Solely contributed measurement system and did analysis. Wrote paper jointly with BR. JCon. and AS contributed as therapists and data collectors
28	Chick J, Gough, K., Wojciech, F., Kershaw, P., Hore, B., Mehta, B., Ritson, B., Ropner, R. & Torley, D. (1992) Disulfiram treatment of alcoholism *British Journal of Psychiatry*, **161** 84-89.	Conceived, obtained funding, designed and analyzed this multicentre study, with technical assistance from the manufacturer. Independent statistical analysis purchased by the manufacturer (KG). BR assisted in design and writing paper
29	Chick J (1999) Safety issues concerning the use of disulfiram in treating alcohol dependence *Drug Safety* **5** 427-435	Literature review
30	Fletcher, K, Faulder, C, Chick J et al (2006) A breath analysis test to assess compliance with disulfiram treatment. *Addiction* 101, 1696-1704	Contributed to concept, design, execution, analysis and write up
31	Chick J, Anton R, Checinski K, Croop R, Drummond C, Farmer R, Labriola D, Marshall J, Morgan MY, Moncrieff J, Peters T, Ritson B. (2000) A multicentre, double-blind, placebo–controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol and Alcoholism* 35, 587-593	Conceived, obtained funding, chief contributor to design and analysis, contributed to data collection with investigators from other centres, with technical assistance from the manufacturer and independent statistical analysis purchased by the manufacturer... (RA contributed craving questionnaire)

32	Chick J, Howlett H, Morgan MY, Ritson B (2000) United Kingdom Multicentre Acamprosate Study: a 6 month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol & Alcoholism,* 35, 176-187	Conceived, obtained funding, chief contributor to design and analysis, contributed to data collection with investigators from other centres, with technical assistance from the manufacturer and independent statistical analysis purchased by the manufacturer
33	Chick J, Lehert P, Landron F. (2003) Does acamprosate improve reduction of drinking as well as aiding abstinence? *J Psychopharmacology,* 17, 387-392	Conceived the study and wrote paper. Meta-analysis designed and conducted by PL; database provided by FL on behalf of manufacturer

	SSRIs , ALCOHOL AND IMPULSIVITY	
34	Chick J, Aschauer H, Hornik K. (2004) Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double blind, placebo-controlled multicentre study with analysis by typology. *Drug and Alcohol Dependence*, 74, 61-70.	Conceived, obtained funds and wrote the paper, contributed to data collection (multi-centre study n= >500). HA provided decided typology measures. HK did the analysis.
35	Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, Evans S, Gunnell D. (2005) Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study *British Medical Journal,* **330**, 389-393	Actively contributed to the concept, design, interpretation and writing up of both studies
36	Bateman N, Chick J, Good A, Kelly C, Masterton G (2004) Are SSRIs associated with an increased risk of admission to hospital for self-harm? *European Journal of Clinical Pharmacology* **60**, 221-4	Actively contributed to the concept, design, interpretation and writing up of both studies

	COSTS AND COST EFFECTIVENESS OF RELAPSE PREVENTION TREATMENTS	
37	McKenna, M., Buxton M, Chick J, Hewlett H, Patience D, Ritson B (1996) The SECCAT survey: 1. The costs and consequences of alcoholism *Alcohol and Alcoholism* **31** 565-576	Joint conception, design and write –up. MM did analysis. DP collected data supervised by JC
38	Slattery J, Chick J, Craig, J, *et al* 'Prevention of Relapse in Alcohol Dependence' *www.docs.scottishmedicines.org/docs/pdf/Alcohol%20Report.pdf* *See Table 1 above*	JC chaired the Research Group; major contributor to concept, data gathering, interpretation and write-up. JS did the quality review and meta-analysis. J Craig performed the economic analysis.
	TREATMENT FOR SPECIFIC GROUPS.	
39	Kelly, M,. Chick, J, Gribble R, Gleeson, M Holton, M, Winstanley, J, McCaughan, GW, Haber P. (2006) Predictors of relapse to harmful alcohol after orthotopic liver transplantation *Alcohol and Alcoholism,* 41(3):278-283	Contributed to concept, design, assessed subjects' follow-up status, aided analysis and writing up.
40	Chick J. Doctors with emotional problems : How can they be helped? (in Hawton K, Cowan P. eds. *Practical Problems in Clinical Psychiatry*, 1992, Oxford Univ Press, pp242-253)	Literature review and position paper
	EVIDENCE-BASED GUIDELINES	
41	The Management of Harmful Drinking and Alcohol Dependence in Primary Care. www.sign.ac.uk/pdf/sign74.pdf)	Systematic review; evidence based guidelines. JC chaired the group, contributed to the reviews of all areas, wrote most sections and edited final product

END

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Alcohol Dependence: Methodological Issues in its Measurement; Reliability of the Criteria

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Summary
Instruments measuring alcohol dependence have seldom been presented with evidence of their reliability. There are a number of difficulties in designing such instruments which contribute to unreliability. The items in a standard interview, The Edinburgh Alcohol Dependence Schedule, are shown in this paper to have acceptable inter-rater reliability, although difficulties in operationalising 'impaired control' remain.

Introduction
Operational criteria of alcohol dependence
Operational definitions of alcohol dependence based on traditional criteria include items from conceptually distinct domains. A recent example is that of Hilton and Lokare [1]. Out of 34 items 5 referred to a subject's reasons for drinking (e.g. 'drink because of loneliness'); 6 to his attitudes to his drinking (e.g. 'felt ashamed of your drinking'); 2 to the attitudes of others to his drinking (e.g. 'been advised to cut down on your drinking'); 8 to consequences (mainly adverse) of drinking other than 'dependence' *per se* (e.g. '. . . been violent after drinking'). Of the remaining 13 items, 4 were about short-term withdrawal symptoms; 4 were about frequency of 'salience' (e.g. '. . . drink whenever you have a chance'); 1 was about being a drink ahead of one's companions; and 2 perhaps reflected intensity of need (e.g. 'does it bother you if there is no drink available?').

These criteria are derived from the definition of Jellinek [2] which led to Glatt's instrument [3], to the ALCADD and MAST screening tests and the 'criteria' of the National Council on Alcoholism [4]. A more restricted definition would omit those aspects which can be viewed as consequences of drinking or the effects of the interaction of the drinker and his social environment. It would thus be conceptually more homogenous and would reflect the finding of general population studies (rather than studies of help-seeking populations) that there is only partial overlap between scores on heavy consumption itself, reasons for drinking, adverse consequences of drinking and items denoting withdrawal phenomena and the subjective experiences of intense desire and impaired control [5–9].

Edwards and Gross [10] provided such a circumscribed definition of alcohol dependence listing seven elements: narrowing of the drinking repertoire; salience of drink-seeking behaviour; increased tolerance to alcohol; repeated withdrawal symptoms; relief or avoidance of withdrawal symptoms by further drinking; subjective awareness of compulsion to drink; the tendency for the syndrome to be

reinstated after a period of abstinence. This paper presents an assessment of the reliability of the criteria offered in this definition. However, first a comment will be made on the literature on reliability studies in this area followed by a discussion of some of the pertinent methodological difficulties.

The Reliability of 'alcoholism' criteria

An important step in evaluating a proposed syndrome is to establish the reliability of the criteria which were used in its provisional description, that is, to establish that measurements of the criteria can be made and repeated without significant error.

In the literature, the issue of the reliability of 'alcoholism' criteria is frequently sidestepped. Mulford [11] in his paper on an Alcoholic Stages Index stated that if an instrument has *validity* 'that should also dispose of the reliability issue'. The argument is that if an instrument does the job it is predicted to do, its error must be insignificant. The applicability of this argument to measures of alcohol dependence depends on the validation criteria being appropriate. The demonstration that an instrument said to measure dependence distinguishes between patients attending an alcoholism treatment unit and a general population sample (as, for example, Hilton and Lokare [1] provided) is not an absolute demonstration that the items are valid measures of alcohol dependence. The finding might occur in part because a hospital sample are 'people with problems', or 'people who are worried about their drinking and seek help', or they have a different response set to the instrument since they identify themselves as alcoholics [12, 13].

When the reliability issue is not sidestepped, but investigated, the results are perturbing. Gillies et al. [14] devised a questionnaire containing 30 items (or 35 items in another version) about 'alcohol involvement'. The list contained most of the commonly asked alcoholism questions, excluding those about adverse social or medical consequences. Reliability was assessed by test-retest. Amongst individuals who were neither heavy drinkers nor alcoholics, test-retest correlation was good (.87), though this is not strong evidence since in such a population very few items would be acknowledged. In contrast, in 30 alcoholic in-patients the rank order of subjects produced by the second administration after a varying period while still in-patients was statistically speaking unrelated to the rank order on the first test. On the scale from 0 to 140 points the 95 per cent confidence limits of the score derived from the test-retest study was $\pm$ 30 points. The authors suggest that the in-patient experience affected the subjects' evaluations of their own drinking behaviour, but do not indicate whether this is a consistent trend in one direction (e.g. to acknowledging more items reflecting perhaps a more self-critical attitude) or a random effect. The importance of these data on reliability would depend on the use to which the questionnaire was to be put. However, the result raises doubts about whether any questionnaire items on alcoholism can be sufficiently unambiguous to elicit responses unaffected by the subject's self-evaluation.

A self-completed questionnaire is unlikely ever to provide the clauses and qualifications necessary to define precisely complex experiences such as comprise alcohol dependence. A standardised interview in which items are rated by an individual trained in the definitions being used, with guide notes to refer to, provides greater hope of reliability.

Caetano et al. [15] presented preliminary data on a standardised alcoholism

interview. Some of the interview was about background factors, and physical and mental consequences of drinking, but there was a section on recent drinking behaviour, which is of interest to this discussion. The interview was conducted with ten patients, by one interviewer, and tape-recorded. Four other raters also rated the tapes. Weighted Kappa, a coefficient of between-rater agreements which takes account both of chance agreements and the degree of disagreement, yielded values of from 0.37 to 0.91 on eight items concerned with symptoms and consumption on 'a typical heavy drinking day'. The authors did not report on the distribution of scores obtained from individual items. (Studies of inter-rater agreement are most informative when the cases represent the whole range of possible scores on the items.) The use of tapes and several raters make for a stringent test of reliability. Unfortunately the published series has not as yet been extended to include more cases.

An examination of test-retest reliability of a semi-structured drinking history interview was reported by Summers [16]. Twenty-eight male voluntary patients in an alcoholism treatment unit were interviewed on admission, and the 15 who stayed for two weeks or more were reinterviewed on about the 14th day, with respect to the same period of time. It was stated that inter-rater reliability between two interviewers was high, but it was not specified whether the second interview was conducted by the same or a different interviewer. However, test-retest correlation was low.

Though few instruments assessing alcohol dependence have been presented with evidence of their reliability, there are hints that items in common use in such instruments are ambiguous and subject to varied interpretations. For example, Glatt [3] used Jellinek's questionnaire to study the drinking experiences of alcoholic in-patients. He also gave nine of the items to a sample of 'moderate drinkers' (mainly doctors and nurses, representing the same social class distribution as the alcoholics) who were 'not showing at the present time any evidence that drinking over a period of several years had affected their work or health'. Of the 80 men in the 'moderate' sample, 7.5% reported early morning drinking, 8.8% reported 'needing more drink to get same effect', and 16.3% reported 'decrease in tolerance'. Clearly the 'moderate drinkers' may have included some extreme drinkers who had remained free of social or medical consequences. However, it is surprising that early morning drinking had apparently occurred first at a mean age of 24.7 years in the moderate drinkers but at a mean age of 35.3 years in the alcoholics. 'Needing more for same effect' and 'decreased tolerance' if it was acknowledged by the moderate drinkers also apparently occurred earlier than in the alcoholics. However, the groups had not differed significantly in the age at which they started drinking. One explanation, and perhaps the most likely one, is that the moderate drinkers were using a lower threshold for reporting these items. That is, these items, as defined, were unreliable.

This cursory review is sufficient to show that the reliability of alcohol dependence criteria is an issue that deserves to be investigated rather than evaded.

Methodological difficulties

Three issues in designing a reliable instrument to measure alcohol dependence will be discussed and illustrated from the literature.

Specifying the Items. Of the elements of alcohol dependence described by Edwards and Gross [10] perhaps the most difficult to operationalise are 'subjective awareness of compulsion to drink' and 'reinstatement after abstinence'.

Stockwell et al. [17] tackled the first of these in a cautious manner using two questionnaire items on intensity of subjective disposition to drink in the morning during a heavy drinking period. They only specified the morning perhaps because they appear to have tried to avoid eliciting experiences cued by stimuli external to the individual. The experience of morning craving is arguably more dependent on stimuli arising within the individual, for example those associated with falling blood alcohol. However, the element of subjective compulsion to drink suggested in the Edwards and Gross description is more general than merely morning craving.

Also included in that element is the subjective experience of impaired control of drinking. Stockwell et al. do not attempt, in the limited format of a questionnaire, to assess this.

They tackled 'reinstatement after abstinence' as follows: they devised an item 'Imagine the following situation: (1) You have been completely off drink for a few weeks, (2) you then drink very heavily for two days. How would you feel the morning after those two days of heavy drinking?' The reliability of Imagine-the-following-situation-questions requires special attention. The authors have not commented on the reliability of the individual items in their questionnaire.

Specifying the time period and allowing for fluctuating severity. The time period to which the respondent should refer is a crucial specification. From longitudinal general population studies it is known that individuals move into and out of dependence on alcohol (e.g. [5]). Classical bout drinkers could certainly be said at times in their lives to move frequently into and out of the 'physiological', if not the 'psychological', elements of the syndrome. A study of the drinking habits of 'alcoholics' at large in the general population [18] amongst whom very few were classical bout alcoholics, showed that for many subjects 'alcoholic drinking' was interspersed within the same year by periods during which they could be said to drink like other people.

In questionnaires, often no time period is specified. Instead the present tense is used (e.g. Mulford, [11], 'Would you say these things about your drinking: without realising it, I end up drinking more than I had planned to? . . . etc.'). Such vagueness probably makes for unreliability.

One alternative is to ask the subject to make a judgement about a 'typical' drinking period. Stockwell et al. [17] asked the subject to 'recall a recent month . . . when you were drinking heavily in a way which, for you, was fairly typical of a heavy drinking period'. (The instrument used was a questionnaire.) Caetano et al. [15] asked the subject to judge his own 'typical drinking day'. The interviewer was directed to identify the period with some objectivity to which the patient referred.

This approach sidesteps astutely the difficulty that some symptoms fluctuate in severity. The chief snag is that the term 'typical' is subject to interpretation. To some it implies 'average'; to the self-critical respondent it may imply a 'typically bad' period; to the equivocating respondent it may define a period when nothing striking took place; to the committed alcoholic it may define a period when he was experiencing the 'typical' that is, 'textbook', symptoms of alcoholism.

Another objection to using the 'typical drinking day' at least in the Scottish

setting where the present author works is that a significant proportion of patients are mainly weekend drinkers, whose drinking increases from Thursday to Saturday and then subsides on Sunday and Monday. They are unable to offer a 'typical drinking day', and would probably find it hard to answer questions about a typical heavy drinking period. Shift workers, who have less access to alcohol in a country with restricted licensing hours during the week when they are on evening ('back') shift, present a further problem.

The third alternative is to specify a recent time period in terms of weeks or months. Ahlström-Laakso [18] found that the past 12 months was too long a period for subjects to recall accurately and this is borne out in clinical experience. Furthermore marked fluctuation may have occurred during such a long period.

Ideally, current degree of dependence would refer to the respondent's state on the day of the interview, which is experience immediately available to him, without memory intervening. However, if an instrument is to have a use in populations attending agencies, who have perhaps been 'detoxified' in the week or so prior to interview, this definition of current will be inappropriate.

The reference period for determining recent, or current dependence, needs to be long enough to avoid immediately recent detoxification and to catch recent heavy periods for those whose drinking fluctuates markedly, but no so long as to be hazy in the memory. The past three months might be a convenient period to specify. However, the difficulty remains that some symptoms, for example morning tremor, will in many subjects fluctuate in severity and/or frequency even during that relatively brief period. One is forced back to asking the subject to specify for the three-month period either a usual or average severity/frequency (e.g. 'tremor three days per week on average'), a typical severity/frequency (with the reservations mentioned above) or, severity/frequency 'when at its worst' or 'when at its most frequent'.

Is there a place for *cumulative* measure? This subsection quoted the view that individuals move into and out of dependence on alcohol. The early instruments, such as the Grapevine questionnaire [2], and most of the widely used 'screening' instruments phrase many items in the form 'Have you ever . . .?'. Such items yield a cumulative lifetime score. An individual who had a long history, but recently had been drinking little, could have a low score on 'recent' severity of dependence but a high cumulative score. The cumulative score would be of little relevance to research on, say, short-term physiological correlates of dependence. However, it might be relevant to genetic research, or outcome research.

Aim of the Present Study

The aim of this study was to assess the inter-rater reliability of a set of criteria of alcohol dependence, loosely based on the description of Edwards and Gross [10]. The pilot phase was to improve definitions of items and to test various ways of specifying reference periods.

Method

The pilot phase – developing the instrument

A standardized interview seemed to be more likely than a self-completed

questionnaire to avoid the vagueness and ambiguity which besets instruments in this field. Items were based on the elements of the syndrome as described by Edwards and Gross [10] and were brutal simplifications, being preformed precoded items, of the complexities portrayed by these authors. Considerable effort was put into the detailed wording of the items, some of which went through as many as four versions during pilotting on 25 male patients in psychiatric and general hospitals who were regular drinkers. Guide notes evolved.

No item on reinstatement after abstinence was included because of the difficulty found in operationalizing it. (With hindsight these may not have been insuperable. However, since many respondents in this sample had never been abstinent, many 'not applicables' would have been rated.)

'The past three months' emerged as a time base for measuring 'current' dependence which caught the last heavy drinking period of the few classical bout drinkers in the pilot sample, but which was not too long for respondents to recall. An attempt to provide a different format for bout drinkers was abandoned in the pilot phase because the overlap between bout and non-bout drinking made the distinction difficult to operationalize.

The final instrument

The final schedule ('The Edinburgh Alcohol Dependence Schedule', available from the author) dealt with 26 'symptoms', with sub-items dealing with 'recent' (past three months) severity and frequency, yielding 44 items in all. These are listed, abbreviated, in Table 1. For reasons which no longer seem pertinent four items only had a rating in the 'ever' form, and a 'recent' rating was not included. These were two items on changes in tolerance, **14, 41**, one item tentatively deemed to represent tolerance relative to one's drinking companions, **15**, and the item on 'true' alcoholic amnesia, **44**. Two items on Narrowing of Repertoire, **1, 2**, had a rating only in the 'recent' form because it was found in the pilot phase that answers to this question in the 'ever' form were difficult to rate.

(Items on diminished tolerance and amnesias, **41–44**, were included for historical reasons. Traditionally they are regarded as symptoms of alcoholism and their relation to dependence was to be tested using this instrument. However, they do not appear in the Edwards and Gross conception of alcohol dependence. Diminished tolerance and amnesias are each end-experiences of several differing psychophysiological paths. This obvious fact makes them poor candidates for inclusion in the syndrome.)

A response bias towards permitting acknowledgement of socially deviant behaviour and experience was sought, using the preamble: 'This interview is about your pattern of drinking and about certain experiences that are common in regular drinkers. The questions take about 25 minutes. It is not connected with your treatment and it is confidential. It is to help us understand more about the different varieties of drinking patterns.'

The guide notes specified that interviewers were to use the exact wording provided, and ask each question, regardless of whether the respondent had already discussed the experience involved in earlier replies. *Specific occasions* were to be recalled and described by the respondent wherever either the interviewer or the

Table 1

	Scale Points	Uneven Distribution of responses	Could not be rated by one or other rater n_1	Disagreement over Applicability n_2	Remaining cases n_3	K on n_3 cases	% agreement of total cases $(n_1 + n_2 + n_3)$
Narrowing of Repertoire							
1 Day[1]	2	–	0	0	41	.85	93
2 Mood[2]	2	–	1	0	40	.87	95
Salience							
3 Spending more time drinking	2	–	0	0	41	.90	98
4 Giving up interests	2	–	0	2	39	.95	93
6 Missing meals	2	–	0	0	41	.88	95
7 Frequency	3	–	0	0	41	.96	98
Need							
8 Restless without	2	–	0	1	40	.95	95
9 Severity[3]	4	–	3	0	23[12]	.75	77
10 Think[4]	2	–	0	0	41	.94	98
11 Frequency	4	–	1	0	40	.96	95
12 Organise day[5]	2	–	1	0	40	1.00	98
13 Frequency	3	–	1	0	40	.91	93
Tolerance							
14 Increased tolerance	2	'absent' in only 4	0	1	40	.77	93
15 More than companions[6]	2	–	0	0	41	.93	98
Impaired control							
16 Limit[7]	2	–	0	3	38	.95	90
17 Frequency	4	–	2	3	36	.89	85
18 Drunk[8]	2	–	0	3	38	.94	90
19 Frequency	4	–	1	3	37	.91	88
20 Passing out[9]	2	–	1	0	40	.88	93
21 Frequency	4	–	1	0	40	.95	95
22 Difficulty cutting down	3	–	0	0	41	.83	90
Withdrawal							
23 Tremor	2	–	0	0	41	.90	98
24 Frequency	4	–	0	0	41	.89	93
25 Severity	5	no ratings of points 1 and 3	0	0	26[13]	.78	90
26 Morning drink	2	–	0	0	41	1.0	100
27 Frequency	4	–	1	0	40	.87	90
28 Timing	4	–	0	0	41	.91	95
29 Retching	2	–	0	0	41	1.0	100
30 Frequency	4	–	0	0	41	1.0	100
31 Sweat	2	–	0	0	41	1.0	100
32 Frequency	4	–	0	0	41	.86	90
33 Tense[10]	2	–	1	3	37	.89	85
34 Frequency	4	–	1	3	37	.92	85
35 Panic	2	–	0	0	41	.90	95
36 Frequency	4	–	1	0	40	.89	93
37 Fit	2	'present' only in 3 cases	0	0	41	1.0	100
38 Frequency	3	–	0	0	41	1.0	100
39 Hallucinations	2	–	0	0	41	1.0	100
40 Frequency	3	–	0	0	41	1.0	100

(Continued overleaf)

Symptoms not conceptually part of dependence							
41 Diminished tolerance	2	–	1	0	40	.93	95
42 Amnesia[11]	2	–	0	0	41	.93	98
43 Frequency	4	–	0	0	41	1.0	100
44 'True' amnesia[12]	2	'present' only in 2 cases	2	0	24[13]	.78	88

[1] Change from drinking less on a weekday to drinking same or more nowadays.
[2] Change from drinking according to mood, to not drinking according to mood nowdays.
[3] Certain situations or times of the day when regularly restless or irritable without a drink.
Applies = Scores 1 point. Score a further point for either 'restless when interferes with what you're doing' or 'others notice you feeling restless'.
[4] At times can't think of anything but how to get a drink.
[5] Organize day beforehand to ensure you can obtain a drink at times you think you'll need one.
[6] Going for a drink between rounds or getting a start on companions.
[7] Set a limit but felt completely unable to keep to it.
[8] Had difficulty preventing yourself getting, what you would call, drunk.
[9] Passing out while drinking, in a public place.
[10] Wake up tense after drinking the day before, even though no obvious problems ahead that day.
[11] Completely unable to remember things you did while drinking (the events of 5 mins. or more).
[12] As 11, '. . . when you did not have a good drink in you, were not drunk (and other people, if they had seen you, would not have thought that you were drunk)'.
[13] Item amended at mid-point of study; therefore only coded on last 26 cases.

respondent were in doubt about a response. Contained in the guide notes were expanded definitions of the items, permitted probes, and criteria for inclusion and exclusion.

The items about the frequency of certain experiences were either of the form 'How many times has that happened in the past three months?' (e.g. 'passing out', 'hallucinations'); or 'How many times *per week* has that happened during the past three months?', qualified by 'at its most frequent' for tremor and morning drinking to allow for fluctuating frequency. Individuals who stated that the frequency of their other symptoms fluctuated (e.g. sweats, tenseness, etc.) were to be rated according to the frequency of the symptom 'at its most frequent'.

'Severity' in the past three months as well as or instead of 'frequency' was rated for certain items (tremor, restlessness without alcohol, morning drinking). Thus severity of tremor was graded according to whether in the past three months tremor had ever been severe enough to make it 'difficult to hold a cup or glass', or had caused 'legs or body to shake', etc.

Recent severity of 'restlessness', **9**, and recent frequency of tremor, **25**, together with 'true amnesia', **44**, were only included in the schedule midway during the study, and thus only for 26 subjects.

The sample

For the present study, 41 male admissions to the Edinburgh Unit for Treatment of Alcoholism were interviewed. They comprised two cohorts of approximately consecutive male admissions under 65 years. A patient was not approached for his co-operation if he was known to the ward staff to be demented or to have memory impairment. In addition, two patients on whom an interview was commenced were

not included because of dementia on simple clinical criteria evident to the research interviewers.

The 41 men ranged in age from 21 to 61 years, mean 41.1 years. They represented the following occupational categories:
professional (2); technical/managerial (11); other non-manual (8); skilled manual (11); non-skilled manual (9).

The raters

Two raters were present at each interview, the author plus one of five colleagues, selected to represent a range of experience. None of these six was on the ward staff or had prior knowledge of the patients to be seen. The colleagues comprised two psychiatrists, with special experience of alcoholism (who rated five and seven interviews respectively) a psychiatrist without special experience (10 interviews); a trainee psychiatric nurse (7 interviews) and a psychology graduate (12 interviews), both without special experience. Only the psychology graduate had practice with the schedule before the study (he had never interviewed an alcoholic before). Otherwise raters only read the guide notes and discussed the schedule in detail with the author before seeing their first subject.

The procedure

The subject was asked if he would be interviewed in confidence 'as part of a research project about patterns of drinking'. None refused. One rater conducted the interview, the other was present but silent. Rating was completed independently. Seventeen of the interviews were conducted by the author, 24 by the other rater, the author conducting a similar proportion of each rater's set of interviews.

Analysis

For each rating, the numbers of the possible types of disagreement and agreement were counted and Cohen's Kappa (K) calculated, a coefficient of agreement which takes account of chance agreement [19]. Its significance was calculated by the method suggested by Cohen. For some items, where three or more possible levels would be rated, weighted kappa (a modification allowing for some disagreements being less serious than others), would have been an appropriate coefficient. However, such high levels of significance were obtained using unweighted kappa for these items that there was nothing to be gained by complicating the analysis.

Results

Table 1 lists the items. Where an item is followed by a rating of 'frequency', 'severity', or 'timing', that item refers to *lifetime occurrence*, the sub-items to the *past three months*.

The first column gives the number of scale points on which an item could be rated.

The second column notes instances where the distribution of responses was

markedly uneven. This factor limits the use which can be made of percentage agreement as an index of agreement, but is reflected in kappa and its confidence limits.

The third column records the number of cases where one or both of the raters failed to rate the item. These instances appeared to be due to lack of precise enough information rather than careless omission. This indicates deficiency either in the definition and guide notes, the probes, or the rating scale. Severity (in the past three months) of being 'regularly restless or irritable without a drink in certain situations or at certain times of the day' could be 'present' (score 1) or could be 'noticeable by others' (add one point) and/or 'interfere with what you are doing' (add one point). This item was introduced after 15 cases had been interviewed and had not been properly pilotted. In three of the 26 interviews where this item was used, the author could not make a rating from the information elicited by the interviewing co-rater, though the converse never occurred. (The guide notes and probes were presumably not specific enough, given the wording of the question, and are being revised.)

The fourth column records where one rater felt an item to be 'absent' or 'present' while the other specified 'not applicable'. This highlights particularly an unreliability in two items about impaired control. This will be discussed later.

Kappa is shown in the sixth column. It was calculated on the number of cases shown in column five, which omitted cases (n_1 and n_2) where the anomalies noted above had occurred. To give an impression of reliability throughout the whole sample column seven defines these anomalies as disagreements and presents as a percentage the ratio of the total number of agreements to total number of cases.

With four exceptions, every item yielded a kappa which was significant at the level $p < 0.001$. The exceptions were 'increased tolerance', ($k = .77$, $p < 0.005$); fit ($k = 1.0$, $p < 0.01$); recent fit ($k = 1.0$, $p < .02$); 'true' alcoholic amnesia ($k = .78$, $p < .05$).

Discussion

In the context in which they have been examined these items yield high inter-rater agreement. The results compare favourably with those obtained in alcohol dependence by Caetano et al. [15] and for symptoms of anxiety and depression [20]. This was achieved without extensive practice with the schedule or training, but the cost was that on some items inadequate information was elicited by the unpractised interviewer (see discussion above of severity of 'restlessness').

The acid test of inter-rater reliability has yet to be conducted namely between pairs of raters not including the author. However, probably most items and their specifications are robust enough to withstand this test, with the following reservations.

The two items which subjects found most *difficult* to answer (in the author's memory) and which raters reported finding difficult in their debriefing, were **16/17** 'Have there been occasions when you set yourself a limit on how much you'd have, but found yourself completely unable to keep to a limit?' (inability to keep to a limit which could confidently be ascribed to social pressure, the too generous host etc. was not included); and **18/19** 'Different people mean different things by "getting drunk". Have there ever been occasions when you found it difficult to stop yourself

from getting, what *you* would call, drunk?'. The snag was deciding whether or not the subject did on occasions *intend* to keep to a limit, or not get drunk. And, if he did so, but continued to drink, whether that intention was overcome by forces from within him 'beyond his control' or whether he simply changed his mind. This obscure area and the findings in this sample will be the subject of a subsequent paper. Suffice it to say, for the present, that obtaining a response was difficult, and these were the items where, more than in others, there was disagreement over applicability (usually over whether the subject had or had not *tried* on occasions to limit his drinking); and where there were instances where one rater felt unable to make a rating. Several versions of these items were pilotted, along with items on impaired control used by previous workers. Depending as it must on the language of intention, impaired control as couched in these two items is conceptually too nebulous for inclusion in a schedule where more than 90 per cent agreement between raters is expected. It might however be worth trying a more direct item, such as, 'Have you felt an irresistible compulsion to continue drinking once your start?'

Three other items failed to yield 90 per cent or more agreement between raters:
9, recent severity of 'restless without a drink', where the snag was a combination of inadequately defined scale points and difficulty in deciding whether a subject had ever been 'without', giving a rating 'not applicable'.
33/34, 'tense after drinking the day before, even though no obvious problems ahead that day'; the caveat about 'obvious problems' is required because it is common for people in a treatment unit to have pressing problems (impending separation from wife, or loss of job) which fill the mind on waking. However, if this item were to be retained further delineation of 'obvious problems' would be necessary.
44, 'true' alcoholic amnesia: this was defined using Jellinek's understanding of the alcoholic 'blackout', being a memory lapse occurring after moderate drinking ('not more than 50 or 60g of absolute alcohol' in Jellinek's definition) unaccompanied by signs of intoxication. The raters agreed on its presence only in one out of 26 subjects, disagreed once, and in two subjects a rating was not made by one rater because the caveat 'when you were not drunk and the people would not have thought you were drunk' was not sufficiently explored. This item, it has already been mentioned, is not part of the Edwards and Gross [10] description of dependence.

Conclusions

Of four items lacking the very high degree of reliability obtainable by the majority, two can be improved fairly simply and hopefully made fully reliable:
Tense in the morning following drinking
Degrees of severity of restless without a drink.
The other two items failing this criteria are inherently difficult to operationalize and it is unlikely they can be made more reliable:
Inability to keep to a limit
Difficulty preventing getting drunk.

The level of reliability of all the items seems, however, sufficient for data gathered using the instrument to be used for further analysis. The hypothesis that the items form a unidimensional syndrome is explored in the accompanying paper [21].

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Is There a Unidimensional Alcohol Dependence Syndrome?

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Summary
The elements of the provisional description of the Alcohol Dependence Syndrome were operationalised into a structured interview given to 109 men attending an alcoholism treatment unit. A single underlying dimension could not be demonstrated. The main dimension comprised Subjective Need, Withdrawal, and aspects of Salience. Narrowing of Repertoire and Impaired Control formed separate dimensions.

In their attempt to supercede the conglomerate concept of alcoholism, the WHO Group of Investigators on Criteria for Identifying and Classifying Disabilities related to Alcohol Consumption decided to set apart 'one important disability requiring definition and clarification . . . the alcohol dependence syndrome'. 'The reality and significance of this syndrome seemed to be well supported by a review of present evidence' [1].

As proposed initially, the syndrome of alcohol dependence was to be seen as a 'clustering', but one which would yield a 'range of severity' [2]. It is suggested that, despite variety of manifestation, it is to be seen as a unitary phenomenon: 'Symptoms (are) ranged upon a continuum of severity. . . . The syndrome of alcohol dependence is given expression and, in various ways, both facilitated and hindered by an individual's personality and general circumstances, but remains, nevertheless, a unitary syndrome' [3]. One type of evidence for the syndrome being 'a psychobiological reality not an arbitrary social label' was to be, therefore, its unidimensionality.

If the notion of an alcohol dependence syndrome is upheld there are implications in many areas. In research, it suggests that physiological, genetic and learning theory approaches to aetiology deserve support. In planning treatment services, the implication is that some drinkers require help from specialists and that parts of treatment programmes from one culture may be transportable to other cultures since there is universal core component to the condition. With a view to prevention, the implications may be those drawn by, for example, the British Royal College of Psychiatrists: 'The tactics for remedying the situation are not (therefore) simply commonsense . . .'. 'Any person who drinks should be aware that he is using a drug which can induce dependence' [4].

Illustrative Review of Empirical Studies on the Unitariness of Alcohol Dependence

Two commonly used methods of investigating whether a set of data lie on a continuum are factor analysis and Guttman scaling.

Factor analysis gives rise to several criteria against which to test a hypothesis of unitariness. Different authors in the alcohol literature have used different criteria but the common feature is a demonstration that the major factor accounts for a very substantial part of the variance.

Guttman scaling provides a more stringent test of the unitariness of a set of items. If items meet the requirements of Guttman scaling it implies that they are cumulative (in terms of severity, not natural history) as well as unidimensional. (If items form a perfect Guttman scale then individuals at a given point on the scale will, by definition, have that item and also every item on the scale below that one, but none above it.*)

Factor Analytic Studies

Horn and Wanberg [5] analysed questionnaire responses from 2,300 patients admitted to an alcoholism treatment facility. The 41 items were about style and quantity of drinking, consequences, attitudes of self and others to one's drinking, reasons for drinking and withdrawal symptoms. Principal component analysis yielded 13 factors with eigenvalues greater than unity. The proportion of the variance accounted for by the first factor was not reported. These 13 factors tended to correlate positively but weakly with each other. From this the authors concluded that 'alcoholism', if it was a unitary attribute, was an attribute made of poorly associated components.

In contrast are factor analytic studies which demonstrate a reasonable degree of unitariness. With one exception, however, which will be described, these have not shed light on the concept of alcohol dependence as defined by Edwards and Gross [2]. To illustrate, two such studies will be mentioned.

Overall and Patrick [6] gave a questionnaire containing 135 items concerned with alcohol abuse and related behaviours to 160 psychiatric in-patients 'with a wide range of alcohol use'. The factor analysis they performed yielded a first factor which accounted for 27.2% of the variance. The other factors to emerge each only accounted for between 1.9% and 3.5% of the variance. The 42 items most highly related to the primary 'alcohol abuse' factor were about adverse consequences of drinking (six), reasons for drinking (four), amount of alcohol (four), drunken periods (two), attitudes to one's own drinking (six), other people's attitudes to one's drinking (two), the remaining 18 about 'dependence' as described by Edwards and Gross. The correlation matrix of these 42 items yielded a major factor with an eigenvalue of 18.2 which was more than nine times the root of the next most important factor. The authors reasonably concluded that they had demonstrated that the set of 42 items defined a unidimensional factor domain. Did their main factor look like a core syndrome of 'alcohol dependence'?

The items which loaded most heavily on it were in order (1) Do you feel that drinking is a real problem for you? (2) Do you frequently skip meals when you aj drinking? (3) Are you now an alcoholic? (4) Do you drink more than most of your friends? (5) When you get drunk do you sometimes stay that way for two to three

* Guttman scaling can generate scales which are conceptually meaningless. As with factor analysis a judgement must be made as to the practical sense of a revealed dimension.

days or longer? (6) Do you frequently take a drink to calm your nerves? This does not look like the Edwards and Gross description of dependence. In a sample of patients, especially of voluntary in-patients, if items about self-identification as an alcoholic or problem drinker are included it is perhaps not surprising that the main factor to emerge is influenced by perceiving alcohol as a problem. This will be the feature which, above all, alcoholic in-patients will have in common.

Hilton and Lokare [7] derived a general factor which, though they called it 'alcohol dependence' might also more aptly have been given another name, for example 'problematic drinking experiences' factor. It was a dimension which depended heavily on adverse consequences and other items best conceived of as properties of the interaction of the individual and his social environment. (This study is commented on in [8]).

These sort of results, then, will not do as evidence for a unitary alcohol dependence syndrome as proposed by Edwards and Gross.

Stockwell et al. [3] designed a questionnaire specifically to measure alcohol dependence as defined by Edwards and Gross. In 104 patients of an alcoholism service, 19 already refined questionnaire items defining four aspects of the syndrome were factor analysed 'to determine whether one major factor would account for a majority of the variance to comply with the concept of a single syndrome of alcohol dependence'. A general factor emerged accounting for 53 per cent of the total variance, strongly suggesting that the aspects of the syndrome studied reflected a single phenomenon. The aspects measured were physical withdrawal symptoms, affective withdrawal symptoms, withdrawal relief drinking, morning craving and reinstatement after abstinence. 'Salience of drinking-seeking behaviour', some features of the proposed 'subjective awareness of compulsion to drink' and 'narrowing of the drinking repertoire' are elements of the Edwards and Gross description that were not included. Thus the unitariness of the whole of the Edwards and Gross conception was not tested.

It also remains to be seen whether such a clearly unitary picture emerges in samples of alcohol dependent individuals which span the whole range of severity which the syndrome is supposed to show. In the study of Stockwell et al., clinical ratings of severity were made in 75 of the subjects. This included only 4% deemed to have minimal dependence, 24% with mild to moderate dependence, with a preponderance (68%) being in the moderate or severe category. It is not stated whether the range of scores of these 75 was similar to the whole sample of 104, but if it was, then one may conclude that their factor analyses were performed on responses from a sample somewhat weighted towards the severe end.

Guttman Scaling Studies

The searcher after unidimensionality of alcohol dependence via Guttman scaling is somewhat deterred by Cahalan and Room's conclusion that symptom scales in alcoholism 'have never fulfilled traditional standards for Guttman scales' [9]. True, Jackson [10] in populations of identified alcoholics from various sources produced the scales of 'Preoccupation with Alcohol' and 'Psychological Involvement' (whose items bear some resemblance to the Edwards and Gross description) which did meet Guttman criteria. However, this was only achieved when

contrived items were used, that is scale points composed conjunctively or disjunctively of two or three of the individual questionnaire items.

Descendents of these scales had considerable use in prevalence studies but were mysteriously inefficient at identifying 'known alcoholics' in survey populations [11, 12]. This fact was one of several influences on Mulford's most recent attempts to design instruments in this area [13]. Out of step with fashion, he retained the notion of alcoholism (though stridently a social rather than a biological phenomenon) but stated his intention to 'avoid a unitary perspective'. The index he has produced does not illuminate the question that is central to this paper – namely, within the conglomerate of 'alcoholism' is there a unidimensional core syndrome of alcohol dependence. Apart from Stockwell et al. [3] whose answer, while clear, is not complete, there is no definite help from the client literature or the survey literature. The present study hopes to go further towards providing an answer.

Aims and Design

The present study tests the hypothesis that there exists a core syndrome which is unidimensional. An experimental approach to this question in humans cannot, *pace* Isbell, today be contemplated. One is constrained to gathering data from self-reports*,†. The sample should be ideologically uncontaminated subjects, that is from a population rather than an agency sample, but a yield of 100 definitely alcohol dependent individuals could only be obtained in a population survey of, say, 40 times that number. In the present study, feasibility dictated that subjects attending an agency were studied, and the hypothesis tested on their self-reports. To increase the homogeneity of the sample, only men were chosen.

How can the comforting palingenesis which dogs self-report research in agency samples be avoided? First, one must obtain a sample which represents a range of previous exposure to ideologies of alcoholism, and of self-identification as alcoholics, in order that the effect of each on the self-report instrument can be quantified. Second, the instrument must be robust, without room for ambiguity, to minimize bias to response set: in short, of proven reliability. Each of these steps with respect to the present paper is reported on separately [8, 14].

Further, subjects should be interviewed as close as possible to the time of their initial attendance at the agency to reduce the degree of exposure to the agency beliefs about alcoholism.

The Method

The data

The Edinburgh Alcohol Dependence Schedule is described in [8] together with evidence of the reliability of its items. These items dealt with 'recent' and 'lifetime'

* The criteria of the National Council on Alcoholism, in contrast, comprise physical signs and blood abnormalities as well as self-report items but these are direct indicators of heavy consumption and only indirect indicators of 'dependence' as defined by Edwards and Gross

† Withdrawal phenomena (e.g. amplitude of tremor) can of course be measured objectively but only give information on severity of withdrawal on a given occasion. Severity of dependence fluctuates and a measure that summarizes a recent period is more appropriate to the hypothesis being tested here. This can only be achieved by asking the subject to recall that period.

occurrence of 24 symptoms which were operational attempts to define the concepts in the Edwards and Gross [2] provisional description of the alcohol dependence syndrome, excepting the element of reinstatement after abstinence. Twenty-one of these symptoms were deemed to reflect 'recent' dependence.

Two indices of consumption were derived. The subject was asked to recall in detail his consumption during the seven days prior to the interview or, if he was an in-patient, prior to his admission. The total he consumed (in grams of absolute alcohol) in those seven days was called 'last week's consumption'. Degree of prior exposure to beliefs about alcoholism; and self-identification as having 'no', 'slight', or 'definite' alcohol problem, or 'alcoholism', were also recorded.

The subjects

The sample of 109 men attending the Royal Edinburgh Hospital alcoholism treatment unit consisted of two sets of consecutive male admissions plus 17 unsystematically sampled male out-patients. Men over 65 years old were excluded and also those in whom there was clinical evidence of brain damage or memory impairment. Their mean age was 41.1 years.

Information about previous exposure to beliefs about alcoholism was unavailable for 12 subjects, all in-patients. Of the remaining 97, 22 per cent stated they have never sought advice about their drinking previously, and had never read a pamphlet or seen television films about alcoholism. At the other extreme, 56 per cent had had previous psychiatric consultation, or had attended two or more AA meetings, or read a pamphlet on alcoholism or obtained advice at a voluntary agency.

Information about self-identification was unavailable in the same 12 subjects. Of the remaining 97, 67 % stated they would describe themselves as alcoholics, 14 % as having a definite alcohol problem, 9 % as having a slight problem and 7 % as not having a problem.

Their occupational categories were: professional (14 %), technical /managerial (21 %), other non-manual (11 %), skilled manual (28 %), non-skilled manual (26 %). Their consumption during the 'past 7 days' varied between over 1,600 gm absolute alcohol (approximately 7 bottles of 40 % spirits) (40.4 %), to less than 800 gm (28.3 %) and their 'maximum day's consumption' between over 400 gm (28.5 %) to less than 160 gm (30.2 %). Sixty-one per cent regarded that segment of consumption as 'typical', 14 % regarded it as more than 14 % as less than 'typical', and 11 % said they did not recognize such a thing as a 'typical week'.

The approach made to the subjects and the preambles to the interview were described in [8]. The interviewer was either the author, a co-rater (see [8]) in which case the author's ratings were submitted for analysis, or a psychologist trained in the use of the schedule. Out-patients were interviewed on the day of their first visit, prior to their intake interview. In-patients were interviewed as soon after admission as their medical condition permitted, which was always within seven days.

Analysis

The analysis was conducted in three parts:

An attempt to validate the items by analysing the subsets of items deemed to represent the elements described by Edwards and Gross. Guttman scaling analysis was applied to these subsets to determine whether they met the criteria of unidimensionality and cumulativeness (coefficient of reproducibility $CR > 0.90$, coefficient of scalability $CS > 0.60$ [15]). Subsets that fell short of the criteria had items added or subtracted and the points varied as suggested by scale-item correlations, in the hope of generating scales. When this failed, the subsets were factor analysed as a less stringent test of unidimensionality. If items in a subset met one test of unidimensionality, that was taken to indicate at least that they shared some meaning, though could not constitute a test of validity.

A search for a Guttman scale that would cross subsets of items was then conducted. Contrived items, derived from the subsets, were scaled, and also individual items, according to an *ad hoc* procedure, depending on familiarity with the data and the scalability of the subsets, and hunch. This part was concluded before factor analysis was begun.

A search for a main factor suggesting a unitary dimension was then conducted.

1. A principal components analysis of the correlation matrix of the 'Edwards and Gross' items was made.

2. The principal factors so derived were also rotated orthogonally (by Varimax rotation) and obliquely with Kaiser normalisation through a range of degrees of obliqueness, with the object of specifying the simplest factor structure, according to the guidelines summarised by Harman [16]. (These are 'rules of thumb' only and suggest the pattern of 'zeros' in the columns and rows of the factor matrix which accompany the simplest solution. Restated in geometric terms the rules imply that (a) many points will lie near the final factor axes and (b) only a small number of points will remain removed from both axes.)

By this stage in the analysis it was clear that amongst 'cumulative' items unidimensionality was far harder to demonstrate than amongst 'recent' items. So for brevity, only the findings for the factor analysis on 'recent' items will be described.

The factor analysis was not performed on the correlation matrix of *all* the 'recent' symptoms, because there were instances of logical dependency between variables. Factoring intercorrelations among these variables raises the communalities and factor coefficients spuriously.

Two items are 'logically dependent' if response to one imposes a logical constraint on response to the other. In this study, 'timing of a morning drink' could only be rated above zero for an individual who had already scored on the item 'frequency of morning drinking' since zero on that latter item would have meant the individual had not taken a morning drink in the three-month period to which the 'timing' question referred.

'Quantity of morning drinking'; was logically dependent on 'timing', and 'frequency of morning drinking'; and severity of tremor was logically dependent on frequency of tremor.

An *ad hoc* decision was made as to which variables of logically dependent sets to retain in the factor analysis. From the sets of items on tremor and morning drinking only the 'frequency' items of each set were retained.

3. A third step was to enter a further set of items of theoretical interest: age, occupation, in-patient/out-patient status; consumption; and two symptoms not part of the Edwards and Gross description: diminished tolerance and amnesias.

Results

Internal structure of the subsets of items representing the proposed elements of the syndrome.
Seven symptoms were deemed to represent the element of *Withdrawal*: tremor frequency and severity (degree of functional impairment), tension, night or morning sweats, night or morning panic, hallucinations and fits. In their 'recent' form, a scale emerged which closely approached the criteria, but only when the items were restricted to frequency of tremor, retching, tension, sweating and panic (CR 0.89, CS 0.66, n = 98*). These five items plus severity of tremor yielded a principal factor which accounted for 52.5 per cent of their total variance, though they also yielded one secondary factor on which panic and tension were loaded.

The element of *Salience* was deemed to be reflected in the items 'spending more time drinking', 'missing meals', 'organising the day' ('to ensure you could obtain a drink at times you thought you would need one'), 'giving up interests' ('because spending more time drinking instead'). This subset were far from meeting the scaling criteria either in the 'cumulative' or 'recent' forms. The four items comprising Salience were intercorrelated and the matrix factor analysed. Two factors with eigenvalues greater than unity were derived, accounting for 39.9 per cent and 26.6 per cent of the total variance respectively. This indicates that these four items do not reflect a single dimension.

The element of *Relief Drinking*, comprised in the items on frequency, timing and quantity of morning relief drinking scaled very clearly (CR .99, CS .97, n=62†).

The element of *Subjective Awareness of Compulsion to Drink* was operationalized using two sets of items, Intensity of Felt Need, and Impaired Control. 'A feeling that you can't think of anything else', 'organising the day' and 'restless without' (the Need items) in their 'recent' form but not their cumulative form comprised a scale (CR 0.92, CS 0.70, n = 45: higher ratings of 'restless' were amended partway through the study, thus data were only available on the last 45 cases).

Items on Impaired Control included 'difficulty preventing getting drunk', and 'completely unable to keep to a limit' (both of which yielded many ratings of 'not applicable' since intention to control drinking was foreign to many subjects). Amongst those to whom both these items were applicable, a scale including 'passing out in a public place' could be generated in both 'cumulative' and 'recent' forms (CR 0.91, CS 0.67, n = 52 and CR 0.93, CS 0.77, n = 57). 'Difficulty cutting down' which was couched only in the 'ever' form did not scale with all or with any two of the other three items.

The Edwards and Gross element *Narrowing of the Drinking Repertoire* was only represented by two items and thus could not be examined for its tendency to scale

* A case is omitted from the analysis if one or more of the items being scaled was rated 'not applicable in that subject'. Thus, n varies.

† Quantity of morning drinking was only obtained in the first 62 cases interviewed, at which point a shortened schedule was printed, omitting this item in the cause of brevity.

Table 2 also shows the frequency with which items were acknowledged (in any degree). Elements dominating the 1st factor are Withdrawal (excepting hallucinations and fits); Relief Drinking; and the Need sub-element. The Salience item 'missing meals' had a moderately high loading. The 2nd factor is dominated by the Impaired Control sub-element; the 3rd by Narrowing of Repertoire; the 4th by the severe (or perhaps more idiosyncratic) symptoms of withdrawal – fits and hallucinations (fits, it should be noted, were a rare symptom making this an unreliable item in a factor analysis); the 5th by the Salience items 'Spending more time drinking' and 'giving up interests' and the 6th by the two items deemed to represent Increased Tolerance.

The 'simplest' solution, as defined above, was obtained by rotating these factors, with Kaiser normalization to produce a fairly oblique solution (delta = 0, [15]). The structure of this solution is shown in Table 3. There are no major differences between this and the principal components solution though the 1st factor is now dominated slightly more clearly by Withdrawal than by Need and Relief Drinking.

Table 3 Factor structure (after oblique rotation) of the 21 dependence symptoms

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Narrowed repertoire: Day	.05	−.04	.82	.05	.05	−.09	.09
Narrowed repertoire: Mood	−.01	.03	.64	.10	−.31	.16	−.45
Spending more time drinking	.35	.30	.27	−.00	.52	.18	−.37
Giving up interests	.17	.21	.01	.09	.11	.21	−.84
Need more for same effect	.16	.02	.02	.11	.12	.65	−.09
More than companions	.05	.42	.18	.14	−.29	.54	−.23
Missing meals	.51	.17	.48	.25	.16	.30	−.04
Restless without	.31	.19	−.01	.12	.13	.72	−.08
Can't think of anything else	.55	.14	.15	.28	−.09	.59	−.19
Organise day	.54	.31	.02	.23	.06	.58	.29
Can't keep to limit	.20	.86	−.01	−.01	−.01	.15	−.17
Difficult to avoid get drunk	−.02	.83	.04	.26	−.12	.07	−.13
Passing out	.49	.27	.07	.52	−.34	.05	−.13
Frequency of tremor	.84	.03	.10	.09	.26	.36	.08
Frequency of a.m. drink	.59	−.07	.18	.20	−.09	.68	−.02
Retching	.73	.17	.10	.32	.09	.26	−.16
Sweating	.65	.11	.16	.17	−.11	.29	−.10
Morning tension	.60	.31	−.00	.46	−.02	.16	−.40
Panic	.25	.21	.28	.82	−.11	.26	−.16
Fits	−.02	−.18	−.11	.29	.73	.08	.03
Hallucinations	.23	.06	.01	.77	.24	.14	.01

n = 109

Table 4 shows the correlations between these factors. In general, these are positive but low.

In the next stage, to the correlation matrix were added the symptoms of diminished tolerance and amnesia; last week's consumption; age; occupation; and in-patient/out-patient status. The effect of this was not to alter the explanatory power of the first factor which again accounted for only one-quarter (22.3 per cent) of the variance. The inclusion of the consumption variable was responsible for 'passing out' appearing more clearly on the first factor on which consumption

Table 4 Factor correlations: oblique solution, the 21 dependence symptoms

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Factor 1						
Factor 2	.16					
Factor 3	.12	.05				
Factor 4	.25	.13	.07			
Factor 5	.05	−.08	−.06	−.01		
Factor 6	.31	.14	.10	.15	.02	
Factor 7	−.08	−.18	−.11	−.08	−.04	−.10

itself also loaded highly. Other loadings remained very similar. (Frequency of amnesia loaded highly on this 1st factor.) The relative loadings of the individual dependence symptoms on the remaining factors resembled their loadings on the factors produced in the analysis of dependence symptoms alone, though it is of note that consumption loaded negatively (− 0.327) on Factor 2 ('Impaired Control'), until an oblique rotation was performed when Factor 2 had just positive consumption loading (0.126). Frequency of amnesia loaded equally on Factor 1 and Factor 2 (0.470), (0.482). Table 5 shows the loadings on the first seven factors after oblique rotation (Kaiser normalization; delta = 0).

Table 5 Factor structure (after oblique rotation) of the enlarged set of items

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Age	.12	−.08	.07	−.04	.08	−.03	−.03
Occupation	.02	.10	.02	.11	.06	.77	.22
In-patient/Out-patient	−.16	−.03	.09	.05	.72	.17	.06
Narrowed repertoire: Day	.08	−.12	.67	.05	.16	.12	.15
Narrowed repertoire: Mood	−.01	.13	.75	.02	.06	−.20	−.07
Spending more time drinking	.22	.27	.12	.16	.26	−.07	.77
Giving up interests	.09	.29	.12	.11	.06	−.65	.30
Need more for same effect	.14	.06	.02	.13	−.11	.01	.13
More than companions	.27	.41	.17	−.01	.43	−.16	−.30
Diminished tolerance*	.21	.23	−.09	.32	−.60	.20	.05
Missing meals	.45	.10	.39	.18	−.11	.12	.41
Restless without	.41	.24	−.06	.20	.33	.01	.04
Can't think of anything else	.59	.27	.24	.29	−.11	.04	.06
Organise day	.66	.28	−.09	.21	−.07	.21	.00
Can't keep to limit	.16	.80	−.03	−.07	−.05	−.12	.15
Difficult avoid get drunk	.02	.82	.08	.18	.06	−.02	−.10
Passing out	.50	.25	.20	.27	−.02	.06	−.05
Frequency of tremor	.75	.00	.03	.17	−.11	.06	.46
Frequency of a.m. drink	.64	.03	.25	.21	−.10	−.06	−.05
Retching	.73	.23	.13	.40	−.04	−.16	.20
Sweating	.67	.15	.21	.16	.06	−.13	.05
Morning tension	.49	.39	.15	.48	−.06	−.30	.20
Panic	.26	.24	.38	.68	.04	.01	
Fits	.01	−.27	−.32	.49	.21	−.13	.32
Hallucinations	.21	.11	.04	.81	−.09	.07	.07
Frequency of amnesias†	.47	.48	.17	.45	−.15	.17	.27
Last week's consumption	.76	.12	−.05	.18	.26	.14	.00

n = 109
* acknowledged by 33 %
† acknowledged by 77 %

Discussion

The 'aims' section of this paper is a lie. The original chief intention had been to construct a scale of severity of alcohol dependence, somewhat taking for granted the Edwards and Gross provisional description. Therefore, the four main findings of this paper arose in a context which was relatively free of personal bias against a unidimensional syndrome. Indeed, if anything the bias may have been towards finding a single dimension, since then a nice, publishable scale would have arisen. It is important to state this since the procedures employed (scavenging for scales and fishing for factors) give room for subjectivity.

The main findings are summarised below. The discussion will deal first with points arising from the nature of the data; second with more conceptual matters.

1. Only a very limited range of items could be coaxed into a Guttman scale which crossed boundaries between elements of the syndrome. Since the scale obtained was based on data from only half the subjects ('restless without' was modified half-way through the study) replication here is specially required.
2. The items studied did not yield a single factor which could be said to account for 'a very substantial proportion of the total variance'. Nor did the main factors 'intercorrelate highly'.*
3. Turning to the individual elements, Withdrawal, Need, some aspects of Salience, and Relief Drinking form the core of the syndrome, according to the factor analysis. That Relief Drinking did not belong on the 'core' Guttman scale is slightly puzzling, though it was significantly related to it ($p = .0001$). The other symptoms in that scale were those that might have been predicted from the factor analysis had it been conducted first.

   Impaired control, at least the truly subjective aspects of this sub-element of the element Subjective Awareness of Compulsion to Drink, formed a dimension in its own right. (Passing Out loaded on the first factor rather than the second and while being an objective index of impaired control – assuming no subjects like passing out in public – does not strictly reflect *Subjective Awareness* of Compulsion to Drink).

   Narrowing of Repertoire formed a separate dimension.†
4. It is the Core dimension that is most clearly related to high alcohol consumption.

* A more prominent first factor might emerge in a more heterogeneous sample (e.g. drawn from the general population). However Stockwell et al. [3] found a first factor accounting for over 50 per cent of the total variance demonstrating that, depending on the choice of symptoms, a clear major dimension can be revealed by the method of principal components analysis even in a sample as homogeneous as patients attending alcoholism units.

† The separateness of the elements of Impaired Control and Narrowing of Repertoire from the core of the syndrome was perforce also demonstrated by their lack of association with the 'core' Guttman scale (measuring degree of severity). 'Core' Guttman scale score against: Unable to keep to a limit $\chi^2 = 16.2$, 18df, ns. Difficulty avoid getting drunk: $\chi^2 = 10.0$, 18df, ns; Narrowing of repertoire (day of week) $\chi^2 = 5.5$, 6df, ns; Narrowing of repertoire (mood): $\chi^2 = 9.0$, 6df, ns. Also in support of the view that separate dimensions are present are the low correlations between these four items individually and the individual items loading on the main factor. The highest for the Narrowing of Repertoire element was between Narrowing of Repertoire (mood) and Missing Meals (0.22); for the Impaired Control element, between Unable to keep to a limit and Organizing the Day (0.25).

Points arising from the nature of the data

What artifacts could have led the Impaired Control items and the Narrowing of Repertoire items to appear as distinct dimensions?

First, *the snare of logical dependence between items*, already referred to: At first glance it seems likely that 'difficulty preventing getting drunk' must be a consequence of being 'unable to keep to a limit', i.e. logically dependent on inability to keep to a limit. If this was the case one should find not only a high intercorrelation (which was so, 0.57) but also a paucity of cases where 'difficulty preventing getting drunk' was acknowledged in the absence of 'inability to keep to a limit'. This was not the case: 15 out of 45 subjects acknowledged the item 'difficulty preventing getting drunk' who did not acknowledge 'inability to keep to a limit'. The Narrowing of Repertoire items could not be perceived as logically dependent: the 'Day' item was a change from 'drinking more on a day off or weekend than a weekday' to drinking the same or more on a weekday; the 'Mood' item was a change from having at one time drunk according to mood ('happy, depressed etc.') to not drinking according to mood.

Second, *the problem of Not Applicable (N/A) ratings*: For 'unable to keep to a limit' and 'difficulty preventing getting drunk' N/A (in the past three months) was rated respectively in 48 per cent and 30 per cent of subjects. Many subjects said they never set limits and never consciously made a decision to avoid getting drunk. At one extreme were those who didn't because they knew it was pointless; and at the other those who didn't because they never perceived any need. This potential distinction was unfortunately so difficult to pursue in the majority of those rated N/A that attempts to modify the rating in order to make better sense of the data were unreliable (between pairs of rater) and therefore abandoned. In the factor analysis 'N/A' on these two Impaired Control items was entered as 'absent'. Would the analysis have produced a different result if conducted only in those subjects to whom the questions were strictly applicable (those who had on occasions in the past three months 'set a limit' or 'tried to avoid getting drunk')? This proved not to be the case: even amongst these cases, claiming impaired control did not load on the main factor and again appeared separately. (The number of cases (48) was however insufficiently large in proportion to the number of variables (21) for confidence to be laid on this result.)

The same argument does not apply to the two items on Narrowing of Repertoire. Here the proportion of N/A codings was too small to have appreciably biased the result (7 per cent and 9 per cent respectively).

Third, *the problem of operationalising the element of Increased Tolerance* requires separate mention, since the form of the two Increased Tolerance items may have diminished their loading on the 1st factor. Increased tolerance is not an event, like 'passing out' or 'experiencing tremor' whose frequency can be counted.It is a process of which the individual gradually becomes aware. Subjects were not asked whether their tolerance had increased by an increment *in the past three months*, which was the time period for the other items on the 'recent' analysis. The items were rated positively if they had *ever* remarked on their tolerance increasing or their 'needing' more than their companions. Thus it was possible for a subject to score on both these items even though his symptomatology in the recent past had been mild or absent. Indeed, score on the 'core' Guttman scale of recent

severity was unrelated to either of the Increased Tolerance items ($\chi^2 = 5.5$, 6 df, ns; $\chi^2 = 6.9$, 6 df, ns, respectively; n = 36).

No definite conclusions about the place of Increased Tolerance in the range of items studied here can therefore be drawn from this study, because the items were not properly measured.

Fourth, *the lack of association of Consumption with Impaired Control*: was this an artefact of basing the measurement of consumption on the seven days prior to interview (or hospital admission)? Perhaps a systematic bias towards associating consumption with the Core dimension (Factor 1) rather than for example Impaired Control (Factor 2) might have been introduced if, say, those who experienced Impaired Control tended to drink atypically little immediately prior to their first out-patient visit or their admission to hospital. However there was no relation between the two main items about impaired control, and whether or not the week of drinking rated was seen by the respondent as 'typical' (including 'more than typical') or not ('less than typical' or 'no such thing as a typical week'). ('Typical' by 'can't keep to limit': $\chi^2 = 1.29$ 3 df, ns; 'typical' by 'difficult prevent get drunk:' $\chi^2 = 1.70$ 3 df, ns).

Conceptual issues and points arising from the nature of the sample

There are already examples in the alcoholism literature of how easy it is to demolish your own straw man. Is the unidimensional alcohol dependence syndrome another figment of the quarrelsome imagination of jostling alcohol researchers? It is beyond doubt that Edwards and Gross foresaw the complexities of the picture they drew. In defining their use of the term syndrome they stated: 'Not all the elements need always be present, nor always present with the same intensity' and 'The syndrome must be viewed as subtle and plastic. . . .' [12].

Inconsistent with this version are hints, several times repeated by Edwards and Gross, and Stockwell et al. [3], of a hypothesis of unidimensionality: 'Each part of this syndrome relates in some way to each other part'; plus references to 'a coherent whole' [2]. Indeed Edwards and Gross suggest that 'when the elements within a story do not add up to a coherent whole most often the doctor has not taken a sufficiently careful history or the patient is withholding some element of the syndrome'. Taken too literally that statement would put the Edwards and Gross description into the realm of the unfalsifiable like certain versions of psychoanalytic thought whereby uncongenial or missing data are explained away either as lack of sophistication in the investigator or denial and repression in the subject.

The Edwards and Gross description does not belong in the realm of the unfalsifiable and it is legitimate to ask of the present study: did the doctor take a sufficiently careful history? (were the elements adequately operationalised?) and/or was the patient withholding something? (were the subjects minimising or lying?)

It remains for the proponents to decide the first, and if necessary do better; there is no doubt that certain concepts are awkward to operationalise, in particular impaired control and narrowed repertoire, the two elements which most clearly did not fit. For impaired control this is probably mostly due to the difficul-

ties of operationalising a concept which has recourse to the realm of intention and the will.

If subjects minimised or lied, they did not lie in a way that is consistent with prevailing notions of alcoholic denial. That is, of the two elements that most clearly did not fit, one is not commonly regarded by the lay population as a symptom of alcoholism (narrowed repertoire – in terms of day of week and mood) [14]. The other (impaired control) is part of the folk beliefs about alcoholics [14] and therefore, on the alcoholic denial theory should be acknowledged more readily by those who have agreed to define themselves as alcoholics than by those who have not. Thus, at a given level of severity, impaired control items should be more frequently acknowledged by those who self-identified as alcoholics. This was not the case for this sample [14].

Another possible reason for the separateness of the Impaired Control element is that only the subject who had on at least one occasion done something about his drinking would have had the intention to exert control over his intake, and that also such individuals would have recently been drinking and experiencing symptoms in an atypical way – on and off. The data do not support this view: acknowledging impaired control did not relate to degree of previous contact with agencies etc., whether individuals to whom these items did not apply were deemed not to have the item or were excluded from the analysis. ('Previous exposure' by 'can't keep to limit' (N/A = 'Absent') $\chi^2 = 5.9$, 9df, ns, n = 97; (N/A excluded) $\chi^2 = 7.2$, 9 df, ns, n = 47; 'Previous exposure' by 'difficult avoid get drunk' (N/A = 'absemt') $\chi^2 = 15.2$, 9 df, ns, n = 97; (N/A excluded) $\chi^2 = 9.6$, 9 df, ns, n = 65.)

Conclusions

The activities of the Society for the Prevention of Cruelty to Dead Horses are secret. Members of the Society claim that the old doctrines of their disciplines (such as 'classic Marxism' or 'pure behaviourism' or 'the disease of alcoholism') are dead. They request us to refrain from flogging poor dead animals, but surreptitiously re-erect the doctrine in a new guise. Is this why Impaired Control is to be found in the reformulated alcohol dependence syndrome, so that the condition may remain in the realm of disease (by virtue of being 'beyond the will') and the preserve of a chauvinist medical profession? That debate grows tedious. But here is a study which finds that if a unidimensional syndrome exists, it comprises Withdrawal; Subjective Need; aspects of Salience; and probably Relief Drinking and Increased Tolerance; – at least, among the patients at a Scottish alcoholism treatment unit. This finding is compatible with that of Stockwell et al. [3].

The argument is not that Impaired Control* is not experienced by some 'problem' drinkers (and some 'normal' drinkers too [17]), but that it is not part of the core of the syndrome. That two elements form separtae dimensions away from the core dimension is not evidence against the syndrome *per se*. This finding

* For some individuals, impaired control may best be understood as a *post hoc* explanation for problematic drinking, part of the 'search after meaning'. This would account for the findings of reliable investigations of temporal ordering of symptoms in non-ideologically biased samples: namely that Impaired Control items tend to be placed at the beginning of a patient's sequence, if indeed he has chosen to acknowledge those items [16].

does however suggest a need to adjust the description of the syndrome. It also has implications for its measurment, particularly the measurement of its severity. This is the subject of a further paper [18].

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Application to the alcohol dependence syndrome of a method of determining the sequential development of symptoms

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SYNOPSIS Temporal ordering of core items in the alcohol dependence syndrome was investigated in 38 men admitted to an alcoholism treatment unit. An analysis of rank sums yielded a modal sequence which resembled classical descriptions of alcoholism, though 'loss of control' appeared very early.

INTRODUCTION

A recent WHO report has drawn a theoretical distinction between an alcohol dependence syndrome and disabilities related to alcohol consumption (Edwards *et al.* 1977). Classical descriptions of alcoholism, for example by Jellinek (1952), had included a wide range of items which referred to social consequences, symptoms of mental disorders, self-concepts, and attitudes to drinking and seeking treatment. The departure in the WHO report from this classical description has empirical as well as theoretical support. In population surveys (e.g. Knupfer, 1967) and in samples of alcoholics (Chandler *et al.* 1971) social damage from alcohol and dependence on alcohol are not inevitably associated. When the sequential development of symptoms in alcoholics was analysed by Orford & Hawker (1974) it was found that items related to social damage did not occur predictably at any stage of the process. Some degree of order emerged, however, when items related more closely to dependence were examined.

An account of alcohol dependence is needed which is less encumbered by the conceptually distinct area of social consequences and personal attitudes. Edwards & Gross (1976) provided 'a provisional description' of the syndrome, pointing out that, among other types of elaboration, studies of its natural history were required.

The present paper concerns an analysis of the temporal relationship of 23 items, loosely based on the Edwards & Gross description of alcohol dependence. (A subsequent paper will report on the scalability of this set of items.) There could be practical benefits in demonstrating a typical sequence of development of symptoms of alcohol dependence, for example to health educators or to epidemiologists wishing to identify 'early cases'. In alcoholism research, a demonstration of an orderly sequence of symptoms has also been sought for a theoretical purpose: to bolster the proposition that alcoholism is a tangible phenomenon rather than a social label.

The work of Trice & Wahl (1958), Park (1973), Park & Whitehead (1973) and Orford & Hawker (1974) on the developmental ordering of symptoms has, on the whole, supported Jellinek's original claim that there was an order, though small discrepancies were found in all the studies, for example, in the relative position in the order of 'morning drinks' and 'amnesias'. Park and Orford & Hawker imply that, if items related to a core syndrome were studied, then a more definite process might emerge. Our study has tried to restrict itself to studying core items.

The aims of the study were first to determine whether there were systematic deviations from randomness in the orderings of the items produced by alcoholics, and secondly to derive a

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typical sequence capable of describing these deviations.

METHOD

The sample was 38 consecutive male admissions to an alcoholism treatment unit who were aged 65 or below and who one week after admission exhibited no clinical evidence of memory impairment or dementia. Their ages ranged from 21 to 65 years. Twenty-seven (71 %) claimed they would describe themselves as alcoholics, and they all had been diagnosed to be alcohol dependent. As a rough indication of their exposure to beliefs about alcoholism they were asked about their reading and their contact with agencies. For about a quarter, it was their second admission. A further 40 % had had at least one appointment as an out-patient or with their family doctor to discuss their drinking. Of these, a few had read books or pamphlets on alcoholism; 2 had had sporadic contact with Alcoholics Anonymous and 3 had at one time attended A.A. regularly. Fourteen men (37 %) could be regarded as 'unexposed to beliefs about alcoholism'.

A structured interview[1] was administered approximately one week after admission by a psychiatrist not involved in their treatment and without previous knowledge of them. The 23 items had evolved through extensive pilot work and were closely defined in guide notes to avoid the ambiguity and vagueness which line the well-trodden paths of alcoholism questionnaires. Wherever possible before a respondent scored on an item he was asked to recall an example. The items are listed in Table 1.

Eliciting the sequence

Previous investigations of sequencing (Jellinek, 1946; Trice & Wahl, 1958; Glatt, 1961; Park, 1973; Orford & Hawker, 1974) required respondents to recall their age when the item began to happen (Orford & Hawker were more specific in asking for 'age of *first* occurrence'). None of these papers report on the reliability of this method. Subjects in our own pilot studies found it very difficult to recall age but found it easier to offer an ordering of items. Another objection to the method used in the 4 earliest studies quoted was that the items were presented on a list given to the subject. The ordering on the list was plainly not random and may have suggested a sequence to the respondent.

Our method was to hand the subject at the end of the structured interview a pile of cards each naming an item he had acknowledged. The pile was shuffled so that he received the cards in a random order. He was told:

> We are interested in the way people's drinking changes over the years and in which experiences tend to come before others. On these cards are some of the things you mentioned had happened to you. Put them in order so that the things which happened earliest are at the top and so on. Do it according to when the particular item first happened. If two or more items seemed to happen at the same time so that you cannot separate them in your memory, place them side by side.

Subjects found this task easy. The interviewer only intervened if a respondent asked or seemed to need to be reminded of the definition of an item.

Reliability

(a) Of items

An assessment was made of the degree of agreement between 2 clinicians interviewing conjointly but rating independently. The clinicians had to decide whether each item was present or absent or, in the case of some items, not applicable. ('Not applicable' was treated as 'absent' for the analysis of reliability.) Twenty-six subjects were interviewed conjointly. Five clinicians took part in the exercise.

(b) Of eliciting the sequence

Seventeen subjects were re-interviewed after an interval of one week. They were presented with the subset of items they had ordered a week previously and asked to place the items in order on the same basis as the first occasion. They were told that this was a check on the method, not on their memory.

Analysis

As will be seen later, the results of the reliability study of the items themselves were so unequivocal as not to require analysis. The test–retest relia-

[1] Available from the authors.

Table 1. 23 *items comprising a structured interview into alcohol dependence*

Category	Code letter	Symptom
Loss of flexibility	*A*	Change to drinking same on a work day as a day off
	B	Change from drinking according to mood to *not* drinking according to mood
Salience	*C*	Giving up interests because drinking interferes
	D	Missing main meals regularly because of drinking
	Y	Spending more time drinking
Need	*E*	Restless without a drink
	F	Times when can't think of anything else but getting a drink
	G	Organizing day to ensure supply
	H	Needing more than companions (getting a start on them or going for a drink between rounds)
Loss of control	*I*	Completely unable to keep to a limit
	J	Difficulty preventing getting drunk
	K	Difficulty cutting down
	P	Passing out while drinking in public
Withdrawal	*L*	Trembling after drinking the day before
	M	Morning drink
	N	Morning retching or vomiting
	R	Wakening up panicking or frightened
	S	Sweating excessively at night
	T	Tense on waking
	U	Withdrawal fit
	V	Hallucinations
Decreased tolerance Amnesia	*Q* *X*	(Drinking related experiences not central to the alcohol dependence syndrome)

bility of the method of eliciting the sequence was examined by calculating Spearman's coefficient of rank correlation within each subject on the rankings of the items on the 2 occasions.

The analysis of the full set of patient responses proceeded by a test of the hypothesis of randomness. Had each patient ordered all the items, Kendell's coefficient of concordance would have provided a satisfactory method of analysis and an ordering could have been obtained from the rank sums associated with each item. However, in view of the missing data resulting from patients not experiencing all the items, a modification of this method was used (Bernard & van Elteren, 1953). This test uses the information in the data set as a whole and takes account of missing values and ties. There is, however, no description of an ordering method in the work of Bernard & van Elteren, but their procedure suggested such a technique which is now briefly described.

The rank of each item in a patient's sequence was calculated, the earliest item experienced being given a rank of 1. Then the average rank of the items within that patient's sequence was subtracted from that of each item in the same sequence to give a reduced rank. These were then summed for each item over all patients, and the resulting sums were divided by their null hypothesis standard deviation given by Bernard & van Elteren. This gave the 'criterion value' for each item. The rank order of these values was the 'modal ordering'.

There is an element of arbitrariness in this procedure, as will be discussed later. It was therefore thought desirable to reanalyse the data by a modification of the same method due to Prentice (1977) for purposes of comparison. Essentially this method involves *scaling* the reduced ranks of a subject in proportion to the total number of items ordered by that subject and proceeding as before, although the variance of the sums of scaled reduced ranks is rather different. While this method has improved statistical properties, its chief attraction is the intuitive appeal of scaling the reduced ranks.

Finally, Spearman rank correlations of the sequences obtained from each of the subjects, with the ranks of the items in the modal order (obtained by the method of Bernard & van Elteren), were calculated.

RESULTS

Reliability of items

All of the 23 items were assessed as present in some of the subjects. Table 2 expresses the reliability of the assessment of presence/absence in each of the items in terms of amount of agreement attained between the 2 raters.

Reliability of patients' assessments of sequence

Seventeen Spearman rank correlation coefficients (corrected for ties) were calculated, one for each of the subjects. These ranged in value from 0·34 ($N_i = 10$) to 1·0 ($N_i = 4$) with median value 0·75 ($N_i = 8$). All but three of these were significantly different from zero at or beyond the 5 % level. The number of items (N_i) in the sequences of the subjects ranged from 2 to 16.

Tests of randomness

(*a*) The method of Bernard & van Elteren (1953) gave a value of the test statistic of 81·2 which, assuming the asymptotic distribution applies, is a realization of a χ^2 variable with 22 degrees of freedom. This result is extremely significant ($P \ll 0{\cdot}01$).

(*b*) Applying the modification due to Prentice (1977) yielded a test statistic value of 75·4 which again, assuming the χ^2_{22} distribution, is extemely significant.

Orderings

The modal orderings obtained by the 2 methods are displayed in Table 3. The frequencies with which individual items were rated present are shown, along with their criterion values. The Spearman coefficient of rank correlation between the 2 orderings is 0·98.

'*Post hoc*' correlation study: between individuals' sequences and the modal ordering

These correlations ranged in value from −0·56 to 1·00. Eight of the 38 coefficients were negative. The median value of the set of correlations was 0·50.

DISCUSSION

The reliability of the findings will be discussed first, followed by the discussion of the main study. Before commenting on the interpretation of the results, there will be a brief explanation of the factors governing the choice of methods of statistical analysis.

(a) Reliability

Inter-rater agreement on presence/absence of items was so high as to render statistical analysis superfluous. The limitation placed on assessing the statistical significance of the within-patient test–retest study of ordering was that the number of items ordered by the subjects varied between subjects.

All 17 test–retest correlation coefficients were positive, and all but 3 of these were significantly different from zero. Since these are rank correlations and often calculated on small numbers, it is not surprising that a few of the coefficients

Table 2. *Inter-rater reliability (expressed as % agreement) for 23 items in 26 subjects*

Item	% agreement
B, G, I, M, K, L, U, V	100
C, E, F, H, J, N, S, Q, X, Y	96
A, D, P, T, R	92

Table 3. *Typical ordering of 23 symptoms obtained by 2 methods of analysis in 38 male admissions to an alcoholism unit*

Bernard & van Elteren			Prentice modification	
Symptom	Frequency	Criterion	Symptom	Criterion
I	18	−3·34	*I*	−3·18
H	22	−3·17	*H*	−3·07
J	17	−2·24	*J*	−2·20
Y	15	−1·76	*D*	−1·71
D	26	−1·72	*X*	−1·41
X	35	−1·53	*Y*	−1·28
K	12	−1·35	*K*	−1·03
C	17	−0·87	*C*	−0·78
E	14	−0·82	*E*	−0·70
A	8	−0·21	*T*	−0·22
G	21	0·19	*P*	0·36
B	3	0·24	*G*	0·38
T	25	0·37	*B*	0·38
P	10	0·53	*A*	0·47
L	32	1·03	*L*	0·77
F	25	1·03	*F*	0·88
N	28	1·44	*N*	0·99
S	21	1·45	*S*	1·26
U	1	1·60	*U*	1·60
M	30	2·07	*M*	2·11
Q	11	2·50	*Q*	2·67
R	9	2·89	*R*	2·94
V	8	3·91	*V*	3·81

were not large. In summary, the method appears tolerably reliable.

(b) The ordering of items

The main analysis of the item orderings was determined by the nature of the data and the alternative hypothesis, that is, the null hypothesis of randomness. In the present study, the null hypothesis of randomness was initially to be tested against the general alternative (i.e. unspecified 'non-randomness') whereas Park (1973) explicitly tested against the alternative of specified order, that being the ordering due to Jellinek (1952). Orford & Hawker (1974) performed a number of trinomial tests for sequencing determined by their data on mean age of occurrence.

One limitation of the tests used by Park (1973) and Orford & Hawker (1974) is precisely their plurality, giving rise to many statistics and associated significance levels with consequent difficulties in their overall interpretation. Further, these writers considered items in pairs, whereas, of course, items do not arise naturally in pairs in the data. There is a degree of arbitrariness in such assessment, for in general one could consider items in sets of any size, the mathematical theory being given by Wormleighton (1959). An associated difficulty in examining items in pairs is that the ordering relationships established are not necessarily transitive. That is, for example, that for 3 items *A*, *B* and *C* ordered by 10 subjects it might be that *A* precedes *B* in 6 subjects, *B* precedes *C* in 6 subjects but *C* precedes *A* in 8 subjects as follows:

ABC ABC BCA BCA BCA BCA
CAB CAB CAB CAB.

'Missing' data in the sense that not all subjects order the same number of items can only aggravate the difficulties already mentioned.

The unmodified method of testing the null hypothesis in this study circumvents difficulties of interpretation by giving rise to only one test statistic and being designed for the analysis of incomplete data sets. Despite the distribution of the statistic depending on an asymptotic argument requiring the number of subjects to be 'large', it is clear that the high values observed are extremely significant (even if the exact-small-sample distribution is rather different from that given by the asymptotic approximation).

The ordering method used is an '*ad hoc*' procedure (as, indeed, are those of earlier writers on the same topic). It was adopted, as mentioned earlier, because it arose naturally from the Bernard & van Elteren test, and it is reasonable to assume that some of the advantages of the test apply also to the ordering procedure, in particular the inbuilt capacity to take account of missing values. There are methods in existence for obtaining orderings based on maximizing 'objective' criteria which are capable of more detailed specification than the present criterion; for example, Tate (1961) gives one such method which was used in the analysis of the sequence of bone development in the foetal foot. However, the appropriateness of any particular criterion, no matter how clearly it may be defined, will always be a subject for argument. In the present case, the adjustment of Tate's criterion to take account of missing values would necessarily be arbitrary. Even if such adjustment were made, the only way to establish which ordering of symptoms was most satisfactory would be to consider all possible orderings and select the one which yielded the maximum value, a Herculean task, involving considering 23! orderings.

It can be seen, therefore, that our method of analysing ordering is far from unique, and it would thus be wrong to draw conclusions too firmly, especially about the relative ordering of items with similar criterion values – e.g. *C*, 'giving up interests', and *E*, 'restless without a drink'. However, it seems unequivocal, particularly on comparing the results of the modified and unmodified analysis, that there does exist an ordering and that items could be said to fall into early, middle and late categories. The sequences obtained by the 2 methods are very similar, with the major differences occurring in the central part of the sequence where, in any case, the differences between values of the criteria are small.

We turn now to the form of the modal ordering itself, generated by this analysis. This ordering is not to be interpreted as the sequence of symptoms that most alcoholics follow, because not all alcoholics will experience all symptoms. Nor does it imply that later symptoms inevitably follow if early symptoms have been experienced (which the downward gradient of the well known 'Glatt chart' symbolizes). Our modal sequence states only that, if a man experiences symptoms

x, *y* and *z*, they will tend to occur in the order suggested by the sequence.

Two 'loss of control' items, *I* and *J*, appear early. Other early symptoms are features of 'salience' (*Y*, 'spending more time drinking', and *D*, 'miss main meals regularly because of drinking'), and 'needing more than companions' (*H*). Late symptoms are predominantly features of physiological withdrawal: trembling, morning nausea, sweats, morning drinks, panics and hallucinations.

In the classic description of alcoholism based on the self-selected Alcoholics Anonymous members studied by Jellinek (1946), loss of control, while still preceding symptoms of physical addiction was a middle-stage experience. Indeed, it came to be seen as the hallmark of the fully developed disease (Keller, 1972). In the present study, 'being sometimes completely unable to keep to a limit' (*I*), which was acknowledged by about half the sample, typically preceded the first experience of amnesia (*X*) and anticipatory drinking (*H*).

Our result is closer to that of Orford & Hawker (1974) who found that the item 'when you started drinking you found you couldn't stop' clustered with early items which they grouped as representing 'psychological dependence'.

There is, however, a 'loss of control' symptom, *P* ('passing out while drinking in a public place'), which was a middle-stage experience. The findings support the view of Storm & Cutler (1975) that there are *degrees* of impaired control. While it may be extremely difficult for certain alcoholics to keep to their intentions regarding their drinking by the time they have developed physical dependence, a degree of 'difficulty' will have been experienced for much longer.

It could be argued that our subjects' recall of their earlier experiences was markedly influenced by 'search after meaning' – the tendency to reconstruct past events to help explain subsequent experience. Then it would be understandable that those individuals who saw themselves as being unable to control their drinking would have placed this at the beginning of their histories, as an explanation of all that followed. This is possible, though each subject was encouraged to lay out his sequence by recalling specific incidents. Secondly, if this process is an important influence on recall, it is strange that it could not be detected also in the earlier work on sequencing by Jellinek, Glatt, Trice & Wahl and Park.

Attention to the position of certain individual items should not obscure the overall similarity between these results and the classical descriptions of alcoholism. Physiological dependence as indicated by the 'withdrawal' items tends to follow a period in which alcohol is becoming more salient in the individual's life, a sense of increasing need is noticed, and for some, a loss of flexibility in the pattern of drinking has occurred. This study has replicated, using more reliable methods of data collection and simpler, more appropriate, analyses, much of the findings of previous workers.

The overall similarity with previous findings cannot be attributed to sampling, like Jellinek, members of Alcoholics Anonymous (a self-selected group possibly conforming to a stereotyped view of their condition). The present sample of 38 contained only 3 regular A.A. attenders plus 2 who had attended occasionally.

The purpose of the *post-hoc correlation study* was to assess the degree to which the modal sequence generated by the method resembled the sequences provided by the subjects. As would be expected, because the data demonstrate a systematic tendency to ordering, most of the correlations were positive and half were above 0·5. That some of the correlations were low or negative is important. Two possible explanations for this are as follows.

First, perhaps not all of the 23 items possess a tendency to ordering. Those that did not would be 'noisy' and subjects who had experienced many of them might well show low or negative correlations with the modal ordering. (Unfortunately we do not yet know which items, if any, are these 'noisy' items.)

Secondly, perhaps not all individuals share the syndrome which has been assumed common to all; or they might have a variant of the syndrome. Examination of the drinking histories and social characteristics of the 8 patients with negative correlations (the patients with 'atypical' sequences) did not show any obvious common characteristic. Three of the 8 had been classified as 'restrained' drinkers (did not acknowledge *I*, unable to keep to a limit; *J*, difficulty preventing getting drunk; or *P*, passing out); there was only one other patient in the sample of 38 who was a 'restrained' drinker. Thus, 'restrained' drinkers,

uncommon in the sample as a whole, were over-represented in the group with atypical sequences. However, the remaining 5 with atypical sequences acknowledged a wide range of items and no common thread linked their drinking histories. Occupational status and living group did not distinguish the atypical patients, nor did failing to self-identify as an alcoholic or lack of previous exposure to beliefs about alcoholism.

Edwards & Gross (1976) suggest that the syndrome of alcohol dependence 'must be pictured as subtle and plastic'. Perhaps it should be expected that there would be some patients who show considerable, idiosyncratic, variation from the modal sequence.

CONCLUSIONS

A reliable method of eliciting the developmental sequencing of a set of items believed to refer to the core alcohol dependence syndrome yielded a sequence which was not random. A modal order of items was generated. Among men admitted to a Scottish Alcoholism Unit, the early items in the modal order refer to impaired control on single drinking occasions, feelings of need for alcohol and increasing salience. The late items, as expected from earlier work and clinical experience, refer to withdrawal symptoms. This study says nothing about the inevitability or otherwise with which the sequence is followed in a given individual once the early items have been experienced. Some individuals deviate from the modal sequence and possible reasons for this are explored.

We wish to thank the patients and staff at the Unit for the Treatment of Alcoholism at the Royal Edinburgh Hospital for their kind cooperation and Dr N. Kreitman, Dr M. Malone, Dr J. Dyer and Dr L. Whalley for their help at various stages in the study.

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SAVING FACE? SURVEY RESPONDENTS WHO CLAIM THEIR LAST WEEK'S DRINKING WAS ATYPICAL*

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Summary

Thirty-one per cent of survey respondents asked about their last week's drinking claimed it was atypical. They are shown, by examining their levels on two blood tests (mean cell volume and gamma-glutamyl transpeptidase) and by a comparison of their consumption on a recent social occasion with that of their companions, to be reporting a trivial difference between their last week and their typical week and appear to be attempting to deny heavy habitual consumption.

Key words:

Some workers use as a measure of consumption self-reported drinking during a recent fixed period — past seven days as in several British surveys, or past month as in some Scandinavian surveys. A proportion of respondents report that this period was not typical, and Dight [1], in a Scottish population survey, found that the number of people reporting last week's consumption was more than usual is greater than the number reporting it was less than usual. She had avoided interviewing near to festivals and concluded that some of those who claimed last week's drinking was more than usual were people who wished to play down their consumption or were evasive, and were wrong in saying it had been "more than usual".

This conclusion allowed Dight, and has allowed others, conveniently to ignore the possibility that for some survey respondents the past week's drinking is an unreliable indicator of recent, or "usual", consumption. Those who claimed last week's drinking was more than usual reported higher weekly totals than the average respondent, and Dight tentatively concluded that such respondents were drawn disproportionately from among the heavy

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consumers. It is, of course, the heavy consumers that surveyors are usually most interested in. The validity of interview data on alcohol consumption is a matter of the utmost concern to survey methodology.

In this paper, two blood measures are used as tests of the validity of the claim that last week's drinking was "atypical". These are MCV (mean cell volume) and serum gamma-GT (gamma-glutamyl transpeptidase), established indicators of consumption in the general population [2 - 4]. Drinking alcohol (0.75 g/kg body weight) on as few as three consecutive evenings may produce a short-term rise in gamma—GT in some individuals. The elevation is slight, however, unless drinking is repeated at weekly intervals for 3 - 4 weeks [5]. To the authors' knowledge, such short-term elevations of MCV have not been reported. That elevations from short periods of drinking are trivial is suggested by the finding that in alcoholic patients the length of a current drinking bout is strongly related to elevation of gamma-GT, independent of blood alcohol concentration at admission, with bouts of less than 2 weeks' duration being associated with a mean gamma-GT within the normal range [6]. The substantial elevations in these tests found in habitual heavy drinkers take 2 - 6 weeks to return to normal, depending on the extent of the elevation, and probably are slower for MCV than gamma-GT [7 - 9].

Hypotheses

(1) If the difference between "usual" and "last week's" drinking is real and important, then the following predictions can be made:

(a) Respondents who claim that last week's drinking was more than usual should more often than respondents who say that week was "typical" have a gamma-GT and/or MCV lower than their last week's consumption would have predicted had it been their habitual level. This follows from assuming that the blood tests chiefly reflect consumption in the preceding 2 - 6 weeks. If the past 7 days had truly been unusually heavy this is unlikely to have yet expressed itself significantly in the blood tests. The converse of this prediction should hold in those who claim that last week's drinking was less than usual.

(b) Since there is a strong tendency for people to drink the same on an occasion as their companions drink (see for example, refs. 1 and 10) then those who said they drank more than their usual in the last 7 days might be expected to have drunk more than their companions at the social gathering they most recently attended. (This prediction assumes that on the whole the last social gathering was typical for them, whereas perhaps the explanation of their recent atypical drinking was their unexpected immersion in a heavy drinking set — a possibility that will be explored.)

(2) If claiming last week's drinking was more than usual represents evasiveness, such respondents might be expected to refuse a blood sample at a survey interview more often than others and to have been regarded by the survey interviewer as uncooperative.

Method

The subjects were manual workers drawn from pay-rolls of breweries and a distillery (sampling described in ref. 11) and senior company executives drawn from lists of names in local directories. Completed interviews were obtained from 79% of the combined samples: 318 manual workers and 298 executives.

The interview was a 40-minute standardised enquiry into work, life-style and health. No interviewing was conducted near to festivals. A self-completed "personality" form was administered*. At the end of the interview, the rater recorded whether the subject had been "cooperative" or not.

Eliciting consumption

The past 7 days' consumption was obtained as part of a description of work and social events in that week. All subjects were asked to say if that week's consumption was typical, and, if not, whether it was more or less than usual. They could, however, be coded as saying they had "no typical week". Information was elicited about the last social occasion when they met socially (*i.e.* not for business or at work) with two or more other adults.

A blood samples was requested at the end of the interview; 92.4% of the alcohol production workers and 89.1% of the directors interviewed agreed to the blood test. The correlation in the whole sample of past week's consumption with gamma-GT was 0.35 (n = 507) and with MCV 0.34 (n = 498, controlling for age). (MCV was measured by Coulter Counter and gamma-GT by the method of Rosalki and Rau [12].)

Analysis

To test hypothesis 1a the regression of the past week's consumption on each of the blood tests was computed. Subjects who had provided a blood sample were divided according to whether their blood test was above or below the regression line. Subjects who claimed they had no "typical week" amounted to 4.6% of those from whom a blood sample was obtained. They are excluded from all tables and analysis. Also excluded are subjects who were taking drugs such as anticonvulsants or had a physical illness which might have caused abnormality in either of the blood tests. There is a slight discrepancy in the number of analyses between the gamma-GT and the MCV computations because some MCV analyses were not performed owing to leaking tubes or delay reaching laboratory.

Of the alcohol production workers 246 were manual workers from two firms where a high response rate had been obtained. The remainder were

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*This consisted of 14 items with high face validity designed to measure the dimensions of rebelliousness, extraversion, impulsiveness, rigidity and "personal care".

either non-manual workers or were from two low-response-rate firms. Except on the analyses of blood test data the analyses will be presented separately for directors and for alcohol production workers, the latter including only those manual workers from high-response-rate firms, to improve the homogeneity of the samples.

Results

As Dight found, those who claim last week's drinking was more than usual tend to report a week that was heavier than other respondents (Table 1).

TABLE 1

Self-reported consumption in past week by typicality of past week
Consumption is expressed in units [1 unit = 8 grams of alcohol (1 cl)]

	Last week "more than usual"		Last week "typical"		Last week "less than usual"	
Alcohol production workers						
0	0	(–)	18	(10%)	2	
1 - 10	2	(6%)	34	(18%)	3	
11 - 40	20	(62%)	76	(41%)	9	61%
41 +	10	(31%)	58	(31%)	4	
	32		186		18	
Mean consumption	42.5		37.9		28.9	
Directors						
0	0		14	(8%)	5	(19%)
1 - 10	17	(20%)	41	(24%)	6	(22%)
11 - 40	44	(52%)	76	(50%)	11	(41%)
41 +	23	(27%)	38	(22%)	5	(19%)
	84		169		26	
Mean consumption	34.3		30.2		23.3	

TABLE 2

Distribution about the regression line of gamma-GT on consumption by typicality of past week's drinking

	Gamma-GT below regression line		Gamma-GT above regression line		
Last week "typical"	290	(69%)	131	(31%)	Raw χ^2 =
Last week "more than usual"	95	(73%)	35	(27%)	0.83 n.s.
Last week "less than usual"	37	(69%)	17	(31%)	
For the whole table: raw χ^2 = 0.87 n.s.					

TABLE 3

Distribution about the regression line of MCV on consumption by typicality of past week's drinking

	MCV below regression line	MCV above regression line	
Last week "typical"	257 (61%)	164 (39%)	Raw χ^2 =
Last week "more than usual"	70 (54%)	60 (46%)	2.13 n.s.
Last week "less than usual"	32 (58%)	22 (42%)	
For whole table: raw χ^2 = 2.13 n.s.			

TABLE 4

Consumption relative to male companions at last social occasion by typicality of past week

	Last week "more than usual"	Last week "typical"	Last week "less than usual"	Total
Alcohol production workers				
Drank more than companions	2 (6%)	14 (8%)	1 –	17 (7%)
Same	24 (77%)	116 (64%)	11 (61%)	151 (66%)
Less	5 (16%)	50 (27%)	6 (33%)	61 (27%)
	31	180	18	229
Directors				
Drank more than companions	8 (10%)	5 (3%)	1 (2%)	14 (5%)
Same	58 (70%)	110 (70%)	13 (48%)	181 (67%)
Less	17 (20%)	47 (29%)	13 (48%)	77 (28%)
	83	162	27	272

Hypothesis 1a

Tables 2 and 3 show that those who claimed last week's drinking was more than usual did not tend to have blood tests below what would have been expected on the basis of their report of the past 7 days' drinking; nor was the converse true for those who claimed their last week's drinking was less than usual.

Hypothesis 1b

Table 4 refers to consumption at the last social occasion. Subjects were asked whether they drank the same, more, or less than the mean of their male companions. Usually this necessitated recalling the consumption of

each of their companions and calculating the mean, and comparing it with their own consumption on that occasion.

Table 4 shows that whereas few drank more than their companions many claimed to have drunk less! There was, however, only a slight trend for those who reported last week was "more than usual" to have drunk more than their companions, and this occurred only in the directors (10% of the "more than usual" group as opposed to 5% for the whole directors sample).

It was not the case that this subgroup of directors had on that occasion been unusually immersed in a heavy drinking environment. Table 5 shows no trend for "last-week-more-than-usual" directors to have described that most recent social occasion as a session at which the average drunk by male companions was especially high.

TABLE 5

Average consumption of male companions at last social occasion by typicality of past week

Values are companions' average units [1 unit = 8 grams of alcohol (1 cl)]

	Last week "more than usual"		Last week "typical"		Last week "less than usual"	
Alcohol production workers						
<6	8	(28%)	41	(23%)	5	(28%)
7 - 11	11	(35%)	72	(41%)	7	(39%)
12 +	12	(39%)	64	(36%)	6	(33%)
	31		177		18	
Companions' mean consumption	7.2		6.9		6.8	
Directors						
<6	46	(58%)	106	(64%)	12	44%
7 - 11	29	(36%)	46	(28%)	13	(48%)
12 +	5	(6%)	14	(8%)	2	(7%)
	80		166		27	
Companions' mean consumption	5.15		4.9		5.6	

Hypothesis 2

Of those who claimed that their last week's drinking was more than usual, 9.2% refused the blood sample, whereas the proportion of those who said last week's drinking was typical was 8.1% a trivial difference. There were 20 subjects rated as "uncooperative". They did not fall disproportionately among the group who claimed their last week's drinking was more than usual ($\chi^2 = 0.79$ n.s).

Conclusions

The blood tests are rough indicators of consumption. The blood test analysis, taken together with the finding that those who claimed to have drunk more than usual in the last week did not in general drink more than their companions at the last social occasion, point to one of two conclusions: either (1) these people are truthful in reporting taht their last week's consumption had been atypical, but the difference between that and their habitual consumption is trivial, or (2) they wish to deny being *habitual* "heavy" drinkers because of embarrassment. (It is embarrassment rather than evasiveness: they are not so blatant as to refuse the blood sample or be uncooperative.)

It is interesting that the proportion of the directors who claimed last week's drinking was more than usual was significantly greater than the proportion in this catagory amongst the production workers (30% as opposed to 14%, $p < 0.001$). We know from our other work that when an individual's past week's reported consumption is "corrected" according to his blood tests, the necessary adjustment is greater for directors than for production workers [13]. It appears that it is more important for the directors than the production workers to give a favourable impression.

None of the self-ratings of "personality" was related to typicality of the past week's drinking.

This study should not be interpreted to mean that our sample has been shown to be accurate in their self-reports. Our regression lines of consumption against blood tests was obtained from within the sample, not using an external criterion; thus self-report cannot be validated absolutely. Rather our study shows that it is permissible to ignore in aggregate analyses claims that last week's drinking was atypical. Widespread underreporting, one of the thorns in the alcohol surveyor's flesh, is possibly still present in our sample.

The reasons why some individuals claim their recent drinking was atypical when perhaps it was not, remains to be investigated. It is probably a way of "saving face", so as not to appear an *habitual* drinker, and appears to be more frequently used by those of relatively higher social status.

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Alcoholism Treatment Evaluation: the Drop out Dilemma*

Jonathan Chick

Key words: alcoholism, treatment, evaluation; drop out; lifetime analysis; intention to treat principle

Summary

Patients requesting help for alcohol problems often do not follow the allocated treatment. This occurs frequently also even in the studies where consent to participate has been given. Also, in the studies they may be withdrawn from the treatment because their condition is not improving or worsening, or because of the adverse effects thought to be due to the treatment, or patients cease attending and the contact may be lost.

Outcome data may be available however on 'drop-outs' of either type, selected systematically or through other channels. The researcher has a dilemma: whether or not to include those patients in the analysis of outcome. If they are omitted, some of the advantages gained by random allocation to different treatment groups may be lost, as happened in a recent rendomized controlled trial of tiapride in alcoholism, when amongst study completers the groups were no longer matched on the important social parameters. If they are included, is it unfair to the treatment(s) being tested because some patients have had little if any of the treatment? This could be especially important with a treatment that only begins to show its therapeutic effect after, say, a month.

Life table analysis permits data on patients to be included for as long as data are available, up to an agreed point (take a drink/relapse into problem drinking/withdrawal from the study, etc.). But, clinical experience is that patients taking a treatment may slip and hesitate, stop and resume, while still overall gaining from the treatment in the long term. 'Intention to treat' includes all patients entered into the study however much or little treatment they actually received, thus avoiding that objection. Matching is retained. What is being assessed is a package that

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the patient has been offered (disulfiram evaluations illustrate this point). It is close to actual clinical practice. But, it is necessary to select data through the follow-up period, maintaining contact. The methods shown to increase patient's compliance in alcoholism treatment, such as empathy and reducing barriers, must be employed. It cannot be assumed that all out of contact are failures.

One way in which alcoholism is unlike most illnesses is that, at times, patients seem not to want to get better. In treatment outcome studies large numbers of subjects drop out:

- some are lost, and there is no data on outcome;
- some are lost, but data is available if the patient's permission had been obtained at the outset, from the family or the work place, or from public records, or the general practitioner;
- some may remain in contact but do not follow treatment, or request to stop the treatment, or are withdrawn by the investigator (for these, data can easily continue to be collected).

The matching of samples that was aimed for in the randomisation may however be lost. A recently submitted report on tiapride, a selective D2 antagonist, in alcoholism treatment met this. In the whole sample of 50 patients in each group (placebo, tiapride), the groups were adequately matched on two variables which previous research has shown to be relevant to outcome: living arrangements, and whether married or cohabiting. But in those patients who took the study drug for a minimum of one month (study completers), there was a bias in the tiapride group towards better social stability at entry: in the »study completers« taking tiapride only 4% were in the »living alone« category compared to 43% in the placebo study completers; 67% of tiapride study completers were married or cohabiting compared to 43% of placebo study completers.[1]

When analyses are made of study completers only, attempts can be made to partial out the effect of variables on which the groups are no longer matched, as was done in the tiapride study mentioned. However it is not possible to know all the ways in which matching may be lost due to drop outs, and there may be important predictors of outcome in alcoholism treatment which are not yet known to us. »Motivation« may be highly predictive though difficult to measure. If the experimental treatment is more demanding to adhere to for some reason that the control treatment, then less motivated patients may drop out more frequently from the experimental group, creating a bias towards more motivated patients.

To avoid randomisation error, no more than 5% of patients should be excluded from the outcome analysis.[2] Drop out rates in alcoholism evaluation research are often much higher than this.

This paper discusses methods for avoiding loss of data, or worse, erroneous results, when studies are conducted with high drop out.

LIFE-TABLE (SURVIVAL CURVE) ANALYSIS

Gordis et al.[3] followed by *Fuller and Williford*[4] were the first to publish an alcoholism treatment outcome study using life-table analysis, a method that has now become widely used. In Fuller and Williford's study of disulfiram efficacy, a single outcome measure was used, complete abstinence (confirmed by relative's reports, absence of progressive alcohol-related physical illness or blood tests, and all blood ethanol tests negative) throughout the 1 year follow-up. Information in this thorough study was available on all 128 men. Though 23% of the disulfiram groups and only 12% of the placebo group remained abstinent, this finding was not significant (chi-square) at the $p<.05$ level. However, the cumulative abstinence over the 12 months achieved by the disulfiram groups was significantly greater than control when analysed by life-table methods ($p=0.022$; and $p=.016$).

This powerful method follows response to treatment over time rather than at a single end point, and patients are counted for as long as they are followed.

The life-table method, as *Fuller and Williford* point out, has a limitation in that it ignores events after failure (in their analysis, taking the first drink). A useful treatment for alcoholism might help, for example, not in preventing taking the first drink but preventing consumption escalating (e.g. *Luintre et al.*,[5] 1990), or reinstatement of dependence, or the return of mental, social or physical problems.

More recent studies have used life-table analysis, and applied several end-points. For example *O'Malley et al.*[6], a 3 month study, found that a group given naltrexone did better than a control group in surviving to time of first drink, and to time of first relapse (drinking five or more drinks per occasion, four for women). This study does not report its drop out rate, except for the number of those who did not complete the first week's medication, but states that an attempt was made to consider potential biases due to differential attrition between groups.

The drop-out rate (non-completion of the protocol) in the 3 month naltrexone study by *Volpicelli et al.*[7] was 36% (25/70), in line with reports of other alcohol treatment evaluations. This study also used an end-point analysis method, including drop-outs up to the point at which the last data were obtained. With »relapse« as end point, a significant advantage to naltrexone was found on survival curve analysis ($p<.01$).

Are drop-outs failures?

As already stated, the problem with survival curve analysis (and other end-point analyses when end-point is the last assessment made while the protocol is still being followed or at termination) is that it implies the drop-out is a failure. Data after the endpoint is ignored or not collected. Whether this is an appropriate assumption can be assessed from a number of reports which have studied non-compliers and drop-outs.

Paredes et al.[8] found that difficulty in follow-up, as indicated by lack of a phone number, and by number of attempts necessary to interview, did not predict abstinence status at 6 months.

O'Donnell,[9] in a follow-up study principally of drug addicts, found that the hard to find were more often abstinent than easy to find (reflecting the clinical impression that some drinkers and drug users stay in contact with clinics because they are needing help).

LaPorte et al.,[10] again for substance abusers, found that the number of attempts to complete 142 follow-up interviews 6 month after admission to a one month programme was not related to outcome status.

Nordstrom and Berglund[11] over a twenty year post-hospital period found that in alcoholics believed to be well adjusted socially, in that recent records showed them to have had little time on sickness benefit and benefit given indicated a fairly high income, the loss to follow-up was 14%. In a poorly adjusted group (many days sick, low level of benefit) the loss to follow-up was 9%. In the good adjustment group, difficulty to achieve follow-up was related to worse outcome, though this was not the case in the low adjustment subsample.

The following studies, however, favour the assumption that for alcoholics drop out is likely to reflect worse outcome:

Ruggels et al.[12] following up over 18 months clients of selected alcoholism treatment centres found that non-contacts had been more severe cases at entry to the centre.

Wolff and Holland[13] showed that 94 patients who did not respond to a follow-up questionnaire were less likely, according to information obtained later, to be abstinent than 135 who had responded, but there was no difference in employment status between the responders and non-responders.

Moos and Bliss[14] found that effort taken to achieve follow-up at 6 months was related to poor outcome on 2 of 7 criteria (and they controlled for the length of time between discharge from the clinic and the follow-up interview).

Moos et al.[15] in their 2 year outcome study found that in those for whom no persuasion was necessary to make the interview, 34% were abstinent, compared to only 15% in those where two or more persuasive efforts were needed.

In the Rand 4 year follow-up[16] subjects not located had been of lower socioeconomic status and lower social stability, and had been more severe cases at entry to the study. Subjects not contactable or who refused at 18 months but were located and interviewed at the 4 year point were less likely to have been abstinent for the past year or more than those who had been seen at 18 months (14% v. 22%).

However, a regression model of drinking status at 4 years found the effort spent locating a case was not a predictor of outcome.

In the German multi-centre study[17] of in-patient treatment programmes offering between 6 weeks and 6 month programmes, at 18 mont follow-up, those who had

dropped out of treatment (17% of 1,410 patients) were doing less well than those who had not (30% abstinent versus 58%).

While it seems, therefore, that to assume a drop out is a treatment failure rather than a success, will more often be correct than incorrect, it still does not seem satisfactory scientifically to make this assumption when as many as a third of subjects are in this category. Patients may stop and start, relapse, and return to treatment, eventually to gain.

THE INTENTION TO TREAT PRINCIPLE; USE OF CUMULATIVE DATA DURING THE FOLLOW-UP

One solution to the drop-out problem lies in the fact that most drop-outs are patients who cease medication or are protocol violators rather than subjects who have disappeared completely: in the Volpicelli study quoted, out of the 26 dropouts there were only 5 who were »unavailable for follow-up«. Studies could, obeying the intention-to--treat principle (ITT), continue collecting data even though medication or other treatment is no longer being taken, or a relapse has occurred and perhaps detoxification has been required. (A practical definition of ITT is »all patients randomised who took at least one dose of treatment and who provided any follow-up data for one or more key variables«[2]). Only if the subject is spending long periods of the follow-up in prison or other residential facility with no access to alcohol would on-going data be meaningless. Thus, a cumulative picture of outcome in the ITT sample can be obtained for the whole period, for example, total number of days drinking, estimated total alcohol consumed, accumulated alcohol-related harm (e.g. *Addiction Severity Index* in the way *O'Malley et al.*[6] used it; or an alcohol-related problems score, e. g. *Chick et* al.[18,19]); or blood test results.

It is relevant that, for example, in very thorough NIMH *Treatment of Depression Colaborative Research Program*[20] differences between treatment groups were clearer in the intent-to-treat sample than in the study completers.

The objection

Some clinicians object that it is unfair to a treatment to evaluate it in patients some of whom have not taken more than an initial dose. As well as the ITT analysis, analysis can still be done stratified for compliance with treatment, so that good compliers with treatment A can be compared with good compliers with control. The *Fawcett et al.*[21] lithium study appeared to show that good compliers with lithium had a good outcome: when those patients in the lithium group who had maintained a serum lithium level of 0.5 umol/L of more were included (63% still abstinent at one year compared with 19% in those who did not maintain that level of serum lithium or who admitted not taking their tablets for at least half the time). However, it was possible to compare them with the compliers in the placebo group. *Fuller et al.*[22] in a very large study of disulfiram were able to measure compliance on the placebo group using riboflavin-labeling of tablets, and urine checks. Good compliers were defined as those submitting at least 15 of a possible 39 urine specimens positive for riboflavin. There was a highly signifi-

cant relationship between compliance with a drug regime and abstinence, regardless of whether it was disulfiram 250 mg, 1 mg or placebo (43% abstinent for one year versus 8%). However, when good compliers were compared across groups, no difference between groups was found, and neither was a difference between groups seen for poor compliers. The snag here is that even in this large study, the numbers begin to be small.*

Including an analysis with stratification for compliance permits at least a separate view of those patients disposed to follow the treatment.

Alcoholism treatment research is well suited to using cumulative data, such as total drinking days or accumulated problems, because the condition is marked by events (a day of drinking, losing a job, having a drunken argument etc.) unlike some other conditions like depressive illness or hypertension which have to be monitored by measures made at the interview. If a contact visit is missed, much of the data can be collected retrospectively at a later point, or collected from an informant.

Analysis by ITT using cumulative data fits with clinical common sense: we are comparing the outcome of a group of patients offered treatment A with a group offered treatment B. The acceptability of the treatment, and the ease with which it is followed, are relevant ingredients if extrapolation to the routine clinical situation is to be possible.

Above all, it meets with clinical experience in that patients taking a treatment may slip and hesitate, stop and resume, while still overall gaining from the treatment.

The value of this, however, depends on getting complete follow-up data. *Fuller et al.*[4] had data on all 128 patients. Many studies have managed 90% follow-up. This requires gaining permission at intake to contact relatives to obtain a follow-up address and preferably also information on the patient's drinking; at intake to record auxiliary addresses and phone numbers for the patient: use of phone contact as soon as the patient misses an appointment;[23,24] barriers at the clinic to patient contact must be removed, and investigators and therapists employed who are warm and empathic. Permission to see the patient at home should be requested and resources provided to fund home follow-up interviews.

CONCLUSION

Analysing data only to the point of termination of protocol adherence, or to an endpoint such as first drink or relapse has its place, particularly when the power of life-table methods are used. Clinicians, however, see much advantage to continuing to collect data on all patients throughout the whole study period to permit an analysis of the intention-to-treat sample. If numbers permit, the value of the treatment, rather than the package including its acceptability, can be estimated by stratification by compliance.

* In *Fuller et al.*[22] if compliance was judged according to contact with the clinic, then a result in favour of disulfiram did emerge: among patients who were not completely abstinent for the year but who were compliant in the sense that they gave all 7 follow-up interviews, those on 250 mg disulfiram reported a mean of 49 drinking days, those on 1 mg disulfiram reported a mean of 75 and those on no disulfiram reported a mean of 86 ($p=0.05$).

Sažetak

VREDNOVANJE LIJEČENJA ALKOHOLIZMA: DILEMA U VEZI S OTPALIMA IZ PROCESA LIJEČENJA

Bolesnici koji traže pomoć zbog problema vezanih uz alkohol često ne slijede predviđeni proces liječenja. Ovo se često pojavljuje i u studijama gdje je dana suglasnost za sudjelovanje u procesu. Također, u studijama mogu biti povučeni iz analize, jer se njihovo stanje ili ne poboljšava ili se pogoršava, ili zbog nepoželjnih učinaka za koje se smatra da su posljedica liječenja, ili pacijenti prestaju dolaziti i izgubi se tako kontakt s njima.

Podaci o ishodu mogu biti na raspolaganju bez obzira na otpale iz procesa liječenja iz bilo kojeg razloga, selektirani sustavno ili na neke druge načine. Istraživač je u sljedećoj dilemi: uključiti ili ne uključiti takve pacijente u analizu uspješnosti liječenja. Ako budu izostavljeni, neke prednosti dobivene slučajnom distribucijom različito liječenih skupina bivaju izgubljene, kao što se vidjelo u nedavnom randomiziranom kontroliranom ispitivanju tiaprida u alkoholičara, kada među ispitanicima koji su završili studiju nije više bilo usklađenosti prema važnim socijalnim parametrima. Ako ih se uključi u analize, to nije sasvim pravedno prema primijenjenom liječenju, jer neki pacijenti imaju malo (ako bilo što) od liječenja. Ovo bi moglo biti od posebne važnosti za liječenja koja počinju pokazivati terapeutske učinke tek nakon npr. mjesec dana.

Podaci iz analiza vitalnih statistika omogućavaju da se uključe svi raspoloživi podaci o pacijentima do ugovorenog stupnja (popiti piće/recidivirati/izostati iz studije, itd.). Ali, klinička iskustva govore da pacijenti na liječenju mogu isklizнuti ili biti neodlučni, stati i razmisliti, dok se ukupni rezultat liječenja vidi tek u dužem razdoblju. »Namjera za liječenja« uključuje sve pacijente uključene u ispitivanje, bez obzira na to koliko su od tog liječenja primili, čime se izbjegava ovaj mogući prigovor. Usklađivanje skupina je održano. Ono što se utvrđuje jest vrijednost paketa ponuđenog pacijentu (vrednovanje disulfirama ilustrira to pitanje). Blisko je trenutnoj kliničkoj praksi. No, nužno je izabrati podatke tijekom duljeg razdoblja praćenja, održavajući kontakt. Metode koje pokazuju bolje pacijentovo podnošenje liječenja alkoholizma, kao što je empatija i redukcija prepreka, moraju biti korištene. Ne smije se pretpostaviti da svi ispitanici s kojima kontakt nije održan nisu uspjeli u liječenju.

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Preventive Medicine

MEAN CELL VOLUME AND GAMMA-GLUTAMYL-TRANSPEPTIDASE AS MARKERS OF DRINKING IN WORKING MEN

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Summary The usefulness of serum-gamma-glutamyl-transpeptidase (γ-GT) and mean cell volume (MCV) as markers of alcohol consumption was assessed in men in employment (266 company directors and 222 manual workers in alcohol-production firms) and in 34 male alcoholic patients. The correlations of admitted consumption with γ-GT were 0·307 (directors) and 0·418 (manual workers) and with MCV 0·439 (directors) and 0·360 (manual workers). A man with an MCV of over 98 fl and a γ-GT level above 50 i.u./l had a 62% chance of admitting to drinking over 450 g alcohol per week. Although the probability of being a heavy drinker increases progressively with elevation in both these tests, as screening tests they lack power, though false positives may be explained in part by inaccurate self-reports by both survey subjects and patients. For clinical purposes, however, the tests have a use in supplementing self-report and in following problem drinkers in outpatient treatment.

INTRODUCTION

DOCTORS must be weary of being told that they often fail to recognise alcohol-related problems. However, alcoholism continues to masquerade as other conditions, patients still tend to minimise their alcohol consumption, and there is now a movement to intervene earlier in problem drinking, before the patient's social supports have been lost. This had led to a search for biochemical markers of alcohol intake.

Alcoholics, even without chronic liver disease, tend to have raised serum-gamma-glutamyl-transpeptidase (γ-GT) levels[1,2] and an elevated mean cell volume (MCV).[3-6] Health-screening studies have shown a relationship of varying strength between self-reported alcohol intake and both serum-γ-GT[7-11] and MCV.[7,8,12-14]

Interpretation of these studies is subject to a number of limitations. In some the base population is unspecified, the subjects having been self-selected attenders at a screening centre.[7-9,11] The number of heaviest drinkers has either been very small[8,9] or unspecified (and probably small).[7,10,12-14] The reported relationships between serum-γ-GT and age and weight,[10] and between MCV and age and smoking[12,13] have sometimes been ignored. Consumption data have been of uncertain quality, elicited only by questionnaire, except in health-screening studies in London,[11] Malmö,[9] and Paris.[12] The London study found that mean reported consumption was higher in the half of the sample who were interviewed than in the half who answered the same questions in questionnaire form. Moreover, the correlation between consumption and serum-γ-GT was higher in the interviewed group, suggesting that interview might be more reliable than questionnaire.

The London study was alone in concluding that serum-γ-GT is only a weak indicator of consumption: even in the interviewed group a correlation of only 0·139 was found. As with most of the other studies cited here, no attempt was made in the analysis to exclude obvious "false positives" (for example, people taking anticonvulsants, a cause of elevation of both MCV and γ-GT). Finally, men attending "routine health examination" at a private clinic—the setting of the London study—have often been encouraged to attend by their companies and may underreport heavy consumption fearing, despite reassurance, that information is not confidential.

The present study is of two populations of men in employment, chosen because of their known high risk of alcohol-related problems. It attempts to overcome some of the limitations in the above studies and provide firmer data on the practical value of these two tests.

The chief difficulty in specifying the relation between blood tests and alcohol consumption is obtaining valid data on consumption. Self-reports have been thought in many studies to be less than valid, with a tendency to under-reporting.[15] Experiments could avoid this, but the heaviest experimental exposure yet reported in relation to either of these blood tests was 0·75 g of ethanol per kg body weight for 2 days repeated weekly for 4 weeks, in only 8 subjects (7 showed a rise, greatest on average at the third and fourth exposure).[16]

In the present study consumption data depend on self-report, but the utmost care was taken to ensure reliability: clinically experienced interviewers were used, and recall of consumption was tied in detail to activities of the immediately preceding week.

METHODS

Data were obtained from two subgroups of men living and working in Edinburgh and the surrounding Lothian region. First, all 312 manual workers at two alcohol-production firms were approached, yielding 247 completed interviews—a response of 79·2%, of whom 92% provided a blood sample. Secondly 369 company directors and senior executives appearing in either of two professional lists were approached by letter and 298 agreed to be interviewed—a response of 81%, of whom 92% provided a blood sample.

To exclude from the study subjects with known causes of elevated MCV and serum-γ-GT other than alcohol, several precautions were taken. Subjects were asked about current medication, current and recent illnesses, and in the event of an abnormal result on either test the general practitioner was asked if he knew of any medication or illness which might explain the abnormality. In addition, in all subjects who had an MCV above 102 fl, serum vitamin-B_{12} and folate were measured to exclude subjects with other causes of macrocytosis. 6 manual workers but no directors were excluded at this point, leaving a final sample of 266 directors and 222 manual workers.

We also report on 34 patients selected from a consecutive series of men newly admitted to an alcoholism treatment unit for whom the past week's drinking had been typical of their recent drinking.

The measure of alcohol consumption reported on here was total intake (coverted to grams of absolute alcohol, a half-pint of 3% lager or a single measure of spirits containing about 8 g alcohol) in the 7 days preceding interview. The male interviewer asked the subject to recall in detail his activities, both work and leisure, during these days and what beverages in what amounts he drank. The mean total for the manual workers was 271 g, SD 374, and the directors 214 g, SD 184.

20% of the manual workers and 39% of the directors said that the past week was not typical for them. We have argued elsewhere that at the aggregate level discrepancies between habitual drinking and the past week's drinking are likely to be trivial.[2] Chick et al 1981

Serum-γ-GT was measured by the method of Rosalki[1] and MCV with a Coulter counter. Subjects were asked their current weight (or were weighed if they could not give this) and were asked about their weekly tobacco consumption.

RESULTS

Data are presented in three forms: (1) as intercorrelations to describe the linear relationships between variables; (2) as graphs showing the probability of reporting heavy consumption at increasing blood-test scores; and (3) as sensitivity/specificity tables to assess the screening power of the tests when "upper limits of normal" are used as cut-off points.

Serum-γ-GT

The directors has a mean serum-γ-GT of 47·2 i.u./l (range 9–700, SD 63·6); the manual workers had a mean of 43·0 i.u./l (range 9–699, SD 67·7).

Serum-γ-GT correlated significantly ($p<0·001$) with frequency and amount of consumption in both directors and manual workers (table I). Only in the manual workers was there a weak relationship to weight ($r=0·129$, $p=0·027$). Its relation to frequency of drinking disappeared when amount, weight, and age were controlled for ($r=0·08$, manual workers; $-0·07$, directors).

TABLE I—INTERCORRELATIONS OF γ-GT, ALCOHOL CONSUMPTION, AGE, AND WEIGHT IN DIRECTORS (ABOVE DIAGONAL) AND MANUAL WORKERS (BELOW DIAGONAL)

—	γ-GT	Frequency of drinking	Amount per week	Age	Weight
γ-GT		0·159	0·307	0·078	0·087
Frequency of drinking	0·331		0·670	0·106	0·032
Amount per week	0·418	0·680		0·009	0·148
Age	0·041	−0·119	−0·182		−0·166
Weight	0·129	0·000	0·048	0·067	

If a correlation is 0·146 or over, $p<0·01$.

Fig. 1 refers to all survey subjects and patients and is derived as follows: serum-γ-GT scores were grouped into eight categories, and for each group the proportion of men saying that they had drunk 450 g of alcohol or more in the past week (equivalent to 4 pints of lager per day) was plotted. The likelihood of an individual drinking at that level increases with rising serum-γ-GT but does not reach 50% until γ-GT reaches 59 i.u./l.

If 50 i.u./l is taken as the cut-off point, serum-γ-GT is not a very powerful screening test, mainly because of "false positives", though it performed better among the manual workers than among the directors and patients (table II).

MCV

The directors had a mean MCV of 91·4 fl (range 78–118, SD 5·3), and the manual workers a mean of 90·0 fl (range 80–104, SD 4·6).

MCV correlated significantly ($p<0·001$) with frequency and amount of consumption in directors and manual workers (table III). Amount of consumption had an independent relationship to MCV in both groups after controlling for frequency, age, and smoking (partial $r=0·29$, directors; 0·14, manual workers). In the manual workers only, frequency of drinking, smoking, and age correlated significantly (0·25) with MCV. (Smoking had an independent relationship with MCV in both groups: after controlling for frequency, amount, and age, its correlation with smoking was 0·240 in the directors and 0·376 in the manual workers.)

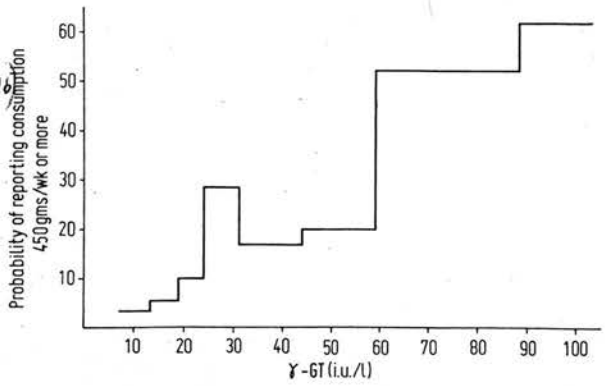

Fig. 1—Relationship between probability of reporting weekly alcohol consumption of 450 g or more and γ-GT.

Fig. 2 is derived for increasing MCV categories in a way analogous to fig. 1. The probability of stating a consumption

TABLE II—SENSITIVITY AND SPECIFICITY OF BLOOD TESTS AS INDICATORS OF ADMITTED ALCOHOL CONSUMPTION OVER 450 g* PER WEEK

—	Manual workers (n=222)	Directors (n=266)	Patients (n=34)
Report ⩾450 g/wk	47	30	30
γ-GT >50 i.u./l:			
n	45	65	20
Sensitivity†	53·2%	50·0%	60%
False positives‡	11·4%	21·9%	50%
MCV >98 fl:			
n	17	23	12
Sensitivity	22·9%	32·1%	40%
False positives	3·6%	6·2%	0%
MCV >98 fl and γ-GT >50 i.u./l:			
n	11	10	8
Sensitivity	17·7%	16·6%	26·6%
False positives	1·7%	2·2%	0%
MCV >98 fl or γ-GT >50 i.u./l:			
n	51	78	24
Sensitivity	53·2%	63·3%	73·3%
False positives	14·8%	25·8%	50%

* Equivalent to 28 pints of 3% alcohol by volume lager, or about 2 bottles of spirits per week.
† Proportion of "heavy" drinkers who had high scores.
‡ Proportion of "non-heavy" drinkers who had high scores.

TABLE III—INTERCORRELATIONS OF MCV, ALCOHOL CONSUMPTION, AGE, AND SMOKING IN DIRECTORS (ABOVE DIAGONAL) AND MANUAL WORKERS (BELOW DIAGONAL)

—	MCV	Frequency of drinking	Amount per week	Age	Smoking
MCV		0·340	0·439	0·216	0·267
Frequency of drinking	0·432		0·669	0·142	0·068
Amount per week	0·360	0·679		0·044	0·159
Age	0·156	−0·118	−0·166		−0·038
Smoking	0·413	0·200	0·140	0·001	

If a correlation is 0·148 or over, $p<0·01$.

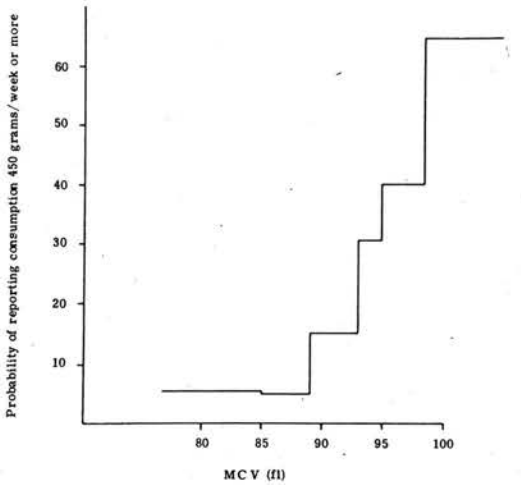

Fig. 2—Relationship between probability of reporting weekly alcohol consumption of 450 g or more and MCV.

of 450 g/week or more increases progressively with rising MCV throughout the range and reaches 66% when MCV is over 98 fl.

Table II shows that MCV (using a cut-off of 98 fl) is a poor screening test for heavy drinking, in that it has a low sensitivity—i.e., it misses many cases.

MCV and γ-GT Combined

Table II shows that when the criterion is serum-γ-GT 50 i.u./l or over *and* MCV 98 fl or over, few false positives are detected, though sensitivity is low, the opposite being true when either MCV *or* γ-GT is raised.

DISCUSSION

In the manual workers alcohol-induced macrocytosis is related not only to total amount of alcohol drunk per week but also to a pattern of sustained moderate exposure to alcohol rather than intermittent intense exposure. This was not the case for γ-GT. Perhaps the putative direct toxic action of alcohol on the developing erythroblast[3] is compensated for during lulls between binges.

Our method has produced larger correlations between admitted consumption and these two blood tests than obtained in previous studies. The graphs in figs. 1 and 2 show that at the higher range of each test there is a high probability that an individual has admitted to "heavy" drinking. For screening, however, these tests appear to lack power—for example, using 50 i.u./l (an often-quoted "upper limit of normal") as the cut-off for γ-GT an unacceptable high false-positive rate was found (21·9% in directors, 11·4% in manual workers). The high false-positive rate in terms of *admitted* consumption may be attributed partly to evasiveness about drinking on the part of some respondents. This possibility is supported by there being a higher false positive rate among the directors and the patients than among the manual workers. With respect to the directors, it has been shown that known alcoholics more often go undetected in self-report surveys if they are of high rather than low social class.[18] As for the clinic patients, it is widely found that some alcoholics underreport their drinking even when they have come for treatment.

Nevertheless, table II shows that a man with both tests elevated has a 2-in-3 chance of being a heavy drinker; and the graphs of probability indicate that a high MCV or serum-γ-GT in a man who does not present as a heavy drinker may be a reason to question him or a relative more closely about alcohol intake. In surveys, aggregate analyses may justify reallocating respondents with elevated tests to higher consumption categories.

Other biochemical tests correlate with alcohol intake,[19] and abnormal heterogeneity of transferrin seems to be relatively powerful.[20] However, MCV and serum-γ-GT are widely available and inexpensive and at present can be recommended for use in clinical practice as markers of alcohol intake, subject to the limitations discussed. It should be emphasised that tests should not be a substitute for a detailed non-judgemental inquiry into drinking (perhaps best tied to an account of work and leisure activities). One study of hospital case-notes revealed that only 36% contained even a barely adequate note of alcohol consumption.[21]

In those patients in whom there is an alcohol-induced elevation of one of these tests, cessation or reduction of drinking leads to a fall in the next 3–6 weeks, which provides the clinician with a useful indication of treatment progress.[2,4,22] Patients whose goal is reduction of drinking rather than abstinence find serial test results an aid to monitoring their consumption.

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Plasma α-Amino-*n*-Butyric Acid : Leucine Ratio and Alcohol Consumption in Working Men and in Alcoholics

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Martin Plant,[3] David Thatcher[2] and Jonathan Waite[4]

SUMMARY. *The ratio of plasma α-amino-n-butyric acid to leucine is higher in alcoholics, especially those who have drunk heavily recently, than in light drinkers. The ratio is of no value by itself as a screening test.*

Alcoholics sometimes minimize or deny their drinking and undetected alcoholism masquerades as a variety of medical conditions. This has led to a search for a biochemical marker. Shaw et al. (1) reported that the ratio of plasma α-amino-*n*-butyric acid (AANB) to leucine (A : L ratio) might be a marker for alcoholism. A subsequent study (2) comparing 130 alcoholics, 100 controls and 31 subjects with liver disease unrelated to alcohol confirmed that alcoholics had a high A : L ratio. Liver disease without alcoholism did not elevate the ratio.

Other workers (3–5) have either failed to find differences between the mean A : L ratios of controls and alcoholics or have found differences which could be accounted for by liver disease alone. However, different definitions of "alcoholic" may have been used, and none of these reports gave sufficient detail about either amount or recency of consumption. Another explanation for discrepant findings is that the measurement of the A : L ratio might be unreliable because AANB is present only in small quantities in plasma. With one exception (5) reliability has not been thoroughly discussed. Moderate drinkers have been found to show greater variation in their A : L ratio than nondrinkers, though in the small sample studied the tendency for moderate drinkers to have a higher ratio did not reach significance (6).

The aim of the present study was to illuminate these contradictory findings by studying the reliability of the biochemical procedure and refining consumption data. We studied individuals drawn not from general hospitals, as was the case in all but one of the above studies, but from groups of relatively healthy drinkers.

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METHOD

We report on two separate samples: alcoholic patients and a survey sample that was obtained from groups known to contain heavy drinkers but that were of contrasting social background.

First, three alcohol production companies were approached. In two firms the total manual work force (312 men) was contacted and interviews and blood samples were obtained from 222. From a third firm volunteers only were requested and 40 subjects were obtained. Second, 369 company directors (senior executives) whose names appeared in two professional lists were approached by letter and interviews and blood samples were obtained from 208.

The patients were 48 consecutive admissions to a psychiatric unit for alcoholics. They represented a wide range of socioeconomic groups according to most recent occupation: professional-executive 22%, other nonmanual 24%, skilled manual 22%, unskilled manual 32%. (On some analyses *N* is reduced because of loss or leaking of sample, delay reaching laboratory, or insufficient blood for analysis.)

In a 40-minute interview, subjects were asked to describe in detail their alcohol consumption in the seven days preceding the interview, facilitated by an account of social and work activities in that week. Sixty-seven percent of survey subjects said that it had been a "typical" week. In community samples there is evidence that the preceding week's drinking provides a reasonable estimate, for aggregate analyses, of usual consumption (7). Estimates of alcoholic patients' recent consumption are notoriously difficult to make but for uniformity consumption in the preceding week was also used for them. In the survey, a question on sporadic heavy consumption was also asked—how many times in the past 2 years had more than 130 g (4.2 oz) or more than 260 g (8.4 oz) of absolute alcohol been drunk in a day.

Blood was obtained by venepuncture at the time of the interview. Subjects were not fasting; for survey subjects the time of day varied. Samples taken in the evening were stored overnight at 4°C; for the biochemical tests they were spun and plasma was stored within 3 hr of venepuncture; and for the hematological analysis they were put into sequestrene tubes and analyzed the same day. Plasma for amino acid analysis was stored at −20°C, thawed and deproteinized with trichloracetic acid. Amino acid measurements were made by automated cation exchange chromatography on a Rank-Hilger J182 Chromaspek amino acid analyzer using a ninhydrin detection system. Although this analyzer uses a high pressure and a microbore column, full physiological fluid analyses have at least a 3-hr duration. The pH gradient elution system is very flexible, and a program which resolved AANB and leucine in 90 min was developed. The analyzer was interfaced with a Digico M16V minicomputer and asr33 teletype input–output peripheral. In order to obtain maximum accuracy in both peak recognition and quantitation the integrator was standardized every fourth sample. Standard solutions contained 100 nmol/ml Sigma amino acid standards with 100 nmol/ml AANB and 100 nmol/ml norleucine in pH 2.2 acidic analyzer buffer. Amino acid recovery was also estimated by direct comparison of peak heights with those of standard analyses and by manual integration of the peaks by triangulation. Mean cell volume (MCV) was measured by Coulter Counter. Gamma glutamyl transpeptidase activity (gamma-GT) was analyzed in plasma stored at 4°C by the method described by Rosalki and Rau (8).

RESULTS AND DISCUSSION

Reliability. Three estimates of the reliability of the procedure were made. First, using standard samples the percentage of standard deviation

in the ratio of the two amino acids was found to be 10.6 (based on 23 samples). Second, 74 specimens were analyzed and the plasma frozen, stored and reanalyzed after 2–20 weeks. The Pearson Product Moment Correlation between the ratios calculated on the two occasions was .93 ($p < .001$) and the Spearman Rank Correlation was .90 ($p < .007$). Third, 9 specimens were analyzed on separate aliquots, on the same day, but on a different run of the analyzer. The Pearson Product Moment Correlation of the ratios calculated from these two analyses was .98 ($p < .0001$), and the Spearman Rank Correlation was .99 ($p < .001$). This level of reliability would appear to be satisfactory.

A : L Ratio and Reported Consumption. The median consumption reported by the directors was 168 g (5.4 oz) of absolute alcohol per week (range 0–904 g) and that by the manual workers was 200 g (6.4 oz) per week (range 0–1904 g). Of the directors 9% reported 578 g (18.6 oz) per week or more, equivalent to 4 "large" measures of whisky per day and of the manual workers 16% were drinking in this range. Among the patients only 35 had been drinking amounts typical of their recent past in the week preceding the blood sample and their median consumption was 1074 g (34.5 oz) (range 24–3500 g): 83% had drunk over 578 g (18.6 oz). The other 19 had either detoxified themselves before admission or had been in the hospital for more than 7 days before the interview and blood sample. In the survey sample, the preceding week's reported consumption correlated with an A : L ratio of .06 ($N = 470$). There might be objections that there was a lack of correlation between the A : L ratio and reported consumption in the survey sample because nonalcoholics lie unsystematically about their consumption. However, controlling for age, fairly high correlations of reported consumption with MCV ($r = .34$) and gamma-GT ($r = .35$), more established indicators of consumption (9), argue against this. Furthermore, the correlation between consumption and the A : L ratio increased only slightly when those with "atypical" consumption in the preceding week were excluded: $r = .11$ ($N = 335$). There was no relationship between the A : L ratio and sporadic heavy consumption ($r = .07$).

We cannot exclude the possibility that inconsistency in sample collection (e.g., some subjects had eaten recently, not all samples were stored overnight before being frozen) added error to the study and obscured emerging relationships.

Discriminating Power of the A : L Ratio. The patients had a mean (± SD) A : L ratio of .15 ± .07, significantly higher ($p < .001$) than that of the manual workers (.11 ± .05) and "light drinkers" (.11 ± .06) in the survey sample. "Light drinkers" ($N = 173$) were those who said that they had drunk less than 120 g (3.9 oz) of alcohol in the previous week and include abstainers. The directors had an intermediate A : L ratio of .13 ± .06. The mean A : L ratio of 14 patients who had consumed more than 1280 g (41.2 oz) of alcohol in the week preceding admission was .19 ± .08 and that of patients who were not "recent heavy drinkers" was .14, a difference that nearly reached significance ($p = .056$).

Age and weight are possible contaminants of the relationship between the ratio and alcohol consumption but neither correlated with the A : L

ratio. A ratio of .2 or above (an arbitrary cut-off) was found in 11% of the 173 light drinkers, 23% of all patients and 43% of "recent heavy-drinking" patients. None of the light drinkers with a ratio of .2 or above had an elevated MCV or gamma-GT and thus were relatively unlikely to be very heavy drinkers.

Thus, alcoholics whose consumption was both recent and heavy tended to have a high A : L ratio. An elevated ratio is a moderately specific indicator of this group because only 11% of light drinkers had a ratio of at least .2. However, it lacks sensitivity, since only 43% of such patients had a ratio at or above that level.

A : L Ratio and Liver Disorder. In the patients, data were available on serum aminotransferase (mean, 52 ± 26 i.u./l), serum alkaline phosphatase (mean, 187 ± 63 i.u./l), serum gamma-GT (mean, 124 ± 152 i.u./l) and serum bilirubin (mean, 13.5 ± 10 mol/l). The only significant correlate of the A : L ratio was the serum bilirubin (r = .25, N = 48, (p = .05). The mean A : L ratio of the 14 patients with elevated serum bilirubin was .18 ± .07. "Recent heavy drinkers" were not disproportionately represented in this group (5 out of 14, or 36% as compared with 33% of the total patient sample), indicating an independent relationship of the A : L ratio with elevated serum bilirubin. However, simply taking any two elevated liver function tests as a criterion of liver disease did not reveal a relationship to the A : L ratio. In the survey sample there was no relationship between serum gamma-GT (mean, 47 ± 64 i.u./l) and the A : L ratio (r = .02, N = 466).

Though the frequency and severity of liver disease in these samples were not great, the indication is that serum bilirubin (but not serum hepatic enzyme concentration) is related to the A : L ratio. This relationship could not be accounted for by recent heavy consumption.

Conclusions

It is possible that there was lack of support for Shaw et al. (1, 2) in the literature because other workers have not studied alcoholics whose drinking was both heavy and recent. However, the present study does not provide evidence that the A : L ratio is a useful marker by itself of heavy alcohol consumption, though it would presumably be useful in combination with other tests. Given the different drinking and nutritional patterns of alcoholics, the range of biochemical systems affected by alcohol, and the likely genetic variability in susceptibility of those various systems, it is unlikely that a single powerful biochemical marker of alcoholism will be found.

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SERUM FERRITIN AS A MARKER OF ALCOHOL CONSUMPTION IN WORKING MEN

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Abstract — For 576 working men the relationship between reported recent alcohol consumption, serum ferritin, mean cell volume, and gamma glutamyl transferase was studied. Serum ferritin was significantly increased in heavy drinkers, but as a screening test it failed to yield a useful advantage over a combination of mean cell volume and gamma glutamyl transferase.

INTRODUCTION

Ferritin is the major storage form of iron in the body. It is found particularly in liver, spleen and bone marrow. Elevated serum levels are found in hepatic diseases where there is liver cell death, and some malignancies, without elevation of total body iron stores (Reeves and Haurani, 1980; Lundin *et al.*, 1981). Alcoholics tend to have elevated values. These elevations recede after about two weeks' abstinence and it seems to be dysfunction in liver rather than erythropoiesis that is important in determining serum ferritin changes in these patients (Lundin *et al.*, 1981).

Kristenson *et al.* (1981) found that serum ferritin was elevated in 67% of men identified in the general population to be heavy drinkers with increased serum gamma glutamyl transferase (GGT), but found only one elevated value in 39 teetotal males. The following report is also based on healthy males — a population of men working in occupations in which drinking is common. We examine the value of serum ferritin as a marker of heavy drinking.

SAMPLE AND METHODS

From 269 manual workers employed in Scottish alcohol manufacturing industries, and 207 senior executives in a range of commercial concerns, information on recent consumption was elicited, a blood sample taken, and results obtained on mean cell volume (MCV), serum GGT and serum ferritin. No subject was included if his current medication or current or recent illnesses might have explained an elevation of MCV or serum GGT. The fieldwork was conducted in 1978/79. We also report here on 30 patients selected from a consecutive series of men newly admitted to the Alcohol Problems Clinic in Edinburgh who reported that their past week's drinking had been typical of their recent drinking, and from whom the three blood test results were obtained.

The measure of alcohol consumption reported here was total intake (converted to grams of absolute alcohol, a half-pint of 3% lager or a single measure of wine or spirits containing about 8 g alcohol) in the seven days preceding interview. The male interviewer asked the subject to recall in detail his activities, both work and leisure, during these days and what beverages, in what amounts, he drank.

Twenty per cent of the manual workers and 39% of the directors said that the past week was not typical for them. We have argued elsewhere that at the aggregate level discrepancies between habitual drinking and the past week's drinking are likely to be trivial (Chick *et al.*, 1981*a*).

Serum GGT was measured by the method of Rosalki *et al.* (1971) and MCV with a Coulter counter. Subjects were asked their current

weight (or were weighed if they could not give this) and were asked about their weekly tobacco consumption.

Ferritin was assayed using an immunoradiometric method (Miles *et al.*, 1974). The specimens had been frozen and then thawed. The coefficient of variation of the assay was 10.4% at the upper value of the reference interval. Amongst Finnish normal men, the range of values obtained is 23–175 mg/l, mean 78 mg/l.

RESULTS

The mean values of serum ferritin obtained were: manual workers 106 mg/l, S.D. 94, range 8–666; executives 151 mg/l, S.D. 96, range 10–500; patients 269 mg/l, S.D. 247, range 8–980. It should be noted that these are slightly skewed distributions, and the statistics to be quoted should be interpreted in that light.

The product moment correlations between serum ferritin and alcohol consumption in the past week were +0.255 ($P < 0.0001$) (manual workers) and +0.296 ($P < 0.0001$) (executives). Serum ferritin had a relationship to serum GGT independently of consumption, partial correlations, controlling for consumption, being +0.410 ($P < 0.0001$) (manual workers) and +0.213 ($P < 0.0001$) (executives). Serum ferritin had no relationship with MCV independent of consumption.

A cut-off point of 250 mg/l gave the best discrimination between light and heavy drinking. As in our earlier paper (Chick *et al.*, 1981*b*), we used 98 fl as the cut-off for MCV and 50 IU/I for serum GGT.

Table 1 shows that serum ferritin does not add any power to the discrimination between heavy and light drinkers which can be achieved using MCV and serum GGT. Even though the sensitivity of the discrimination can be raised slightly (from 51 to 55% among the manual workers and from 64 to 72% among the executives), this occurs at the expense of specificity, i.e. the proportion of false positives (light drinkers with a positive test) also increases.

DISCUSSION

In our earlier report about MCV and serum GGT as screening tests for heavy alcohol consumption (Chick *et al.*, 1981*b*), we discussed the contribution made to the false positive rate of evasiveness about drinking. However, when using these tests, the clinician can make a positive result a reason for questioning a patient more closely about his drinking, or obtaining a history from a relative.

If elevated, they also provide a means of monitoring rises and falls in a patient's consumption. Valimaki *et al.* (1983) show that serum ferritin would likewise be useful in

Table 1. Effect of adding serum ferritin assay to the sensitivity and specificity of a combination of MCV and serum GGT as indicating admitted alcohol consumption of over 450 g per week

	Elevation of MCV or serum GGT %	Elevation of MCV serum GGT or ferritin %
Manual workers		
Less than 450 g/week, $N = 209$	18	21
More than 450 g/week, $N = 47$	51	55
Executives		
Less than 450 g/week, $N = 177$	28	33
More than 450 g/week, $N = 25$	64	72

monitoring rises and falls in consumption *in a given patient* including some of those in whom serum GGT was not elevated. However, the differences in serum ferritin levels between individuals are due to many influences other than alcohol alone. A correlation of 0.29 indicates that only 9% of the variation in ferritin levels can be accounted for by variations in alcohol consumption. The high level of significance of the correlation is due to our use of a large sample.

We have confirmed the observations of Lundin *et al.* (1981) that the rise in serum ferritin in the heavy drinker is related to liver rather than erythropoietic changes. Serum ferritin assay, though kits are now commercially available, does not, in our view, have a practical role as a screening test for heavy drinking, except perhaps in the situation where the subject is taking an anticonvulsant or other enzyme-inducing drug. Our reasoning is that the elevation of serum ferritin may reflect only 'hepatocellular damage', whereas serum GGT and other liver enzyme elevations can also be brought about by enzyme induction (Rosalki *et al.*, 1971). (However, a specific study of serum ferritin in patients taking anticonvulsants has not yet been reported.)

While one or two readily conducted tests with an accepted cut-off point — such as serum GGT and MCV — are useful to today's clinician, discriminant functions derived from a battery of tests may prove more powerful in future. Ryback *et al.* (1982) derived such a function in a hospitalised population, although to date an assessment of its power in other patient samples, or the general population, has not been published. However, when discriminant functions have been derived from a battery of tests in a general population sample, the function's ability to distinguish heavy from occasional drinkers, even within the population from which they have been derived, has, unfortunately, been limited (Whitfield *et al.*, 1981; Shaper *et al.*, 1985).

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DRUG and ALCOHOL DEPENDENCE

Carbohydrate deficient transferrin in detecting relapse in alcohol dependence

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Abstract

Patients' reports together with findings at clinical examination and information from an informant such as a relative were used to categorise patients as relapsed or not relapsed during a 6 month period of out-patient treatment at an alcohol problems clinic. At each fortnightly visit, blood was taken for measurement of serum γ-glutamyl transferase and carbohydrate deficient transferrin (Pharmacia method). A total of 53 patients attended for at least one follow-up visit. Mean CDT differentiated relapsers from non-relapsers at seven of the 11 visits ($P < 0.05$), but at no visit did mean GGT differentiate. CDT tended to become elevated after a relapse more quickly than GGT. However, whether using upper limit of normal (ULN), or defining a 'positive test' as $>$ last test and either $>20\%$ above lowest previous test or $>$ ULN, specificity (averaged over the 11 visits) was greater for GGT than CDT. Some of the false positive results for CDT were in patients who, shortly after having a positive test, relapsed, suggesting that a rising CDT can herald a relapse admitted by the patient. This could not be shown for false positive GGT results. Inspection of individual trajectories of alcohol consumption and blood test results shows that for some patients GGT is the more effective marker of relapse, whilst for others CDT operates better. © 1997 Elsevier Science Ireland Ltd.

Keywords: Alcohol dependence; Relapse; Carbohydrate deficient transferrin; γ-Glutamyl transferase

1. Introduction

As a result of ambivalence about their drinking, problem drinkers are sometimes not frank about their current consumption, which can impede medical decisions and divert therapy. If a medical examination is being conducted for an employment issue or renewal of the driving licence, there are extra inhibitions to frankness. Breath or urine tests for ethanol only reflect very recent drinking. Keso and Salaspuro (1990) categorised 73% of patients followed up for 8 months as achieving controlled drinking. However, only 52% had two normal values for two recognised markers of excessive consumption, γ-glutamyl transferase and mean erythrocyte cell volume, which shed doubt on how 'controlled' some patients' drinking had been.

A review of studies of blood test screening for heavy drinking (Litten et al., 1995) concluded that serum carbohydrate deficient transferrin (CDT) has a similar sensitivity in many populations to serum γ-glutamyl transferase (GGT), but that its specificity was greater. The relation of sensitivity to specificity depends on the cut-off chosen for an abnormal result as well as the population in which the test is studied. Some recent reports in populations with liver disease (e.g. Ouyaha et al., 1995) have found sensitivity of CDT as a marker of drinking to be lower than that of GGT, although its specificity is greater because it is normal in many non-drinking patients with non-alcoholic liver disease. However, it may be elevated in non-drinkers with some

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uncommon conditions such as primary biliary cirrhosis (Bean et al., 1995). Its specificity has been shown to be valuable in the detection of alcohol misuse in 59 men and 19 women with acute pancreatitis. At a cut-off of > 17 U/L, the specificity of CDT was 100% and sensitivity 75%, whereas GGT could not distinguish alcoholic from non-alcoholic pancreatitis (Jaakkola et al., 1994).

GGT may be influenced by factors such as body mass index, coffee consumption, the hour of the day and physical activity (Schiele et al., 1977; Robinson and Whitehead, 1989; Nilssen et al., 1990). None of these factors are yet known to influence CDT.

The GGT is currently used in some clinics and in research as a marker of relapse in alcohol dependent patients in out-patient treatment. The value of rising CDT in detecting relapse has been demonstrated by Borg et al. (1995) and Helander et al. (1996) who examined individual trajectories for each patient. Rosman et al. (1995) found that CDT detected relapse with a specificity of 79% plus a sensitivity of 76% when applying a cut-off of > 20 U/L, and a specificity of 90% plus a sensitivity of 55% when applying a cut-off of > 25 U/L. However, currently a CDT test is more expensive and labour intensive than a GGT test and it has not entered routine practice in most centres. The present study examines whether CDT offers an advantage over GGT as a marker of relapse in the follow-up of a wide range patients at a routine alcohol problems out-patient clinic.

2. Materials and method

A total of 60 patients diagnosed as alcohol dependent (American Psychiatric Association, 1987) agreed to fortnightly blood tests and named an informant such as a spouse or relative to give additional information about the drinking or any signs of relapse.

CDT is not yet known to be an efficient marker in those aged over 65, and does not distinguish alcohol abuse in primary biliary cirrhosis, chronic active hepatitis or drug induced hepatopathy: these were therefore exclusions. Also excluded were patients in whom the clinician would need access to liver function tests for legal reasons, or because there was significant liver disease (defined for this study as bilirubin > 25 μmol/l).

On a fortnightly basis for 6 months, the clinician estimated the previous 2 weeks' consumption and alcohol problems using the self-report time-line follow back method (Sobell and Sobell, 1992) and informants' reports, using physical signs, breath alcohol test and clinical experience to hone up the self report. For most subjects, the same clinician performed all the assessments. The clinician and subject may have been of the same or opposite gender.

Venepuncture was performed at each visit and serum sent for assay. Results were stored at the laboratory. The clinician was kept blind to all blood test results. All patients who attended more than the intake appointment were to be kept in the study, to approximate to the clinical situation where out-patients cease attending without warning, but may reappear weeks or months later.

The plasma CDT assay used a commercially available kit (CDTect, Pharmacia Diagnostics, Uppsala, Sweden) based on the separation of transferrin isoforms on an anion-exchange chromatography microcolumn followed by a double antibody radioimmunoassay. We took normal values to be: males below 21 U/L, females below 26 U/L. The analytical coefficient of variation (CV) in our hands was 10%.

Plasma GGT activity was assayed by SYS 3 BM/Hitachi 747/737 method (Boehringer Mannheim, Lewes, E. Sussex) reference ranges being males: 10–55 U/L, females: 5–35 U/L. For the GGT assay the analytical CV determined in our department was 4%.

2.1. Definition of a 'positive test' for relapse

In order to reflect the way in which a clinician might use test results as they emerge in a patient being followed up on a regular basis, a 'positive test' was defined as a result greater than or equal to the test result at the last visit, and either > 20% above the lowest recorded up to that point, or > upper limit of normal (ULN). We believe that clinicians use variation of alcohol-sensitive blood tests within the 'normal' range, and within the range outside the normal, when they are checking self-reported consumption, and this was why we chose as cut-offs a percentage change in the test results.

(A cut-off of + 2.5% specified in the study protocol was abandoned when analysis of results commenced in favour of + 20%, based on an analytic CV of 10% for CDT in our hands. When composite CV (analytical plus biological CV) was calculated (see Section 3) we realised that even + 20% was rather low (see Section 4)).

2.2. Definition of relapse

A relapse was defined in two ways: (1) In the past 14 days, weekly consumption of > 56 units of alcohol/week (80 g/day) for at least 7 days, chosen because we had used this in our previous work on markers (Chick et al., 1981) and because it represents a clinically significant relapse, beyond 'controlled drinking'. (2) A 'clinician's definition': at least one problem in the preceding 14 days from the Alcohol Related Problems Questionnaire (Patience et al., 1997) comprising 11 social and medical harms related to alcohol (the subject may or

may not have been recorded as drinking > 56 units/week).

2.3. Ethical considerations

Subjects had at least 24 h to decide to participate. If during the study clinicians believed that for the patient's safety blood test results should be examined, laboratory results could be requested and the subject withdrawn. In addition the laboratory informed the consultant (J.C.) if a patient developed a serum bilirubin > 25 μmol/l or liver enzymes > 5 times the upper limit of normal, and a clinical decision about withdrawal from the study was made. The study was approved by the Ethics of Research Committee. Patients gave written informed consent.

3. Results

3.1. Characteristics of the patients and retention in the study

One subject was withdrawn from the study because of an elevated bilirubin. A total of six patients attended only for the intake visit. The remaining 53 patients (43 male, ten female) were white, aged 30–59 years.

Pattern of drinking was continuous in 65%, episodic or 'bout' in 35%. Mean age of onset of heavy drinking was 25 years (S.D. = 8.1). Their alcohol dependence was rated as moderate in 30%, severe in 70%. In the month prior to entry, 19% were abstinent. Some had been abstinent for very much longer (maximum 465 days), but were still in regular contact with the clinic to sustain their resistance to relapse. Of those drinking in the past month, 14% were drinking up to 80 g/day of ethanol, and the remainder more than 80 g/day. At entry to the study six patients had a positive breath alcohol reading and four had severe tremor (mild tremor in 25). Two-thirds regularly smoked tobacco.

Patients frequently missed appointments but returned subsequently. Thus for the 11 follow-up visits, the number of patients with data available on a specific visit varied from 43 to 19. There were 41 patients with at least 12 weeks continuous observations and at least one relapse (32 males, nine females) and these we termed 'per protocol patients'.

A 'relevant medical or surgical history or concomitant disease' was documented in 34 patients. A new physical disorder arising during the study was documented in 27 patients. Medication of some type was being taken at the beginning or was commenced during the study in 49 patients. (These patients were not omitted from the study nor from the analysis, because we wished to test the markers' performance in the worst possible clinical situation, in which full data on concomitant illness or medications is not available, e.g. unconscious patient and unreliable patient).

3.2. Marker reliabilities

The mean composite CV (analytical + biological) calculated in nine non-drinking patients in the study sample (six male, three female) assessed at fortnightly visits (8–12 visits per patient) was 15.3% for CDT and 30.6% for GGT, presumably reflecting the greater biological variation in GGT.

3.3. Comparison of relapsers versus non-relapsers

3.3.1. Sensitivities and specificities of a positive test

Sensitivity was defined as the rate at which individuals who relapsed were correctly identified by the test (i.e. the true positive rate), and specificity as the rate at which individuals who had not relapsed were correctly identified (i.e. the true-negative rate). The sensitivity and specificity of each marker, at each time point, was calculated using either 'above ULN' as a positive test or the definition of a 'positive test' given above. Table 1 shows the means over all time points, for the two definitions of relapse. The specificity of CDT in indicating relapse (either definition) appears to be less than that for GGT. Instances of false positive results were examined separately—see below.

(When the above analyses were performed in the 'per protocol' subsample, only very minimal alterations oc-

Table 1
Sensitivities and specificities of blood tests as markers of two definitions of relapse

Clinical relapse[b]	Sensitivity	Specificity
CDT above ULN[a]	0.75	0.68
GGT above ULN	0.50	0.70
CDT 'positive'[d]	0.54	0.60
GGT 'positive'[d]	0.47	0.80
>56 units/week (mean of 80 g ethanol/day)[c]		
CDT above ULN	0.90	0.60
GGT above ULN	0.59	0.73
CDT 'positive'[d]	0.69	0.60
GGT 'positive'[d]	0.64	0.76

Mean over 11 follow-up visits, *n* varies from 43 to 19 over different visits.

Sensitivity, true positives/(true positives + false negatives); Specificity, true negatives/(true negatives + false positives).

[a] Upper limit of normal. GGT, males 55 U/L; females, 35 U/L. CDT, males 21 U/L; females 26 U/L.

[b] 'Clinical relapse' (at least one problem from the Alcohol Related Problems Questionnaire in the past 14 days).

[c] 'Consumption relapse' (in the past 14 days, weekly consumption of >56 units of alcohol/week (80 g/day) for at least 7 days).

[d] Positive test, ≥test result at last visit and either >20% above lowest recorded up to that point, or >ULN.

2
CDT and GGT (with S.D.) in relapsers and non-relapsers ('clinical relapse') at each visit

	No relapse			Relapse			
	n	Mean	S.D.	*n*	Mean	S.D.	*P*
U/L)							
	24	35	28	19	136	331	0.057
	19	38	43	13	97	173	0.251
	19	50	67	10	365	731	0.125
	16	186	596	13	79	79	0.794
	17	160	443	12	82	89	0.947
	11	33	15	10	64	59	0.219
	11	167	451	17	80	69	0.223
	11	151	319	8	96	77	0.355
	19	51	51	4	49	29	0.749
	13	92	209	6	83	70	0.415
	19	42	33	6	69	77	0.801
U/L)							
	23	22.7	19.5	18	31.1	14.8	0.014
	19	18.4	8.3	11	30.2	11.6	0.005
	19	17.3	10.8	10	29.1	21.7	0.021
	16	21.2	113.2	13	29.8	17.6	0.102
	17	20.8	13.2	12	45.1	38.2	0.007
	11	20.9	7.7	10	44.8	34.4	0.011
	11	28.4	23.3	17	35.6	21.5	0.162
	11	29.7	23.4	8	29.1	12.1	0.516
	19	24.4	14.4	4	43.8	18.1	0.110
	13	19.4	9.6	6	41.8	27.5	0.034
	19	21.4	16.1	6	32.0	6.8	0.007

ificance of difference between relapsers and non-relapsers, on rank-sum test.

d in the sensitivities and specificities shown in 1).

Mean test scores

an CDT differentiated clinical relapsers from clin-on-relapsers at seven of the 11 visits (Wilcoxon sum test, $P < 0.05$), but at no visit did mean GGT entiate between the groups (Table 2). For relapse d as excessive consumption, Fig. 1 shows that who had consumed 56 units/week (i.e. an average g/day) or more, for at least 7 days, tended to have cantly higher CDT than those who had not drunk t range (statistically significant ($P < 0.05$) at six points), while GGT did not differentiate signifi- at any time point between those drinking below bove that level.

ause there was such wide dispersion of the GGT s, the analysis was repeated using logarithmically formed blood test results. Mean log CDT discrim- significantly ($P < 0.05$) at five time points, but log GGT failed to discriminate at any points.

Timing of test elevation

m the drinking record, there were 33 subjects had at least 1 week when they consumed > 56 units/week (i.e. an average of 80 g/day) for 7 days. The first visit at which this was recorded was noted, and corresponding and subsequent blood tests results examined. GGT and CDT rose simultaneously at seven of these instances; in three instances, neither rose; GGT rose before CDT in five instances and CDT before GGT in 17. (In one subject blood tests at the time of the drinking were incomplete). Thus, it can be concluded that CDT tends to react more briskly than GGT.

3.5. Test relationships to quantity consumed

At each time point, correlations were calculated between the test and the previous 2 weeks' consumption. There were no significant correlations between GGT and past 2 weeks consumption (range $-0.4-+0.26$), while at three time points correlations between CDT and previous two weeks' consumption were significant at the level $P < 0.05$ (range $+0.10$ to $+0.66$). Because of the wide dispersal of the GGT results, this was repeated using log GGT and log CDT. No correlations were significant for GGT (range -0.02 to $+0.29$), and four were significant at the level $P < 0.05$ for CDT (range $+0.28$ to $+0.60$).

4. Discussion

In its heterogeneity, this sample was probably typical of attenders at an alcohol clinic linked to medical or psychiatric services. More than 1/2 had another medical condition, and almost all took medication of some kind during the study. More medical disorders and drugs have been shown to affect GGT than CDT. Examination of individual trajectories revealed one example where a GGT 'false positive' had been due to a drug (lofepramine), but there may have been others. The clinician will often prefer a marker which is less susceptible to confounding influences.

Unfortunately, the great number of missing values has prevented a more appropriate analysis such as a multivariate repeated measures analysis. In presenting data at each time point as in Fig. 1, Table 1 and Table 2, an apparent trend may be inflated, because some of the same individuals appear in each analysis. To answer the questions posed by this study, the required population is of patients who are prepared to be seen regularly and frequently, and who are likely to relapse. Unfortunately, relapsers miss appointments. It is therefore inherently a difficult study to conduct.

The comparison of the mean scores at the different time points (Table 2,Fig. 1) suggests that overall CDT appears to be an earlier indicator of relapse than GGT. Table 1, however, reveals that when our definition of a 'positive' test is used, there appear to be on average more false positives with CDT than GGT. This may be in part because CDT 'heralds' relapse—as explained above. Rosman et al. (1995), like ourselves, reported that a rise in CDT sometimes occurred before the relapse was admitted or obvious. Borg et al. (1995), basing their conclusions on daily urine 5-hydroxy tryptophol as a marker of recent drinking, found that alcohol-dependent out-patients frequently drank in a way that was initially not obvious and was only revealed later.

Another factor contributing to false positives was a cut-off (20% above lowest recorded at that point for that patient) that was only just at the upper limit of the composite coefficient of variation, and thus 'positives' for both markers are (statistically) likely to occur without drinking alcohol.

4.1. Studies suggesting CDT may be more 'responsive' than GGT

The half-life of CDT in newly abstinent alcoholics was 16 ± 5 days in the study of Behrens et al. (1988), and the review by Allen et al. (1994), put it at about 15 days, while for GGT it has been found to vary between 14 and 26 days (Litten et al., 1995). CDT can thus be said to be a slightly more responsive indicator.

Behrens et al. (1988) suggest that the CDT test has increased sensitivity in abstinent alcoholics given a new alcohol challenge. They found that serum CDT increased within a few days of starting drinking. Stibler et al. (1986) suggested that less than the 10 days was necessary for an elevation in non-alcoholics taking a daily alcohol consumption of 60 g/day. They found that in the six patients who drank after discharge and in whom CDT level soon rose again, GGT and transaminases remained normal in all but one. Our results support this sensitisation hypothesis.

(It should be noted that there is currently some confusion about how much alcohol needs to be consumed by non-heavy drinkers, and for how long, to elevate CDT above normal. Stibler et al. (1986) suggested that at least 60 g/day for at least 3 weeks was required. Salmela et al. (1994) found that 60 g/day for 3 weeks caused CDT (Pharmacia method) to rise above cut-off (ULN) in only two out of ten volunteers, but an elevation was found in nine out of ten. Lesch et al. (1996) failed to show consistent elevations (Axis % method) in 51 healthy men drinking either 60 or 80 g/day.)

4.2. Limitations of CDT as a relapse marker

The apparent high false positive rate at the cut-offs we used may, of course, also reflect a weakness in the test. There are various methods for assessing CDT and there is currently debate about whether tri-sialo-transferrins should be included when calculating CDT (Heggli et al., 1996). There are limitations on the absolute meaning of a single positive CDT test.

4.3. Clinical application of CDT in detecting relapse

Ideally patients who are receiving treatment for alcohol dependence are frank with their therapists about resumption of drinking. However, even the most empathic therapist may not achieve such a completely open relationship. When resumption of drinking may escalate to a relapse with very serious medical or social consequences, aids to the recognition of return to drinking have an important clinical role. This study shows that, if repeated tests are being done at relatively short intervals, in some patients CDT will perform better than GGT as an objective early marker of resumed drinking.

In patients taking antidepressants or anticonvulsants, a drug-related false positive test is less likely with CDT than with GGT. In patients taking disulfiram, there is no specific advantage of CDT over GGT, because neither test appears to be elevated by this drug (Helander and Carlsson, 1996; for GGT, Chick et al., 1992).

When a patient requests assistance in reassuring an employer or a professional licensing body, or in the case of child protection procedures a social work panel, or reports are requested for the court when an offender has a deferred sentence pending following treatment for alcohol dependence, then CDT is a helpful aid to the clinician monitoring response to treatment.

We would agree with Helander et al. (1996) that the two markers should be regarded as complimentary. In the individual case, by following changes in the tests during alcohol withdrawal, the most sensitive marker for that individual can be determined.

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LIMITATIONS OF CDT AND GGT IN DETECTING RELAPSES IN PATIENTS ATTENDING AN ALCOHOL PROBLEMS CLINIC

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Abstract: *Biochemical markers of alcohol consumption are useful for the detection and monitoring of problem drinking. Blood samples from 37 patients attending an alcohol treatment clinic were analysed for GGT and %CDT, and results were compared with self-reported periods of abstinence and alcohol consumption. Poor correlation was obtained between GGT and %CDT, and between these assays and self-reported alcohol use. The apparent sensitivity and specificity of GGT (57%, 63%) and %CDT (43%, 88%), were considerably lower than those reported by other workers.*

Keywords: Alcohol dependence, carbohydrate deficient tranferrin, gamma glutamyl tranferase, biochemical markers of alcohol consumption.

Alcohol (ethanol) abuse is a serious problem for the individuals concerned and has serious social consequences for the user's relationships in the family and the workplace, and also for society at large.

Alcohol is a CNS depressant which leads to loss of concentration, impaired judgement and vision, slower reaction, over estimation of personal ability, dizziness, nausea and disturbances of balance and co-ordination.[1] Elevated concentrations of alcohol in the blood can have an adverse effect on driving ability and give rise to errors and accidents. Driving ability can also be affected by sensory and mental defects occurring in chronic alcohol abuse. In the workplace, alcohol abuse can lead to a deterioration in the standard of workmanship particularly in occupations requiring high levels of concentration and skill, rapid reactions, and visual acuity. In addition there is a greater risk of accidents and injury, and an increase in absenteeism from work. As a result, alcohol abuse has serious financial implications for employers and for the national economy.

Measurement of the concentration of alcohol in plasma or blood is used routinely in the investigation of road traffic accidents but is of limited value in detecting possible alcohol abuse because of the rapid rate of metabolism of alcohol in blood (about 120 mg/kg per hour). Measurement of mean cell volume (MCV) has been used as a marker of drinking but is of limited value.[2]

Self-reporting of alcohol use is notoriously unreliable but it is still considered to be important in the management of alcohol abusers and forms the basis of many evaluations of analytical procedures.[3-8] The accuracy of information obtained can be improved considerably by the use of collateral reporting which involves not only the patient but a spouse or relative and/or a working colleague.

Measurement of serum gamma glutamyl transferase (GGT) together with other liver function tests is widely used for the investigation of possible alcohol abuse and for the management of patients with alcohol problems.[2-9,10] In the UK, it is also used for processing applications for renewal of driving licences. Despite its wide use, several reports have drawn attention to the diagnostic inaccuracy of GGT for these purposes.[9-11]

It has been suggested that carbohydrate deficient transferrin (CDT)[12] has a greater sensitivity and/or specificity than GGT in detecting alcohol dependence.[9-13] There have, however, been only a few studies of non dependent hazardous drinkers.[10] The half-life of CDT, about 15 days, is probably slightly shorter than that of GGT (14-26 days), and hence CDT may be considered to be a slightly more responsive indicator.[8,9,12,13] In addition, GGT may be influenced by factors such as body mass index, coffee consumption, the hour of the day and physical activity.[14-16] None of these factors are yet known to affect CDT.

Carbohydrate deficient transferrin

Serum transferrin contains two complex carbohydrate chains consisting of four different carbohydrates (N-acetylglucosamine, mannose, galactose, sialic acid) but the exact content varies considerably.[12] The terminal sialic acid is the only charged carbohydrate in serum transferrin.

Regular high alcohol consumption results in the appearance of isoforms of serum transferrin. which are deficient in their carbohydrate content. These isotransferrins have a decreased sialic acid content and are less negatively charged and have higher isoelectric points than normal transferrins. The isoforms can, therefore, be separated by methods based on charge.

Daily alcohol intake of more than 60g ethanol (about 45 units/week) for at least one week usually results in elevated concentrations of CDT. During alcohol abstinence, concentrations are reported to return to normal levels with a mean half-life of 12-17 days.[8,9,12,13] CDT is a potentially useful marker of drinking 2-3 weeks previous to a blood test.

Heggli et al[17] investigated the sensitivity and accuracy of using relative concentrations of the different isotransferrins in serum for the diagnosis of chronically elevated elevated alcohol consumption. They found that including the tri-sialo-transferrin fraction into the definition of %CDT resulted in an increased accuracy in the detection of chronically elevated alcohol intake.

A commercial kit for the measurement of serum CDT is marketed by Pharmacia Diagnostics (Uppsala, Sweden). The CDTect™ assay is based on the separation of transferrin isoforms on a microcolumn followed by a double antibody radioimmunoassay. A fluorimetric immunoassay version of the kit is also available.

More recently, Axis Biochemicals ASA (Grunerlokka, Oslo, Norway) developed a commercial turbidimetric immunoassay which measures the percentage of the CDT isoforms (a-, mono, di-, and trisialotransferrin) relative to total transferrin in serum.

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10.

Predicting relapse in problem drinkers

Ideally patients who are receiving treatment for alcohol dependence are frank with their therapists about resumption of drinking. However, even the most empathic therapist may not achieve such a completely open relationship. When resumption of drinking may escalate with very serious medical or social consequences, aids to the recognition of a return to drinking at an early stage have an important clinical role.[18]

Conventional markers, including serum GGT, have been used to detect increased consumption of alcohol, but by the time it is detected, people are frequently already dependent on alcohol and suffer from major complications caused by their consumption.[19] For early identification of heavy drinking and monitoring during treatment of out-patients, markers with higher sensitivity and specificity are needed.

Serum CDT is reported to be an accurate biochemical marker for the detection of recent excessive alcohol consumption, with a greater sensitivity and/or specificity than GGT. There have also been several reports of the use of CDT in the detection of relapses in alcohol-dependent patients.[7,12,19]

We describe here a study in which blood samples from patients attending an alcohol treatment clinic were analysed for %CDT, GGT and liver function tests and results were compared with reported periods of abstinence and alcohol consumption.

Subjects and methods

Thirty seven patients (29 males, 8 females) attending a Scottish alcohol treatment clinic volunteered to give a venous blood sample. They were mainly out-patients attending for follow-up, and the remainder were in-patients admitted within the past 10 days. The interval since their last drink of any alcoholic beverage was recorded and using the Timeline follow-back method[22] their consumption in units of alcohol in the preceding 14 days was totalled (one unit is equivalent to about 10g ethanol).

Abstinence from alcohol for less than 14 days and alcohol consumption during this period greater than the "safe limit" (Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1994) ie greater than a mean of 20 units per week, were taken as an indication of relapse. Definitions of relapse and possible relapse, are given in Table I.

The plasma GGT activity was measured by the SYS 3 BM/ Hitachi 747/737 method (Boehringer Mannheim, Lewes, E. Sussex). Reference ranges of 10-55 u/L for males and 5-35 u/L for females were used. The coefficient of variation (CV) of the method is 4%.

Percentage CDT was measured by the Axis turbidimetric immunoassay. Serum transferrin in the sample was saturated with Fe^{3+} and the isoforms separated on an ion-exchange microcolumn.

The eluted CDT isoforms form immune complexes with antitransferrin antibodies and the CDT content was determined by a turbidimetric assay on a Cobas Mira analyser (Roche Diagnostics, Welwyn City, UK). The total transferrin content of the samples was determined separately using the same anti-transferrin complexes. Measurements were evaluated using a calibration curve and the %C DT value calculated according to the manufacturer's instructions. [23]

Daily intake of alcohol exceeding 60g ethanol for periods longer than two weeks, may result in %CDT values higher than 6%. The %CDT range for total abstainers is found to be 0-5%.[23]

Results

There was a low correlation between %CDT and GGT (correlation coefficient, 0.370). Percentage CDT also showed a low correlation with self reported days of abstinence (correlation coefficient, -0.151) and only a moderate correlation with self reported alcohol consumption in the preceding 14 days (correlation coefficient, 0.302); the corresponding correlation coefficients for GGT were -0.222 and 0.283, respectively.

A summary of the findings for samples from the 37 patients investigated is given in Table I. Of the 23 samples from patients with a reported abstinence time of less than 14 days, and consumption greater than 40 units in the preceding 14 days, GGT and %CDT were above the reference ranges for 13 (57%) and 10 (43%), respectively. Of these patients, seven (30%) showed neither GGT nor %CDT outside the reference ranges. For eight patients with a reported duration of abstinence of 14 or more days, five (63%) of the GGT results and seven (88%) of the %CDT results were within reference limits. Using a higher cutoff (90 units in the preceding 14 days), the %CDT was greater than 6% in six of 20 patients.

The sensitivity and specificity of the %CDT assay in detecting relapse based on self reporting were 43% and 88% respectively; the corresponding values for GGT were 57% and 63%, respectively.

Efficiency (the proportion of the total number of patients correctly classified using the test) was 58% for GGT and 55% for CDT.

Discussion

A comparison of the use of GGT and CDT as biological markers of heavy alcohol consumption has been reported in a large number of publications.[9] Although the findings differ widely depending on the investigative procedures employed and the populations studied, GGT is considered to have equal sensitivity but to be less specific than CDT. Behrens et al[13] report that CDT proved to be a more sensitive marker than GGT for chronic alcoholism whereas GGT was more useful only in patients with normal CDT levels before alcohol withdrawal.

In our study the sensitivity and specificity of GGT and %CDT were considerably lower than those reported by other workers.[9,11] There was also relatively poor correlation between these markers and self reported time since last alcoholic drink and alcohol consumption over the preceding 14 days. This may in part be because some others make a comparison between newly admitted alcoholic patients in a general hospital and non-alcoholic admissions to that hospital, while we have attempted

Table I
Summary of performance of GGT and %CDT assays compared with clinical assessment based on days of abstinence and consumption.

Clinical Assessment Based on Self-Reporting	Number of Patients	Number of GGT and %CDT Results Above Reference Ranges [1]			
		GGT Only	%CDT Only	Both	Neither
Relapsed [2]	23	6	3	7	7
Possible relapse [3]	6	2	0	1	3
Abstinent[4]	8	2	0	1	5
Total	**37**				

[1] Reference Range
%CDT 0-6%
GGT (males) 10-55u/L; GGT (females) 5-35u/L
[2] Relapsed Abstinent days: <14 days, and Consumption (14 days): >40 units
[3] Possible Relapse Abstinent days: <14 days, and Consumption (14 days): <40 units
[4] Abstinent Abstinent days: ≥14 days

to examine drinking within a sample of alcoholics. Some other studies have used wholly in-patients in detoxification units, eg Stowell et al,[11] when estimates of time since last alcoholic drink and recent total alcohol consumption are likely to be more reliable than in our sample comprising mainly out-patients. Nevertheless, a previous study from our clinic of newly admitted in patients,[24] like our present study, also found a very poor correlation between GGT and self-reported alcohol consumption. The results from our relatively small study do, however, support the previously reported finding that CDT is more specific but less sensitive than GGT for the detection of alcohol abuse.[9]

Combined use of CDT and GGT is reported to increase the sensitivity of detecting alcohol abuse in patients admitted to hospital to 95% and proved to be useful in the evaluation of treatment.[13] In our study, measurement of CDT in addition to GGT gave only a limited improvement in the detection of relapse.

Our definition of relapse (see Table I) was lower than the cut-off of 60g per day for at least two weeks (ie about 45 units per week) at which the %CDT can be expected to exceed 6%. This might seem to explain the lower sensitivity of %CDT reported here. However, even when we use 90 units per two weeks as cut-off, the %CDT was greater than 6% in only six out of 20 patients (30%).

Assays for GGT can be performed on automated analysers, are inexpensive, and are readily available in most clinical biochemistry laboratories. In contrast, CDT is a highly labour intensive assay requiring specialist equipment, reagent costs are high, and the shelf-life of RIA kits is short (about one month). A CDTect™ fluorimetric immunoassay has been introduced but the assay is still labour intensive and reagents are expensive although the shelf-like of kits is considerably longer (6-9 months). The Axis turbidimetric immunoassay for %CDT involves a preliminary separation stage similar to that of the CDTect™ method and hence this stage is labour intensive. The Axis assay can, however, be performed using analytical equipment which is readily available in most clinical biochemistry laboratories, eg Roche Cobas Mira/Fara and IL 900/1800, but the calculation has to be done manually.

Allen et al[8] have drawn attention to the need for further research to establish more precisely the period of abstinence necessary for CDT levels to return to the normal range and to determine the extent to which duration of CDT elevation might reflect the initial level of the marker, typical drinking pattern, age and gender, as well as type of laboratory test, and which is the optimum CDT quantitation method to use. In addition, there is a dearth of information on subsequent CDT levels should drinking moderate but not cease.

Conclusions

Current markers of alcohol use have obvious limitations, and it seems unlikely that for clinical purposes, laboratory tests will completely replace a physician's judgement in the diagnosis of hazardous alcohol intake or dependence.[10,25] A serious problem with the introduction of new markers is unreliability of self-reported periods of abstinence and quantity of alcohol consumed which are used as criteria for the evaluation of analytical methods. If however, their limitations are clearly understood, laboratory tests provide useful aids in detection and objective monitoring of hazardous alcohol consumption and many of its pathological sequelae.[10,25]

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EPIDEMIOLOGY OF ALCOHOL USE AND ITS HAZARDS

With a Note on Screening Methods

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1 Prevalence Estimates of Alcohol-Related Disorders

The vagaries of recording cause of death and the variation in different epochs and between regions in referral policies and hospital admission policies conspire against the use of official statistics as prevalence estimates. In the epidemiology of alcohol-related disorders the alternative method, the direct survey, is handicapped because of the reticence of the heavy drinker and, indeed, the difficulty the door-to-door interviewer has finding him at home. Figure 1 shows trends in England and Wales in some of the "indirect indices of alcoholism".

FIG. 1. Deaths from alcoholism and cirrhosis, offences of drunkenness and consumption of alcohol in England and Wales, 1860–1978
(Reprinted, with permission, from Taylor, 1981)

Deaths are expressed per million, drunkenness offences as rate per 10000 population, and per caput alcohol consumption as litres of absolute alcohol

Cirrhosis. The death rate in the UK has risen since 1950, though it is still appreciably lower than it was in 1900. From a rate of 23/million in 1950 it rose by 3% a year to 44/million in 1979. Standardized mortality rates show that the trend is not accounted for by slight changes in the age structure of the population (Registrar General's annual reports). Figure 2 shows that this increase cannot be accounted for merely by a shift in doctors' preference for the term "cirrhosis" as against other categories of liver disease.

Hospital admissions. Admissions for alcoholism have also risen in most developed countries during the past 20 years. For example, in Scotland, in 1906, many years before the 1960s movement to provide specialized in-patient treatment for alcoholics, the typical mental hospital recorded alcoholism as one of the three major causes of admission. By 1957 it was relegated to a position of minor importance, accounting for only a total of 840 admissions. By 1974 total admissions for alcoholism and alcoholic psychosis had reached 5417 and in 1978 were still 5222, despite a growing interest in out-patient and "community" care. First admissions, a somewhat more accurate indicator of inception, rose as shown in Table I. The work load contributed to by alcoholism also increased during this period, discharges from general hospitals with the diagnosis of alcoholism or alcoholic psychosis nearly quadrupling in the decade 1968–78.

Survey estimates. There are two main precautions in obtaining direct estimates of prevalence of alcohol-related disabilities from community surveys. First, surveys are known to under-estimate the number of heavy drinkers (Pernanen, 1974). Second, prevalence rates in surveys are very sensitive to alterations in the definition of a "case". In a North American survey analysed by Clark (1966) changing the definition with respect to severity yielded a variation in rates from 3/1000 to 62/1000. When he made the criteria lax enough to include past as well as present alcohol-related problems a figure of 272/1000 was reached. Clearly, the epidemiologist is not looking at a fixed condition, "alcoholism", which is either present or absent, and where a case remains a case, but at a range of alcohol-related problems which are reported by members of the community in different degrees and which may be either past or present.

FIG. 2. Deaths from cirrhosis and other liver disease, England and Wales, 1946–79
(Data from Registrar General's annual reports)

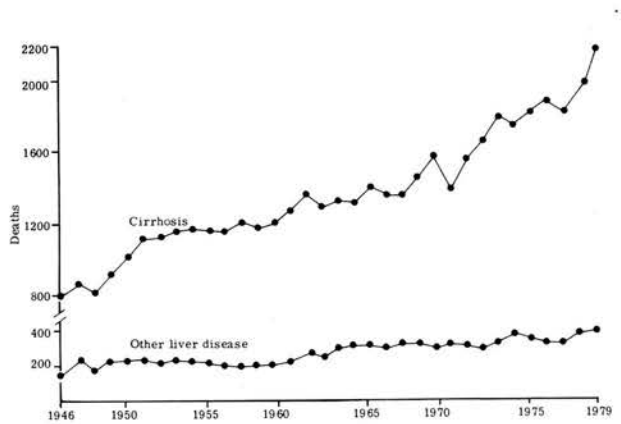

TABLE I. Scotland: first admissions to psychiatric hospitals with a diagnosis of alcoholism and alcoholic psychosis

(Data from Scottish Home and Health Department)

	1965	1967	1969	1971	1973	1975	1977	1979
Males	960	1000	966	1120	1509	1647	1621	1532
Females	194	182	213	301	379	434	497	558

2 Patterns of Alcohol Consumption

i *National Variations*

National data on consumption patterns are as subject to important errors as those on prevalence of problems (Kreitman, 1977). Government revenue statistics are the usual source of information on over-all consumption in nations.

Grape growing is, of course, associated with high consumption, with France, Portugal, Spain and Italy having the highest per caput consumption in Europe. The relation between agriculture, gastronomic customs, symbolic meanings of alcohol and national styles of drinking has to date only been the subject of discursive papers. In the UK, revenue on beer and spirits has been collected since the 17th century. Spring & Buss (1977) note that beer consumption was at its maximum in 1689 and spirits in the early 1870s. The lowest point in per caput consumption of all forms of alcohol for three centuries was reached after the Second World War. The next two decades have seen a steady rise. The trend until 1978, shown in fig. 1, is still present (Brewers' Society, 1980).

The causes of temporal fluctuations in national consumption are incompletely understood. Number of outlets and to a less extent price and advertising can be demonstrated by econometric analysis to have some effect (McGuinness, 1980). "Formal controls" comprise laws on drinking and driving, and drunkenness, and taxation and licensing laws. A recent change in legislation in Scotland provided an opportunity for studying the effect of an extension of licensing laws. "Before" and "after" surveys were conducted (Knight & Wilson, 1980) and showed that, during this period, though there was a reduction in average speed of drinking, over-all consumption increased in women and in men aged $\leqslant$45 years. Changes in prevailing customs and attitudes to drinking—"informal controls"—are probably equally if not more important, but their effects are even less well understood.

ii *Trends amongst Women*

In the past decade, in several countries, the long-standing gap between men's and women's consumption appeared to be diminishing. Comparisons between successive surveys provide the only direct means of testing this impression. For example, a World Health Organization survey in 1978 in the Lothian region of Scotland repeated measures already available for that area from a survey in 1972 (Dight, 1976). While not finding an increase in the proportion of male drinkers who fell into the higher-consumption categories, the WHO survey found that now 11% of women admit to consuming 11 or more units[1] a week, whereas previously only 4% of women drinkers fell into that category. The increase was accounted for chiefly by younger, single women (World Health Organization, in preparation).

Some possible causes of these changes in women's drinking are discussed by Shaw (1980): greater female employment and higher earnings; the recent increased availability of alcohol in supermarkets; advertising aimed specifically at women; the growing numbers of women employed in public houses and clubs; blurring of the traditional sex differences in both leisure and work activities.

iii *Influence of Age*

The increase in consumption which took place after the Second World War in most developed countries was accompanied by more frequent drinking amongst 14–18 year olds. In the USA and Finland where survey data over successive years are available the trend was not continued into the 1970s: Ahlstrom (1979[2]) in Finland and Rachal *et al.* (1980[3]) in the USA found a slight decrease in regular drinking and a slight increase in abstaining. In the UK, the rate of offences for drunkenness amongst this age-group also reached a plateau in the 1970s. In all surveys in the UK and Scandinavia in the past 15 years, men in their early twenties are the heaviest consumers. In Scotland, high consumption amongst young men appears to continue for longer than in England and Wales and Northern Ireland (Wilson, 1980a).

iv *Regional Variations within the UK*

Edwards *et al.* (1972) found that London survey respondents who were Scottish and Irish reported heavier consumption than respondents born in England. Wilson (1980a) compared results of similar surveys conducted in 1978, in England, Wales, Scotland and Northern Ireland. Reported abstention rates, mean consumption and proportion of heavy drinkers were the same in Scotland and in England and Wales, but Northern Ireland had a greater proportion of abstainers and lower consumption amongst those who drank. Drinking was concentrated into fewer days in Scotland, so that 40% of all adult male drinkers in Scotland had drunk 8 units or more on one day, compared with 27% of English adult male drinkers.

v *Occupation, Social Class and Leisure*

Plant (1979) discussed the various reasons for the association of heavy drinking and certain occupations: availability of alcohol at work; social pressure; separation from normal social and sexual relationships (e.g. seamen, servicemen); freedom from supervision (which has been proposed as a contributing factor to the heavy drinking of doctors, lawyers and company directors). In the 1978 England and Wales survey, workers from the construction industry had the highest proportion of men drinking over 50 units/week (19% as opposed to 6% for the whole male population). Men from the drinks industry had the highest average per person consumption, 18% drinking over 50 units/week. In Scotland (Chick *et al.* 1981a) 25% of manual workers in an alcohol production firm admitted to drinking over 50 units/week. In that study it was also found that 15% of company directors and senior executives from a wide range of companies admitted to drinking in that

[1] 1 "unit" is designated as equivalent to 10 ml or 8 g of alcohol, i.e. ½ pint beer, a single measure of spirits (40% by volume), 4 oz of table wine, and so on

[2] Ahlstrom S (1979) Paper presented at the meeting of the Epidemiology Section, International Council on Alcoholism and Addiction, Tours

[3] Rachal V, Maisto S, Guess L & Hubbard R (1980) Paper presented at the meeting of the Epidemiology Section, International Council on Alcoholism and Addiction, Cardiff

range. A comparison of reported consumption with data from blood tests suggested that the directors minimized their reports more than the manual workers. In fact, the directors had a higher mean γ-glutamyltransferase (γ-GT) value. Drinking during the working day was as common in the work setting of the directors as that of the distillery workers.

By following through for two years new recruits to a brewery and, as a control, a biscuit factory, Plant demonstrated that brewery work attracts men who are already heavy drinkers as well as leading to an increased consumption amongst new recruits.

Earlier surveys found fewer heavy drinkers in the upper social classes than did recent surveys. By 1978, Wilson (1980b) found the same proportion of heavy drinkers in social class II (managerial and junior professional) as amongst manual workers. Drinking in the lower social classes is more concentrated. "Going out for a drink" is the commonest evening leisure activity of both men and women nowadays (Wilson, 1980b).

vi *The Relation between per Caput Consumption and Number of Heavy Drinkers*

A controversial issue is whether a social or economic influence which produces a rise in the average consumption in a population tends to increase the proportion of heavy drinkers (see Bruun *et al.* 1975). Clearly there is no necessary reason why this should be so. For example, if retailing forces were directed at a hitherto predominantly abstinent group and caused many to become light drinkers a rise in per caput consumption at national level would result without more individuals becoming heavy drinkers. One cannot predict statistically from per caput consumption to numbers of heavy drinkers, only empirically.

Where successive surveys in the same population are made against a background of increasing consumption the link between per caput consumption and prevalence of heavy consumption can be tested. Comparable surveys of national samples in the USA were conducted in 1964, 1966, 1969, 1970 and 1971, a period when per caput consumption was increasing at the rate of 30%/decade. The proportion of abstainers in the population did not change. The shift was towards somewhat heavier drinking by those already drinking and a greater number of individuals drinking, at least occasionally, at levels where they might be intoxicated (Room, 1974).

Between two surveys, in 1969 and 1976, Finland experienced a 67% rise in per caput consumption. There was a trivial rise in the proportion of the population drinking in the highest consumption category, but a greater proportion of drinking occurred on occasions when blood alcohol was likely to have exceeded 100 mg/100 ml (Simpura, 1978).

Cartwright *et al.* (1978) compared surveys carried out in south London in 1965 and 1974. The mean admitted consumption of respondents in the second survey was 47% greater than in the first. The proportion of individuals drinking over 50 units/week increased from 1·3% to 4%. However, the number of individual subjects in this category in 1974, because of the small size of the survey, was merely 10. Furthermore, different sampling frames were used in the two surveys.

In Scotland it is assumed that consumption has been rising throughout the 1960s and 1970s, though separate customs and excise figures are not available. In the UK as a whole, consumption rose continually throughout this period (Brewers' Society, 1980), and it is assumed that this applied to Scotland too. Nevertheless, Scottish surveys found the prevalence of those admitting to over 50 units/week to be unchanged: 7% in 1972 (Dight, 1976) and 6% in 1978 (Wilson, 1980a).

The survey is a blunt instrument, which leaves particularly ragged edges at the heavy end of the consumption distribution. A possible link between rising per caput consumption and proportion of heavy users cannot be regarded as proved or disproved by the above examples. General population survey data about heavy consumers are too unreliable. It would in any case be dangerous to extrapolate from the results of surveys in one culture to conditions in another culture. A more pressing question is whether or not there is a link between trends in availability and attitudes to drinking in a nation, as reflected in per caput consumption, and rates of harm from alcohol (see section 6).

3 The Relation Between Alcohol Consumption and Adverse Consequences

i *Collation Studies*

Correlation of per caput consumption with age-specific mortality rates across a number of countries or regions suggests a link between alcohol and cirrhosis (e.g. Schmidt, 1977a) and alcohol and cancer of the gastrointestinal tract (e.g. Knox, 1977). The method has also demonstrated a link between alcohol and deaths from road accidents and a negative link between wine consumption and death from ischaemic heart disease (St Leger *et al.* 1979).

ii *Health Hazards in the Individual Heavy Drinker*

Schmidt & Popham (1976) have reviewed the extensive international literature on morbidity and mortality of alcoholics. In the UK, Adelstein & White (1976) found a sample of alcoholics known to mental hospitals to have an over-all excess mortality of 2·2 to 1. As well as cirrhosis, suicide and accidental death, other conditions also contribute. Cancer, pancreatic and gastrointestinal disease and circulatory disorders are discussed elsewhere in this number. The raised mortality from bronchitis and pneumonia is thought to be due to the smoking habits and social decline of some alcoholics in hospital-identified populations. The raised rate of stroke death is mediated by high blood pressure (e.g. Kozarevic *et al.* 1980). Rates of disease obtained from a "clinic" population may be fallacious if applied generally, as they are biased by the factors that led to the patient attending hospital and so being identified. For example, the increased risk of suicide (Ritson, 1977) in alcoholics known to a psychiatric hospital reflects the fact that the initial presentation may have been emotional distress or depression. Alcoholics driven to attend clinics have usually suffered many reverses.

However, other factors probably also contribute to the relation between alcoholism and suicide. Young alcoholics tend to abuse other drugs. An underlying "depressive constitution" may contribute in some instances. Alcohol may cause depression pharmacologically (Whitlock & Evans, 1978). Recently it has become clear that alcohol and depression are related, not only in psychiatric clinic samples, but also in the general population (Weissman *et al.* 1980).

Factors such as social disruption and lower social class, which lead to referral to some types of clinic, may be why some and not all clinic samples of alcoholics have a raised prevalence of peptic ulcer. Community surveys do not show links between

heavy drinking and peptic ulcer. However, they are limited in that they usually detect few if any subjects admitting to drinking in the alcoholic range. In a review of 14 studies in this area and from a survey of relatively heavy-drinking distillery workers and company directors, I have concluded that on balance it is unlikely that alcohol causes peptic ulcers (Chick, in preparation).

Nevertheless, heavy drinkers identified in community surveys do also have an excess mortality. Among white male employees of the Chicago Western Electric Company, consumption (admitted) of 6 or more drinks a day was associated with a trebling of mortality. An excess mortality was still demonstrable after allowing for cigarette consumption and this applied to death from cancer and cardiovascular disease too (Dyer *et al.* 1980). These authors review mortality studies in other community-based cohorts, and note agreement with their own findings.

Peterson *et al.* (1980) invited a group of 48–49-year-old men from the general population to a screening clinic. Of the 41 who died in the initial 1–4 year follow-up, 16 were "heavy drinkers" confirmed by a raised γ-GT value that was unlikely to have been due to another cause (my analysis).

iii *Level of Drinking and Adverse Consequences*

A man who drinks 50 units/week (80 g/day), but concentrates it all into Friday and Saturday evenings, is clearly more at risk of injury or accidental death from drunkenness than if he spreads his drinking through the week. There is no evidence that this pattern puts him more or less at risk of damaging his liver (Schmidt, 1977b). However, it is controversial whether at that level of consumption he is "significantly" at risk of contracting cirrhosis.

The most important study of the quantity drunk by patients with alcoholic liver disease is that of Lelbach (1974). In 417 male alcoholics with reliable consumption data, he showed that quantity of alcohol consumed was related to severity of liver damage as determined by biopsy. All patients with cirrhosis reported drinking over 196 g/day. In two studies on defined populations in France (Bouches du Rhône and Ille et Vilaine), patients with ascitic cirrhosis were interviewed about their consumption (Péquignot & Tuyns, 1976; Péquignot *et al.* 1978). The same interview was given to a general population sample drawn from the electoral roll. Whereas 74% and 72% of the cirrhotics admitted to drinking over 80 g/day, only 20% and 14% of the general population did so. The relative risk (an index of "observed" to "expected" cases) is already 6 times greater at 40–60 g/day than at 0–20 g/day. At 60–80 g/day it is 14 times greater. Lelbach had no cases where consumption was <196 g/day: perhaps some cirrhotics who might have fallen into the lower-consumption category were excluded as "not providing reliable consumption data". One would expect in a population attending an alcohol clinic only to find heavy drinkers. On the other hand, perhaps Péquignot's estimates of his subjects' consumption were considerably minimized, a possibility he freely admits. Furthermore, as in most general population studies, the heavy drinkers not in hospital with cirrhosis may have been missed: in the Ille et Vilaine study, for example, the non-contact rate (males) was 18% and in the Bouches du Rhône study it was 34% (whole sample). Excessive drinkers, particularly, may not only refuse to be interviewed but also tend to be socially unstable and difficult to contact. A final caveat to interpreting Péquignot's finding that nearly a third of the male cirrhotics admitted to drinking <80 g/day is that "cryptogenic" cases were deliberately included: some of these may have had a non-alcoholic cause.

Saunders *et al.* (1981) reviewed the evidence that women develop alcoholic liver disease after a shorter and lighter exposure to alcohol than men. Péquignot's Ille et Vilaine study (though not the Bouches du Rhône study) shows a significantly greater proportion of women than men cirrhotics in the 21 40 g/day consumption category (my analysis). However, perhaps a sample of female cirrhotics contains a higher proportion of cases of non-alcoholic aetiology than does a sample of male cirrhotics.

iv *Other Mediators of the Relationship between Consumption and Consequences*

Cultural forces are an important influence on whether or not at a given consumption an individual has problems from his drinking. Within nations, higher social class has been shown to protect an individual from adverse social consequences. Between cultures, the meaning of drinking, the comportment expected of the drinker by his peers and the permissiveness or otherwise of the orthodox culture towards drunken behaviour influence the rate and type of social problems (Mäkela, 1978).

Surveys find only limited overlap between high consumption and problems from drinking. Not all "problem drinkers" are heavy consumers and vice versa. Style of drinking has some bearing: a measure of consumption in terms of amount drunk on each occasion improves predictions of who will have social problems, but by no means completely (Cartwright *et al.* 1978). Amongst "alcoholics" social problems accrue more readily amongst those with few resources (lower social economic groups). Death from liver disease is commoner in those from higher-status occupations, perhaps because they are not subject to the criticism, for example from employers, which intermittently or permanently puts a brake on the drinker in a less privileged position (Edwards *et al.* 1974).

Type of beverage is of little relevance for adverse health consequences, though it seems likely that spirits are important in the link between alcohol and cancer of the oral cavity and oesophagus (Wynder & Mabuchi, 1972).

Certain personality traits are predictive of harm from drinking. When cohorts of young men have been followed into adult life those who were impulsive, gregarious and rebellious as teenagers are more likely to have subsequent problems from drinking. Amongst working men, impulsivity, rebelliousness and carelessness predict problems even when consumption is held constant, as do early separations from mother or father (Chick, in preparation).

4 Alcohol and Longevity

Two recent papers describing prospective studies designed to examine risk factors in heart disease report that light drinkers (consuming <4 drinks/day) have a lower total mortality than abstainers (Blackwelder *et al.* 1980; Marmot *et al.* 1981).

The difficulties in interpreting these data are as follows. First, if heavy drinkers deny their drinking they will inflate the mortality of the non-drinkers. However, there is no evidence that very heavy drinkers are more likely to totally deny their drinking rather than just minimize it. Secondly, those who were already fatally ill might have become abstainers, because of their illness. Marmot *et al.* showed that this was unlikely to have introduced much of a bias in their sample, but Day (1978) in a longitudinal study of mortality found that the increased

mortality associated with abstention was confined to those who had become abstainers and was not found in lifetime abstainers.

A major difficulty is in the inference that *not* drinking is the cause of the slightly greater mortality in the abstainers. Personality characteristics, believed to be relevant to death from heart disease, have not been studied in abstainers: for example abstainers might contain a greater proportion of those driving, ambitious individuals prone to coronary disease than light drinkers.

More important is that (i) the effect noted by Marmot *et al.* is very small (the relative risk of abstainers is only 1·6 that of light drinkers); (ii) it apparently occurs with reported drinking as low as 1 unit (half a pint of beer) a week to 1 unit a day, which is a small dose if a direct pharmacological action is hypothesized; (iii) it disappears at fairly low levels of drinking (4 units/day); (iv) it is not demonstrable in the 40–49 year olds, only in the 50–64 year olds; (v) a similar effect is not demonstrable in the study already described of Dyer *et al.* (data analysed by me). Further specifically designed studies are now required.

5 Natural History of Problem Drinking

Epidemiologists have demonstrated that the problem drinker is not an individual irredeemably condemned but rather that people move into and out of problem drinking. Surveys record low rates of drinking problems after age 50. Drew (1968), examining the ages of alcoholics known to agencies, concluded that the prevalence of alcoholism in the population diminishes more rapidly with age than can be accounted for by mortality and successful treatment. One-half to one-third of respondents in two large US surveys who reported a given "problem" no longer reported that problem when re-interviewed 4 years later. Though some accrue a different alcohol-related problem in the meantime it is by no means inevitable (Clark & Cahalan, 1976). Öjesjö (1981) re-interviewed after a 15 year interval a general population cohort and found that of the 96 alcoholics identified originally 29 were now inactive or "much improved"; (25 had died). Work in this area has shown that, of the external influences, changes in social circumstances such as job and personal relationships are important.

6 Per Caput Consumption and Prevalence of Harm

A most pressing question is whether influences on mean consumption, such as availability of alcoholic beverages and prevailing attitudes to drinking, affect the prevalence of harmful consequences of drinking. Although this is related to the issue discussed above, of whether rises in mean consumption are linked with rises in proportion of heavy consumers, it is clearer to discuss each issue separately. It is, of course, the prevalence of harmful consequences that is practically more important than the numbers of heavy drinkers. Falling real price, increasing sales outlets and greater advertising, as already mentioned, may have had a role in increasing consumption since 1945. These factors are unlikely, however, to be sufficient explanations for the rise in prevalence of harm in this period. Other relevant changes in society include: increasing secularization, continuing weakening of the extended family and the blurring of sex roles, to name but a few.

Nevertheless, comparisons between nations and regions undoubtedly show covariation between per caput consumption and cirrhosis mortality. Furthermore, there is considerable evidence that within regions there is covariation over time between consumption and indices of harm (Bruun *et al.* 1975; Skog, 1980), though there is no example where a sudden decrease in per caput consumption has occurred that was not in wartime. This correlation is not seen so clearly in a recent report by de Lint (1981) of changes in the Netherlands in the period 1950–75.

Two of the examples cited above (section 2(vi)) of successive surveys in the same population provide data on changes in problem rates. In the Finnish study (Simpura, 1978), where per caput consumption increased by 67% from 1969 to 1976, an increase in the percentage of drinkers reporting problems also occurred: "Worrying about controlling my drinking" was reported by 15% of men in 1969 and 29% in 1976 (women, 4% and 14%); "social problems" were reported by 22% of men in 1969 and 32% in 1976 (women, 3% and 7%). However, the proportion having problems rose at every consumption level, meaning that either a certain amount of alcohol caused more problems in 1976 than in 1969 or, more likely, the threshold at which people admitted a problem had fallen.

The London comparison between 1965 and 1974 (Cartwright *et al.* 1978) also does not provide strong evidence. Although the authors found that an increase in admitted problems had accompanied the 47% rise in per caput consumption, 3 of the 5 problem items were rather trivial. Because of the small sample size in the 1974 study, only 2 individuals were identified who had had 4 items and none who had had 5.

It is not going beyond the current evidence to state that a change in per caput consumption is a marker of change in problem rates and, indeed, that recent trends (in particular increased availability) have made a contribution to rise in the indices of harm. What is not known is whether this association can be put into reverse, though it is widely advocated as the most expedient solution given the magnitude of the alternative task of educating whole populations to drink safely.

APPENDIX: SCREENING METHODS

i *Screening for Problems*

Questionnaires such as the Michigan Alcoholism Screening Test (MAST) (Selzer, 1971) and the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell *et al.* 1979) have shown that a variety of populations will admit, in a pencil and paper exercise, to a range of alcohol-related problems and symptoms. Some of the MAST items are rather trivial. The SADQ restricts itself to "dependence" items. Where skilled personnel are available reliability can be improved by direct interviewing (Chick, 1980). Decisions about cut-off points in terms of number and severity of problems are an arbitrary matter. The time-frame in such instruments is also arbitrary. Many of the MAST questions are phrased in the form "Have you ever . . .?", thus identifying "cases" who may now be "in remission".

ii *Screening for Heavy Consumption*

As in survey work, consumption is best elicited by taking a very recent period and asking the subject in detail about each drinking occasion during that period. He should be asked to recall his leisure activities and his daily routine for each day, to jog his memory. In countries where drinking tends to be relatively infrequent such as Norway, the past 4 weeks is a suitable period. In Britain, the last 7 days suffice. It has been shown that in working populations those who claim their last 7 days were atypically heavy tend to be reporting a trivial difference (Chick *et al.* 1981b). However, in hospital samples, patients whose life leading up to admission was far from normal should be asked to detail a "typical" week. If they do not have a typical week, a "typical heavy week" is the next best measure.

Informants, such as spouse, have not been shown to improve the accuracy of self-reported consumption. However, several blood tests may be abnormal in regular drinkers and return to normal, with a roughly logarithmic decline over 2–3 weeks, when drinking ceases. Mean red-cell volume (MCV) and γ-GT are the cheapest and most commonly available of the existing tests, though they lack power. Chick *et al.* (1981a) describe their use as indicators of heavy drinking in working men. Fifty per cent of men who admit drinking over 450 g (56 units) a week have a γ-GT of >50 iu (false positives about 15%) and 23–32% have a MCV of over 98 fl (false positives about 5%), after men with other causes of increased values, such as taking anti-convulsants or specific physical disorder, have been excluded. Raised MCV is commoner in heavy smokers and in men whose pattern of drinking is sustained rather than episodic.

The false-positive rates, when self-reported consumption is the criterion, are in part probably due to lying and minimizing. The crucial study, of the risk of having a raised value on either of these two tests in a population whose consumption is known with certainty to be slight, has yet to be conducted.

Of the more expensive tests which have been proposed, abnormal heterogeneity of transferrin is still being investigated (Stibler *et al.* 1979) and the ratio of α-aminobutyric acid to leucine is probably only useful in detecting alcoholic patients who have drunk heavily and very recently (Chick *et al.* 1981c). Phillips (1981) has measured alcohol content of a sweat patch which collects for up to 10 days. The fact that drinking is being monitored may alter habitual consumption, however, and clearly a degree of co-operation is required.

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SCREENING FOR PROBLEM DRINKERS AMONG MEDICAL INPATIENTS

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Summary

Among 275 patients aged between 18 and 65 admitted to general medical wards, 19.3 per cent were found to have a current alcohol-related problem and/or previous treatment for alcoholism. 13.2 per cent were newly identified cases, with men significantly outnumbering women. The house physician's history referred to alcohol consumption in 32 of 34 new cases but often underestimated consumption, adverse social problems and dependence symptoms. Laboratory markers were not sufficiently sensitive to be used as screening tests on their own.

Introduction

Treatment of patients with established alcoholism is often unsatisfactory and the importance of early detection is currently being emphasized [1]. Population screening has been advocated on the assumption that intervention will be more effective if cases are detected at an early stage. Alcohol-related problems are common among general hospital inpatients [2, 3] and this is one group for whom selective screening has been recommended [4]. The extent of the problem, however, means that treatment should be widely available and easy to administer. Cases should also be readily identified during their hospital admission, but there is evidence that in routine clinical practice doctors fail to record the drinking habits of many of their patients [5].

We are conducting a study on medical wards to determine the effectiveness of brief intervention in newly-identified problem drinkers. The treatment consists of a counselling session of approximately one hour's duration conducted by a nurse with training in the treatment of alcoholism; patients are also given a booklet informing them of the health hazards of alcohol and advising on safe levels of consumption and approaches to cutting down Similar counselling in general practice has been shown to have a significant effect in helping patients to stop smoking [6]. In this paper we report the detection rate obtained during the first six-month period using a screening

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interview. We have also examined the ability of the house physician's history and of two laboratory indices to detect the cases identified by our screening interview.

Subjects and methods

We studied a consecutive series of patients aged 18 to 65 admitted for at least 48 hours to one of four medical wards in the Royal Infirmary, Edinburgh. The wards, two male and two female, covered a wide range of medical specialties, including a service for gastro-enterological and liver disease. There were no admissions following attempted suicide as the hospital has a special poisons treatment unit for these patients.

A structured interview (available from the authors) of proven inter-rater reliability covering drinking habits, recent and previous medical history and social background was administered by the research nurse. Patients were excluded if they were of no fixed abode or if their mental state precluded a reliable history. Those who had attended a psychiatric unit because of an alcohol problem or who had been to four or more meetings of Alcoholics Anonymous were deemed to have had previous treatment and were not interviewed further. Patients were identified as having a current alcohol problem if they acquired two or more points according to the criteria listed in Table 1.

Two laboratory markers of alcohol consumption [7, 8] were examined. Mean corpuscular volume (MCV) was measured in all patients; serum gamma glutamyl transpeptidase (γGT) was measured in the identified cases only. The adequacy of recording alcohol-related problems in the medical notes of identified cases was assessed, the recorded drinking history being classified as either "quantitative", "descriptive", or "no record".

Results

Of 275 patients interviewed, 53 (19.3%) had a current alcohol problem or had received previous treatment for alcoholism. When the sexes were compared fewer females (11.1%) than males (27.1%) fell into one of these categories ($\chi^2 = 11.35$; $p < 0.001$). This distinction was accentuated when patients who had received previous treatment were excluded. Only four new cases were identified among the women (3.2%) whereas 30 new cases were discovered among the men (22.7%). This information is summarized in Table 2.

γGT was raised (>40 i.u./l) in 21 (62%) of the newly identified cases. MCV was elevated (>98 fl) in nine (26%) of these cases and in six (32%) of the 19 patients who had received treatment previously. Ten (4%) of the remaining patients also had a raised MCV: in four there was an obvious pathological basis other than alcohol; two patients had admitted regular alcohol consumption but not quite sufficient to warrant inclusion in the study; in

TABLE 1

Criterion		Points
Consumption*	More than 12 units in a day on 10 or more occasions in last year	1
	More than 50 units in typical week	1
	More than 12 units in 24 hours in typical week	1
Current medical problem	Present illness potentially alcohol related	1
	Present illness definitely alcohol related	2
	Weight problem due to alcohol	1
Medical conditions in past 2 years	Peptic ulcer aggravated by drinking	1
	Liver disease	1
	Accident due to drinking	1
Symptoms of dependence on alcohol	Restlessness	1
	Tremor	1
	Morning drinking	1
	Difficulty reducing consumption	1
	Hallucinations	1
	Seizure	1
Alcohol-related social problems in previous 2 years	Antisocial behaviour	1
	Problems at work (incl. absence)	1
	Domestic arguments	1
	Violence	1
	Family rupture, either threatened or actual	1
	Financial	1
	Police	1

*1 unit = 1 oz. of spirits, 1/2 pint of beer, or 1 glass of wine (i.e. approx. 8 g ethanol).

TABLE 2

Prevalence of problem drinking

	Current problem and/or previous treatment	Previous treatment	Newly identified cases
Females (n = 135)	15 (11.1%)	11	4/124 (3.2%)
Males (n = 140)	38 (27.1%)	8	30/132 (22.7%)
Total (n = 275)	53 (19.3%)	19	34/256 (13.3%)

the other four subsequent information strongly suggested excessive drinking. Patients with liver disease were more likely to be problem drinkers (χ^2 = 10.55; $p < 0.01$) but otherwise there was no association between case identification and medical diagnosis.

The medical notes referred to alcohol consumption in 32 of the 34 newly identified cases (Table 3). However, the quantity consumed as noted

TABLE 3

Drinking history of newly identified cases as recorded in medical notes

Record of consumption (n = 34)		Recorded adverse consequences (n = 29)	Recorded withdrawal symptoms (n = 21)
Quantitative	25	—	—
Descriptive	7	12	5
No record	2	17	16

by the house physician was often considerably less than that uncovered by the detailed interview. In the 25 patients for whom a quantitative record was noted the mean weekly consumption recorded was 51.9 units while the equivalent figure identified by the interview was 72.9 units. There was also an underestimation of adverse consequences of drinking and of symptoms of physical dependence.

Discussion

Reported rates of alcoholism among general hospital inpatients have ranged from nine to 55 per cent [2], but direct comparisons between studies cannot be made because of varying sampling methods and diagnostic criteria. Our study differs from most others in not including cases of attempted suicide and patients of no fixed abode, groups known to contain a high proportion of problem drinkers. Yet 19.3 per cent of our sample had a current alcohol-related problem or previous treatment for alcoholism, 13.2 per cent being newly identified cases. The greater prevalence among men is in keeping with previous reports but we were surprised to detect only four new cases of problem drinking among female patients. Women may be reluctant to admit their alcohol consumption because of the greater stigma attached to problem drinking among females and our questionnaire may have favoured the detection of males because several questions pertaining to work were included. However, among the patients with alcohol problems, a greater proportion of female patients reported previous treatment for alcoholism ($\chi^2 = 12.78; p < 0.001$); so these factors cannot entirely explain the low detection rate. In any case, to be suitable for treatment patients have to be prepared to acknowledge their problem. If they remain undetected after a detailed interview they are not likely to benefit from counselling.

One third of our newly identified cases had a normal γGT and three-quarters had a normal MCV. These findings support recent evidence that laboratory markers lack sensitivity as screening tests [7]. Many cases are detected by clinical interview, but are missed by blood tests. It is therefore encouraging that the house physicians' notes referred to the drinking histories in all but two of those cases we identified. The fact that this study was known

to be in progress may have alerted house physicians to look for alcohol problems with greater suspicion than usual. Also alcoholism is commoner in Scotland than in England, so it is possible that Edinburgh doctors are more aware of alcohol as an aetiological factor in illness than their London counterparts [5]. However, although our junior doctors are well-placed to identify problem drinkers at an early stage they underestimate consumption and miss important complications of drinking. More attention might be given to taking an accurate drinking history and this could be incorporated in routine clinical practice, especially in men. The alternative is a formal screening interview by a special worker. However, the value of either procedure depends on whether intervention is effective. We will report on this in a larger sample in the future.

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Problem Drinkers in Medical Wards: consumption patterns and disabilities in newly identified male cases

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Summary

One hundred and sixty-one male medical inpatients were identified as problem drinkers according to criteria previously defined. This paper describes the pattern of their drinking and the associated medical and psychosocial problems. Over half had been admitted with an illness not typically related to alcohol and a similar proportion reported levels of consumption which have previously been considered safe. Classical symptoms of dependence were uncommon but specific enquiry revealed a broad range of social problems related to alcohol. Recognition of this profile is necessary if problem drinkers are to be identified at an early stage and to benefit from counselling.

Introduction

Medical inpatients are known to have a high prevalence of alcohol problems. Reported rates vary widely according to the diagnostic criteria used and the nature of the hospital studied[1] but British figures show an impressive consistency with regard to male inpatients, indicating that just over a quarter have a current or previous alcohol problem.[2–6] The rates for women are lower and more variable, reflecting both women's lower consumption and greater reluctance to admit to alcohol problems. Several reports have described patients with advanced complications, particularly liver disease, and have stressed the need for earlier detection.[7–9] Saunders *et al.*[10] interviewed 156 patients with newly-diagnosed alcoholic liver disease. Thirty-five per cent claimed they had never been advised to reduce or stop drinking before their presentation with liver disease and only 22% had been referred to a hospital clinic for specific management of an alcohol problem. The failure to detect alcoholism at an earlier stage in its evolution has been attributed to doctors' neglect to ask the appropriate questions about drinking habits.[11] It has become apparent that many patients who are drinking to excess are admitted to a general hospital for an illness not classically related to alcohol abuse and their drinking will not be detected unless specific enquiries are made. Several alcohol-related illnesses develop insidiously over many years, during which time they remain asymptomatic. Screening and early detection have been advocated on the assumption that intervention will give the patient an opportunity to modify his drinking habits before irreversible physical complications have developed.

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We have conducted a study on medical inpatients to identify early problem drinkers who had at least a minimum of social support and to evaluate the effectiveness of nurse counselling on their subsequent alcohol-related problems. Those with previous treatment for alcoholism were excluded because we wished to define the characteristics of patients identified at an earlier stage than is usually the case. We have already reported on the effectiveness of counselling in this group.[12] In this paper we describe the pattern of drinking and the medical and psychosocial characteristics of a cohort of newly-identified male problem drinkers.

Subject and Methods

We studied patients aged 18 to 65 who had been admitted to one of four medical wards for at least 48 hours. The wards covered a broad range of medical specialities but there were no admissions following attempted suicide because it is the hospital's policy to treat these patients in a special unit.

Patients were excluded at the outset if they were of no fixed abode, if they were terminally ill, if their mental state precluded a reliable history or if they had already been referred to the psychiatry department. A nurse with experience in the treatment of alcoholism carried out a structured interview whose reliability had been established during a pilot study. Details of consumption were obtained by completing a drinking diary for the week prior to admission to hospital (or a 'typical' week if the previous week was atypical for any reason). The total weekly consumption and the maximum daily consumption during a typical week were recorded in units of alcohol (1 unit=8 g alcohol). Symptoms of dependence, social problems related to alcohol, previous medical history, family and social background were recorded in a standardized manner. The main current medical diagnosis was noted in each case and classified according to its apparent relationship to alcohol. Definitely alcohol-related illnesses include cirrhosis, alcoholic hepatitis, delirium tremens, Wernicke's encephalopathy and alcoholic cardiomyopathy. Potentially alcohol-related illnesses included upper gastro-intestinal disorders, gout, unspecified liver disease, and unexplained peripheral neuropathy.

Patients were identified as problem drinkers if they acquired two or more points according to our previously defined criteria[12] which are shown in Table 1. To be included in the study, they also had to satisfy two of the following criteria: currently employed or employed for 6 of past 12 months; married; has a 'confidant' or close friend; lives with at least one other person. Those who satisfied these criteria completed the 60 item General Health Questionnaire.[13] Mean cell volume (MCV) and gamma glutamyl transpeptidase (gamma GT) were measured as laboratory markers of alcohol consumption.

During the first 6 months of screening 27% of men and 11% of women were identified as having a current alcohol problem or had received previous treatment for alcoholism.[6] When those with previous treatment were excluded 23% of men and 3% of women were regarded as newly identified problem drinkers; in view of the low yield among women the study was subsequently confined to male patients.

Results

The screening interview showed that 731 men eligible for inclusion were admitted during the course of the study of whom 161 (22%) met our diagnostic criteria. The mean age of the problem drinkers (42.4 years; SD 12.5) was significantly lower than the mean for the other 570 patients (48.6 years; SD 12.3) ($F=31.7$; $p<.0001$) and the mean MCV was significantly higher (92.8 fl; SD 6.0 versus 89.2 fl; SD 7.4); ($F=31.7$; $p<.0001$). In 15% of the problem drinkers and 6% of the other patients the MCV was above 98 fl. The gamma GT was above 40 i.u./1 in 52% of problem drinkers but was not routinely measured in the others.

Alcohol Consumption, Withdrawal Symptoms and Social Problems

One hundred and forty-one of the problem drinkers (87.6%) had drunk alcohol during the 7 days before admission. The remaining 20 reported that they would normally have had a drink but had not because of illness or some other factor. One hundred and fifty-two (94.4%) reported that they normally drank alcohol more than once weekly; 67 (41.6%) drank every day. Heavy drinking on a single occasion was common, with 126 (78.3%) admitting that they had consumed more than 14 units of alcohol (7 pints of beer or its equivalent) in 24 hours on at least 10 occasions during the previous year. Forty-one (25.5%) admitted drinking more than 28 units in 24 hours on at least 10 occasions during the previous year. The mean consumption

Table 1. *Criteria for Inclusion as a Problem Drinker*

		Points
Consumption	More than 14 units* in a day on 10 or more occasions in last year	1
	More than 50 units in typical week	1
	More than 12 units in 24 hours in typical week	1
Alcohol-related problems		
Current medical problem	Present illness potentially alcohol-related	1
	Present illness definitely alcohol-related	2
	Weight problem due to alcohol	1
Medical problems in the past 2 years	Peptic ulcer aggravated by drinking	1
	Liver disease due to alcohol	1
	Accident due to drinking	1
Alcohol-related social problems in past 2 years	Antisocial behaviour	1
	Problems at work (inc. absence)	1
	Domestic arguments	1
	Violence	1
	Family rupture—threatened or actual	1
	Financial	1
	Police	1
Dependence on alcohol in past 2 years	Difficulty in reducing consumption	1
	Restlessness without alcohol	1
	Tremor (more than 1 day per week)	1
	Morning relief drinking (more than 1 day per week)	1
	Hallucinations	1
	Withdrawal seizure	1

*1 unit = 1 oz of 40% spirits, ½ pint of beer, 1 glass of wine, etc. (i.e. approx. 8 g ethanol).

during a typical week was 68.3 units (SD 43.3) and the mean maximum daily consumption in a typical week was 19.7 units (SD 10.8). Of the 570 patients who did not satisfy our criteria for problem drinkers 352 drank regularly, at least once weekly, and their consumption figures were also recorded. The mean weekly consumption of these non-problem drinkers was 16.3 units (SD 11.3; mode 12 units) and the mean maximum daily consumption in a typical week was 7.1 units (SD 4.5; mode 6 units). Figures 1 and 2 show the distribution of weekly and maximum daily consumption figures for both the problem drinkers and non-problem drinking group.

It can be seen that consumption was distributed continuously, with no evidence of bimodality. The groups overlap to some extent and a substantial proportion of the problem drinkers reported levels of consumption which have previously been regarded as safe. Indeed 50% of the problem drinkers reported a typical weekly consumption within the limit of 56 units suggested by the Royal College of Psychiatrists.[14] The criterion which separated the problem drinkers from non-problem drinkers with the lowest number of mis-classified cases was a weekly consumption above 39 units. Only 5% of non-problem drinkers were drinking above this level although 25% of the problem drinkers reported that they drank 39 units or less. When similar calculations were carried out on the maximum daily consumption figures the equivalent criterion which separated the two groups was a consumption of over 13 units. Seven per cent of non-problem drinkers reported a maximum daily consumption above this figure while 24% of the problem drinkers claimed 13 units or less.

Symptoms of dependence during the previous 2 years were reported by less than half the group. Seventeen per cent had experienced difficulty

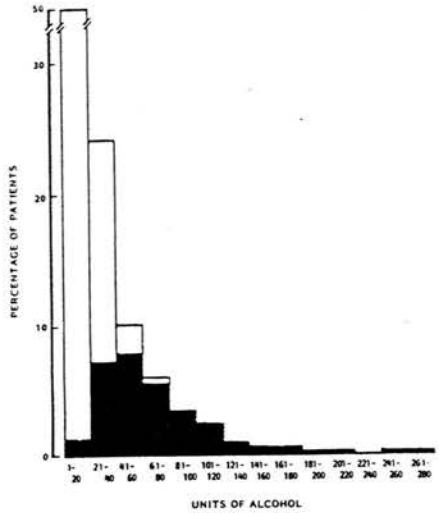

Figure 1. *Mean weekly consumption:* n=*161* ■ *Problem drinkers;* n=*352* □ *Non-problem drinkers.*

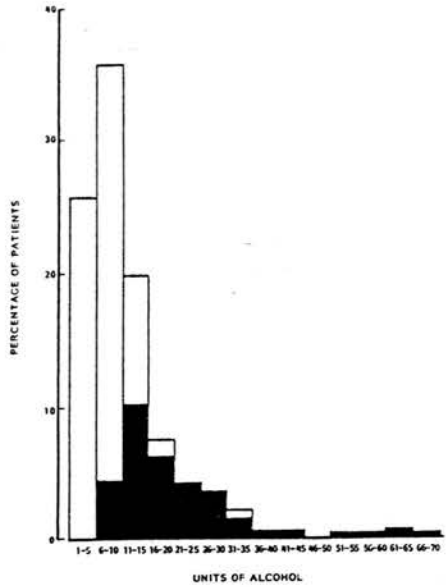

Figure 2. *Mean maximum daily consumption in typical week.* n=*161* ■ *Problem drinkers;* n=*352* □ *Non-problem drinkers.*

reducing consumption, 12% reported restlessness or irritability if they did not have a drink and 9% reported regular morning relief drinking. Withdrawal fits and hallucinations were reported by 5% and 3% respectively. Social problems related to alcohol were commoner; 25% reported domestic arguments, 19% reported difficulty preventing drunkenness and 17% had been absent from work because of alcohol.

To determine whether consumption was related to dependence symptoms and social problems the problem drinkers were divided into three groups according to their mean weekly consumption: 0–40 units; 41–80 units and 81 or more units. Those in the highest consumption category were more likely to have experienced severe tremulousness ($p<.001$), otherwise there were no differences between the groups with regard to dependence symptoms. The high consumption group were more likely to report difficulty preventing drunkenness ($p<.05$), family rupture ($p<.025$) and a family history of alcoholism among first degree relatives ($p<.01$). They were also more likely to be divorced, separated or widowed ($p<.01$). Weekly consumption was significantly correlated with MCV ($r=0.25$; $p<.001$) but not with gamma GT.

Associations with maximum daily consumption were calculated by dividing the problem drinkers into two groups: those with a maximum daily consumption of 1 to 15 units and those with a maximum daily consumption of 16 or more units. The groups did not differ with regard to any of the dependence symptoms. The higher consumption group were more likely to have had absences from work ($p<.025$), less likely to be in a technical, managerial or professional job ($p<.025$) and less likely to be responsible for other people at work ($p<.025$). Maximum daily consumption correlated weakly with MCV ($r=0.13$); ($p<.002$) but not gamma GT.

Medical Illness

The medical diagnostic categories of the problem drinkers are shown in Table 2 with the diagnoses of the other patients given for comparison. The groups differed significantly ($p<.001$) with regard to the distribution of diagnostic categories. The problem drinking group contained proportionately more patients with liver, upper gastro-intestinal and respiratory disorders and fewer with cardiovascular disorders. We did not, however, record smoking habits which may have accounted for some of these differences. In 43 of the problem drinkers (26.7%) the medical illness was considered to be definitely alcohol-related; in 30 (18.6%) it was potentially alcohol-related while in 88 (54.6%) it was definitely not alcohol-related. Fifty (31.1%) considered themselves to have a weight problem due to alcohol.

Table 2. *Medical Diagnostic Categories in Problem Drinkers and Others (percentages in brackets)*

	Problem drinkers (n=161)	Other patients (n=570)
Myocardial infarction	28 (17.4)	117 (20.5)
Other cardiovascular disorders	22 (13.7)	156 (27.4)
Liver disorders	18 (11.2)	18 (3.2)
Upper gastrointestinal disorders	35 (21.7)	68 (11.9)
Lower gastrointestinal disorders	6 (3.7)	23 (4.0)
Respiratory disorders	18 (11.2)	41 (7.2)
Peripheral neuropathy	8 (5.0)	21 (3.7)
Cerebrovascular disorders	5 (3.1)	26 (4.6)
Renal and urogenital	10 (6.2)	43 (7.5)
Locomotor	6 (3.7)	20 (3.5)
Blood disorder	1 (0.6)	7 (1.2)
Metabolic	3 (1.9)	23 (4.0)
Psychiatric	1 (0.6)	4 (0.7)
No diagnosis	0 (0.0)	3 (0.5)

Table 3. *Comparison of Problem Drinkers whose Illness was Alcohol-related with those whose Illness was not Alcohol-related (numbers in brackets)*

	Alcohol-related			Not-alcohol related				
	Mean	SD	*N*	Mean	SD	*N*	*F*	*p*
MCV (fl)	94.5	6.6	(70)	91.5	5.0	(88)	10.70	0.0013
Gamma GT (i.u./l)	236.9	459.0	(68)	68.2	109.5	(85)	10.73	0.0013
Age (years)	41.5	12.6	(73)	43.2	12.4	(88)	0.75	NS
Weekly consumption (units)	69.4	41.1	(73)	67.5	45.3	(88)	0.076	NS
Maximum daily consumption (units)	18.8	10.1	(73)	20.4	11.4	(88)	0.867	NS

During the previous 2 years, 27 (16.8%) had experienced peptic ulcer symptoms aggravated by alcohol, 39 (24.2%) had had alcohol-related liver disease and 11 (6.8%) had had an accident related to drinking.

Comparisons were made between problem drinkers whose current illness was definitely or potentially related to alcohol and those whose illness was definitely not alcohol-related. Those with an alcohol-related illness were more likely to have experienced severe tremulousness ($p<.05$) but otherwise there were no differences between the groups on any other dependence symptom or social problem. From Table 3 it can be seen that the alcohol-related illness group had higher values for MCV and gamma GT. The groups were similar with regard to their reported weekly consumption and maximum daily consumption.

Psychiatric Morbidity

The 60 item GHQ was completed by 155 problem drinkers. Fifty-five (35%) had a score above 11, this being the recommended cut-off point to identify probable psychiatric morbidity. When the scores on the 30 item version were derived from the larger version 48 (31%) obtained a score above 4. Scores on both versions correlated significantly with total social problem score (GHQ 60, $r=0.20$; $p<.01$; GHQ 30, $r=0.18$; $p<.015$) and with the total alcohol dependence score (GHQ 60, $r=0.31$; $p<.001$; GHQ 30, $r=0.26$; $p<.001$). There were no significant associations between GHQ scores and weekly or maximum daily consumption.

Discussion

Physicians and general practitioners are well placed

to identify patients with alcohol problems and to advise them to modify their drinking habits or to refer for specialist treatment. But early recognition requires that patients are asked about a broad spectrum of problems. The criteria used in this study included not only data on consumption, dependence symptoms and physical ill-health but also a wide range of social problems related to alcohol.

Previous studies,[4,15] like our own, have relied partly on consumption figures to identify problem drinkers. However there is no generally accepted level of consumption below which drinking can be considered entirely safe. A recent survey[16] demonstrated a wide variation of opinion even among those who are considered expert in this field and a report from the Royal College of Psychiatrists[14] suggested that an intake equivalent to 56 units weekly would constitute a reasonable guideline for the upper limit of safe drinking. This may be a serious over-estimation. Fifty per cent of our problem drinkers reported weekly consumption levels within this figure, but nevertheless qualified for inclusion when other factors were taken into account. Consumption may be under-reported even when information is recorded in a standardized manner by a person experienced in the assessment of alcohol problems. It is also possible that some of our identified patients had been drinking more heavily in the past but had reduced their consumption in the wake of declining health or financial difficulties. There was some overlap in reported consumption between the problem drinkers and those who drank regularly but did not report problems and who therefore did not qualify for our trial of counselling. The best separation between the groups was achieved at a level of 39 units weekly. It was unlikely in this medical inpatient population that anybody drinking above this level would not have alcohol-related problems. Only 5% of the non-problem drinkers were drinking more than this but it must be emphasized that 25% of the problem drinkers reported a weekly consumption of 39 units or less. Weekly consumption was one of the criteria we used to define problem drinkers but the figure we used was over 50 units. It is clear that many patients had problems related to alcohol even though they reported consumption below our stipulated level. In this context it is interesting that general practitioners tend to recommend a much lower limit for healthy drinking, the mean figure reported in a recent study being 18 units per week for men.[17]

Classical symptoms of dependence were uncommon in our patients and their prevalence was intermediate between that observed in a community sample of drinkers and that seen in patients attending a psychiatric hospital clinic for alcohol problems.[18] This finding confirms other work showing that classical symptoms of dependence develop relatively late in a drinking career.[18] Although it is important to enquire about dependence, a doctor should not be misled into believing that alcohol problems are absent if a patient does not report such symptoms.

Over half our patients had been admitted to hospital for an illness which was not related to alcohol, an observation which is similar to that described by other writers.[5,15] Patients whose illness was not alcohol-related reported levels of consumption which were just as high as those whose illness was related to alcohol but the latter group had significantly higher values for mean corpuscular volume and gamma glutamyl transpeptidase. These findings support the view that some individuals might have an enhanced tissue susceptibility to the harmful effects of alcohol. Physicians have realized for a long time that the duration of heavy drinking necessary to cause physical damage varies greatly between individuals. Attention has been directed to other risk factors, including genetic markers, and there is evidence that various HLA antigens are important aetiological factors as far as alcohol liver disease is concerned.[19]

We used the General Health Questionnaire to obtain an estimation of the level of psychiatric morbidity in view of previous claims that many patients with advanced physical complications from alcohol have a primary psychiatric illness which might have led to the development of heavy drinking. Using the recommended cut-off points we found a prevalence of 35% with the 60-item version and 31% with the 30-item version. These are considerably lower than the figures reported from a group of patients with liver disease[20] but similar to estimates of psychiatric morbidity in other groups of physically ill patients assessed using a standardized psychiatric interview.[21,22] The patients studied by Ewusi-Mensah *et al.*[20] probably had more advanced disease than the majority of patients in our study and we believe that the higher prevalence of psychiatric morbidity observed in other studies is likely to have been due to the physical and social consequences of alcohol abuse rather than an aetiological factor in the development of heavy drinking.

Conclusions

This report describes a wide profile of alcohol-related problems in a group of medical patients identified at an earlier stage than is usual in clinical practice. Our observations show that problem drinking can occur in the absence of admitted symptoms of dependence and at levels of admitted consumption lower than those which are generally considered harmful. The patient may not be in hospital primarily because of a classically alcohol-related illness and is not especially likely to admit to psychiatric symptoms. In nearly half the cases there will be no elevation of MCV or gamma GT. However an enquiry into the recent consumption pattern during a typical week and areas of health and social functioning commonly affected by alcohol may reveal whether his drinking is causing problems. At this early stage we have shown that a nurse offering brief counselling can have a therapeutic effect,[12] making it all the more important that medical and nursing staff should be familiar with the profile of problems.

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Occasional Survey

MEDICAL ADMISSIONS IN MEN: THE RISK AMONG DRINKERS

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Summary Information on alcohol consumption was elicited by the same method from men in a general population survey and from male medical inpatients in a hospital serving that population. A measure of risk controlling for age, the logarithm of the odds ratio, showed that for liver disorders, upper gastrointestinal disorders, myocardial infarction, other cardiovascular disorders, and respiratory disorders, rising consumption of alcohol was related to increased risk of hospital admission relative to abstention. The risk of admission for the remaining heterogeneous category of disorders was lower than that for abstention, perhaps reflecting the effect of chronic illness on drinking habits, and also suggesting that the link between alcohol consumption and medical diagnoses is not simply due to greater frankness about drinking in hospital inpatients.

INTRODUCTION

AWARE of the toll of harm from alcohol, the medical profession in Britain has suggested levels for what might constitute safe alcohol consumption. Estimates for men have varied from 56 units per week (80 g ethanol per day)[1] to 18 units per week.[2] (A unit of alcohol has come to mean 8–9 g ethanol, equivalent to half a pint of beer, a single measure of spirits, a glass of table wine.) Such estimates have to be qualified by the pattern of drinking and by whether the subject is likely to be involved in any skilled or dangerous activity—for example, driving.

Data on the relative risks of physical illness associated with different consumption levels have become available only recently. Longitudinal studies noting drinking habits at entry to the study have found alcohol consumption to be associated with excess mortality; the level at which the association becomes significant is about 30–40 units per week. The strength of the association is reduced if smoking is taken into account.[3-6] Cross-sectional studies to determine morbidity risks for certain illnesses compare consumption reported by patients who have the disorder with that reported by general population controls. Using this method Pequignot and his colleagues found that the relative risk of ascitic cirrhosis was raised at levels of consumption as low as 16–31 units per week, the relative risk in this consumption category being three times that of abstainers.[7] This widely quoted study has probably led to some of the more conservative estimates of safe limits. However, a systematic bias towards more frank reporting in one group than the other would affect the relative risk. In particular, relative risk would appear to increase at lower levels if the hospital patient tended to admit more of his drinking than a subject interviewed in a general population survey. The fear that the hospital staff might disapprove of his drinking might be offset by the importance of being honest when health is in question, an incentive that a control subject in a general population survey does not have.

Our study was designed to compare reported alcohol consumption in male medical inpatients with that reported by a community sample, and to determine the relation between alcohol consumption and various medical diagnostic categories by means of the odds ratio, a measure of association approximately equivalent to relative risk. In an attempt to assess whether being a hospital patient itself increases the readiness to admit alcohol consumption, the study reports on a group of patients with miscellaneous disorders in which there is no prior reason to suppose that alcohol has an aetiological role.

SUBJECTS AND METHODS

In 1978–79 a representative sample of homes in the Edinburgh area was drawn from the electoral register and individuals selected at random from these homes were approached.[8] 738 men aged 18–65 years were thus sampled. 21% refused to be interviewed and 7% could not be contacted, leaving 532 men who were interviewed. Consumption data were elicited in a standard manner by trained interviewers, who asked the subject to recall his activities in the previous 7 days and in particular his drinking, which was recorded in detail in units of alcohol.

In 1980, 1274 consecutively admitted men aged 18–65 years in medical wards in the Royal Infirmary, Edinburgh, were screened in connection with a study of counselling for newly identified problem drinkers. This study and the characteristics of the patients have been described elsewhere.[9,10] No self-poisoning patients were treated in the wards we sampled. We excluded men discharged within 48 h of admission, those of no fixed address, those with terminal illnesses or too ill to give an interview, men who were known from their admission case-notes to have had previous treatment for alcohol problems, and men already referred in the course of their stay to the psychiatric department. Consumption data were elicited by the same method as used in the general population study: patients were asked to describe their consumption in the 7 days before admission. If that had been an abnormal week they described a "typical" week. The principal and secondary diagnoses made by the treating physician were noted. A patient with two diagnoses in different diagnostic categories was given a separate entry in the tables of results for each diagnosis. A category of heterogeneous disorders included all diagnoses not covered by the other categories; a small number of alcohol-related diagnoses, such as delirium tremens, alcoholic fits, or neuropathy,

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TABLE I—PERCENTAGE OF MEN IN DIFFERENT CATEGORIES BY AGE

	17–30 yr		31–50 yr		51–65 yr	
—	Patients (n = 100)	Survey (n = 180)	Patients (n = 270)	Survey (n = 215)	Patients (n = 354)	Survey (n = 137)
Abstainers*	5	2	4	2	6	7
< weekly	15	13	19	13	23	20
1–5 units/wk	3	16	8	22	12	20
6–10 units/wk	11	11	9	16	8	15
11–20 units/wk	15	19	19	19	18	18
21–50 units/wk	30	27	21	20	20	12
⩾51 units/wk	18	13	17	8	9	7
Known problem drinkers†	3	..	3	..	3	..
MEAN ± SE IN REGULAR DRINKERS (DRINKING AT LEAST WEEKLY)						
Maximum daily consumption (units)	14·1 ± 1·0	12·0 ± 0·7	11·5 ± 0·6‡	8·3 ± 0·5	9·6 ± 0·6‡	6·4 ± 0·6
Weekly consumption (units)	34·9 ± 3·9	27·6 ± 2·1	36·3 ± 2·6‡	18·8 ± 1·5	26·7 ± 2·4	18·8 ± 2·1

*No alcohol for at least 1 yr excluding (in patients) those who stopped because of problems.
†Had treatment for alcohol problems in the past, or stopped drinking for more than 1 yr because of harm. Not known for survey subjects.
‡Significantly greater than controls' mean ($p < 0.01$)

are not included in that category or in the report, since we wanted the category to represent disorders in which there was no prior reason to implicate alcohol. Thus, data are given here on 724 patient-diagnoses.

To assess the association of alcohol consumption with each diagnosis the odds ratio was used as a measure of risk;[11] the ratio of cases to controls (ie, survey subjects) among those drinking at a given level is compared with the ratio of cases to controls among abstainers. Logistic linear analysis was carried out, allowing a separate assessment as independent variables of age and consumption, and their interactions. This method allows tests of significance and of whether the relations found are linear or non-linear.

To avoid veiling a possible association between alcohol consumption and disease, we omitted from the abstainer category (and from the whole analysis) patients who said they had stopped drinking because alcohol had caused them illness or because of a drinking problem. Only 1 abstainer in the survey population who gave ill-health as his reason for having become an abstainer.

RESULTS

Table I shows the distribution of drinking in patients and the general population sample. Mean consumption and consumption on the heaviest day in those who drank at least weekly tended to be greater in patients than men in the population sample, especially in the older age groups.

TABLE II—ODDS RATIOS RELATIVE TO ABSTENTION FOR INCREASING LEVELS OF ALCOHOL CONSUMPTION

—	Liver	Upper GI	MI	Respiratory	CVD	Other
n	37	110	143	73	188	169
Alcohol consumption (Variate: units/wk; model 3)	1·03	1·02	..	..	..	..
Alcohol consumption (category; model 1)						
0 in prevous wk	0·73	1·18	3·01	4·02	3·06	1·38
1–5 units/wk	0·92	0·41	1·04	0·85	0·42	0·32
6–10 units/wk	0·99	0·76	1·21	0·71	1·63	0·45
11–20 units/wk	1·30	0·89	1·93	2·63	1·85	0·75
21–50 units/wk	2·16	1·01	2·19	4·17	3·04	0·80
⩾51 units/wk	8·13	3·10	3·18	4·32	2·22	0·85

GI = gastrointestinal; MI = myocardial infarction; CVD = cardiovascular disease except MI.

Table II shows the risk associated with increasing alcohol consumption for the various diagnostic categories we used and table III the logarithm of the risk. The risk is expressed relative to the risk for abstainers (no alcohol in the past year or more); thus, the risk for abstainers is 1 ($\log = 0$). Age has been controlled. Data on the category of lower gastrointestinal disorders are omitted because of the small number (26) in that category. The association with alcohol was significant and positive in all categories except the heterogeneous category. The risk of a hospital admission rose with increasing consumption. However, for heterogeneous diagnoses, though there was a significant association between alcohol consumption and being a patient in that category, the risk was lower through the range of those drinking in the past week than for abstainers.

The log-linear analysis did not reveal any significant age by alcohol consumption interactions.

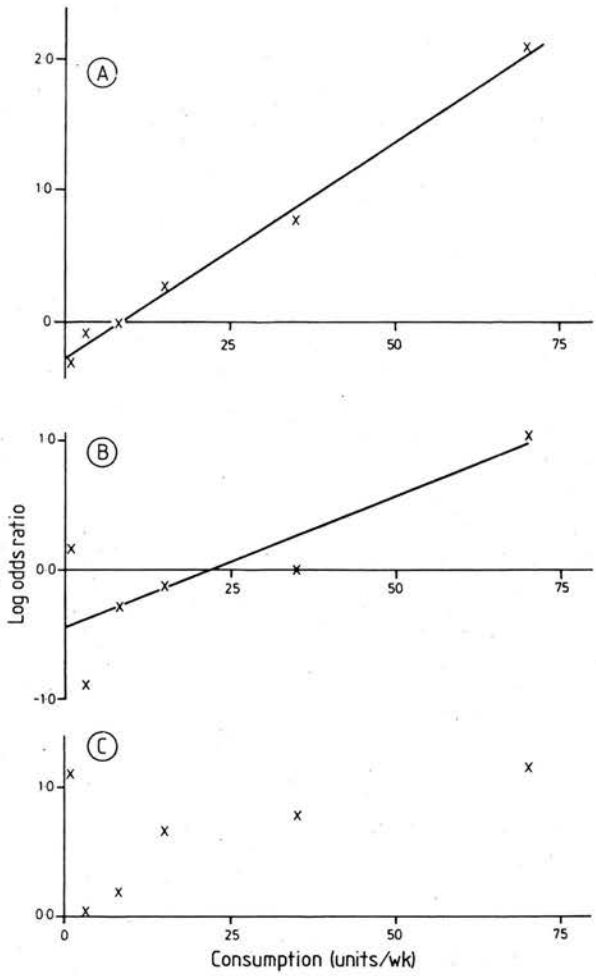
The relation between illness and alcohol consumption was adequately fitted by a linear term only for liver disorders and upper gastrointestinal disorders (see figure). For liver disorders, there were (non-significant) deviations from linearity with estimates indicating a risk lower than that of abstainers at consumption of less than 11 units per week (figure). For upper gastrointestinal disorders, reduced risk was found at consumption levels between 1 and 21 units per week, with the risk becoming steeply positive about that level (figure).

Linearity could not be shown in the data relating alcohol consumption to the other diagnostic categories used. For

TABLE III—LOGARITHMS OF ODDS RATIOS RELATIVE TO ABSTENTION FOR INCREASING LEVELS OF ALCOHOL CONSUMPTION (AND STANDARD ERRORS)

	Liver	Upper GI	MI	Respiratory	CVD	Other
n	37	110	143	73	188	169
Alcohol consumption (variate: units/wk; model 3)	0·033 (0·006)	0·020 (0·004)	..	..	..	..
Alcohol consumption (category; model 1)						
0 in previous wk	−0·313 (1·255)	0·166 (0·536)	1·101 (0·507)	1·391 (0·801)	1·117 (0·472)	0·319 (0·410)
1–5 units/wk	−0·079 (1·151)	−0·899 (0·579)	0·040 (0·518)	−0·160 (0·875)	−0·870 (0·553)	−1·138 (0·454)
6–10 units/wk	−0·012 (1·186)	−0·268 (0·588)	0·193 (0·541)	−0·344 (0·951)	0·487 (0·493)	−0·796 (0·458)
11–20 units/wk	0·262 (1·131)	−0·111 (0·531)	0·659 (0·508)	0·967 (0·801)	0·614 (0·476)	−0·283 (0·415)
21–50 units/wk	0·772 (1·102)	0·014 (0·531)	0·785 (0·521)	1·429 (0·785)	1·113 (0·468)	0·223 (0·411)
⩾51 units/wk	2·096 (1·080)	1·131 (0·528)	1·157 (0·555)	1·463 (0·823)	0·796 (0·532)	−0·160 (0·454)
p*	<0·001	<0·001	<0·02	<0·001	<0·001	<0·001

*Of consumption/diagnosis relation with age controlled; difference between residual deviances of models fitted, first with alcohol and age both as factors, then with age alone (referred to chi-square with 6 degrees of freedom).



Fitted log (odds ratio) for liver disease (A), upper gastrointestinal disease (B), and myocardial infarction (C).

myocardial infarction all log odds-ratio estimates (tables II and III) were positive compared with the abstainers (figure).

DISCUSSION

Most of the patients who drank reported a weekly consumption of over 10 units, so we cannot make firm statements about the relations between disease and alcohol consumption below 10 units per week. However, there was an increased risk of disease associated with the lowest category of drinking (less than weekly) in all categories except liver disorders; it was particularly high for myocardial infarction, other cardiovascular disorders, and respiratory disorders. There are several likely reasons why the numbers of patients in this lowest consumption category may be inflated. Consumption in this category could range from just 1 drink in the previous year up to several drinks once a fortnight. It is likely that in the hospital sample this group included men who had been advised or thought it wise to drink very little because of their illness. Also, illness prevents people from going out, and most drinking by Scottish men is done outside the home. The chronically ill perhaps find that alcohol disagrees with them, or they cannot afford to drink.

One objection to the case/control design we and Pequignot et al[7] used is that hospital cases might be more frank about their drinking than general population subjects. The finding of a reduced risk associated with alcohol consumption in the category of heterogeneous diagnoses (arising out of a lower than expected number of patients admitting drinking at all levels—except that of less than weekly drinking) suggests that being a patient in hospital is not by itself associated with higher admitted consumption.

The odds ratio we used is roughly equivalent to relative risk, and we can therefore compare our findings for liver disorders with those of Pequignot et al.[7] They found for cirrhosis that the relative risk rose exponentially, each gram of alcohol per day increasing the log risk by 0·01473. Converting their measure to ours (9 g = 1 unit) their model coefficient becomes 0·0436/unit/week, comparable and within 2 SE of our finding for our category of liver disease of 0·033 for the increase in log risk for 1 unit per week.

The finding that upper gastrointestinal disorders are strongly associated only with consumption of 21 units per week or more accords with clinical experience; the more common disorders included in this category—acute gastritis, pancreatitis, and acute upper gastrointestinal bleeding—are all linked to heavy session drinking.

It is not surprising that respiratory disorders are linked with alcohol consumption in this study. Chest illness is a major cause of death in alcoholics.[12] Heavy drinking and smoking are, of course, linked. For myocardial infarction too, we do not have data to control for smoking. General population cohort studies[3,13] and a case-control study[14] have found that those who consume low amounts of alcohol are less likely to be admitted to hospital or to die from myocardial infarction than abstainers. Heavy drinking, however, is associated with an increased risk. Among patients diagnosed alcoholic the mortality from ischaemic heart disease[12] and risk of hospital admission for myocardial infarction are raised.[15] An association between ischaemic heart disease and heavy drinking has been found in some[3-5,16,17] but not other[18,19] cohort studies. The U-shaped curve for myocardial infarction (figure) presents less than weekly consumption as the high-risk consumption pattern in our study. However, this consumption category probably included patients who were drinking rarely because they had a chronic illness. We did not find that drinking in the moderate range (1–20 units per week) was associated with a risk of myocardial infarction less than that of abstainers. However, subjects abstinent for health reasons had been systematically removed from our abstainer group in the hospital sample. In other research on this topic, that has not always been possible. Previous cohort studies have also found a link between alcohol consumption and increased mortality from other cardiovascular diseases, particularly stroke. We found positive odds ratios in our category of other cardiovascular disease at the level 6–10 units and above.

If we had included subjects treated for alcohol-related problems and abstainers who had stopped drinking because alcohol caused them trouble or illness, the links found between alcohol and disease would have been even stronger than those reported. We have found a link between hospital admission for medical diagnoses and a personal history of heavy drinking. We can only suggest, not conclude, that alcohol itself is having a pathological effect. The lifestyle of the drinker, particularly his smoking habits, must be considered. We are unable to validate any of the safe limits proposed by others. Thresholds did not emerge from our data, but for each of the alcohol-associated diagnostic categories increased risk was present at 21–50 units per week. Thus, our work supports the Royal College of

Psychiatrists' recommendation of 21 units per week[20] as the upper end of the almost certainly safe zone of consumption.

We must move away from the notion that alcohol is a safe drug except for those few unfortunates who become "addicts". The graded increase in risk of social and personal harm as consumption rises[21] is paralleled by the increasing risk of bodily harm.

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Orthopaedic trauma in men: the relative risk among drinkers and the prevalence of problem drinking in male orthopaedic admissions

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Key words: Problem drinking; Orthopaedic trauma; Relative risk

Admissions to an acute male orthopaedic ward ($n=369$) were asked about their accident, their alcohol consumption, and alcohol-related problems in the past 2 years. Comparing their consumption with that of males from a community survey revealed an increased risk of orthopaedic admission in drinkers consuming 21 units of alcohol/week or over, relative to drinkers consuming less than 21 units/week, in the age group 31–50 years. In all, 34% of the sample met a criterion for problem drinking based on self-reported alcohol consumption and/or medical and social problems associated with alcohol. In 13%, alcohol was viewed by the patient as having contributed to the accident, and in 19% according to the interviewer's perception of whom 76% were classifiable as problem drinkers. Twenty-six men said the accident had made them think about changing their drinking habits. Detection of problem drinking in orthopaedic male admissions is possible and could be usefully linked to a counselling service.

Acute ethanol intoxication and traumatic injury are clearly related *(1–6)*. The role of *chronic* drinking problems and alcohol-related injury requires further study *(7)*. Waller *(8)* found a much higher incidence of cirrhosis and previous arrest for drunken driving in traffic accident fatalities associated with blood alcohol levels in excess of 150 mg/100 ml when compared with victims with no measurable blood alcohol. Although psychiatric interviews with persons convicted for drunken driving suggest that three-quarters reveal a history of problem drinking, such interviews have tended to be rather unstructured and in such studies no comparison group has been interviewed *(9)*.

In a more recent study of 3658 drunken drivers, Gjerde *(10)* reported that only 8% reported daily drinking, 82% denied daily drinking and another 10% gave no information about drinking frequency. Measurements of serum gamma glutamyl-transferase (GGT) activities in a random sample of each of the three groups, however, suggested a high level of chronic alcohol ingestion in those who denied daily drinking as well as those who admitted daily drinking.

In the study reported here we administered a standardised interview to patients admitted to the orthopaedic wards of the Royal Infirmary of Edinburgh after an accident severe enough to result in significant orthopaedic trauma. Our aim was to define the frequency with

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which problem drinkers are admitted to such a service, and calculate the extra risk that a drinker exceeding 'safe' limits takes of having an acute orthopaedic admission.

Subjects and methods

For the period September to November 1987, 400 consecutive male admissions to the acute orthopaedic service at the Royal Infirmary, Edinburgh, were approached for their consent to be interviewed 'for a study about patterns of drinking and accidents'. Patients who were discharged before being seen were either approached at the fracture follow-up clinic, or at home. There were seven readmissions during the study period. Of the remaining 393, six refused (one because of language difficulty), 11 were too ill or confused to be interviewed, seven were discharged early and could not be seen because of a false address or distance. This gave a coverage of 94%.

The instrument used to detect problem drinking comprises questions of high face validity on recent consumption, occasional heavy ('binge') drinking, and alcohol-related problems in the past 2 years in the areas of health, social relationships, the law, work, and dependence on alcohol (Fig. 1) *(11,12)*.

Consumption

Over 14 units* in a day on 10 or more occasions in past year.
Over 50 units in typical week.
Over 12 units in 24 h in typical week.

Current medical problems

Current illness potentially related to alcohol.
Current illness definitely related to alcohol.
Weight problem due to alcohol.

Medical problems in past 2 years

Peptic ulcer aggravated by drinking.
Liver disease due to alcohol.
Accident due to drinking.

Social problems in past 2 years

Antisocial behaviour.
Problems at work (including absence).
Domestic arguments.
Violence.
Family rupture (threatened or actual).
Financial.
Police.

Dependence on alcohol in past 2 years

Difficulty in reducing consumption.
Restlessness without alcohol.
Tremor (over 1 day a week).
Morning relief drinking (over 1 day a week).
Hallucinations.
Withdrawal seizure.

Patients scored one point for presence of any variable except presence of illness definitely due to alcohol, which scored two points. Problem drinking defined as two or more points.

* 1 unit = 57 g (1 oz) of 40% (by volume) spirits; 13.7 ml (half pint) of 3.6% (by volume) beer; one glass of wine, etc—that is, roughly, 8 g ethanol.

Figure 1. Criteria for problem drinking.

Regular drinkers (patients who drank at least weekly or who had occasional days of very heavy drinking) were asked in detail about the previous 7 days' drinking, or if that had been atypical about a typical week or typical heavy week. 'Problem drinkers' were defined as men who admitted to two or more of the items in Fig. 1. The interviewer made a judgement about whether, in her view, alcohol had contributed to the accident, and, if alcohol had been implicated, the patient was asked 'has this led you to consider changing your drinking habits?'

A general population survey in the Edinburgh area had been conducted 8 years earlier, using the same measures of alcohol consumption *(13,14)*. National surveys had shown no change in consumption patterns in men during that interval *(15)*. This enabled a calculation of the relative risk (odds ratio) *(16)* of incurring an orthopaedic admission when admitted consumption exceeds the 'safe zone' of admitted alcohol consumption as now recommended (21 units per week) *(17)*, compared to consumption within that zone.

Results

In the age group 31–50 years, there is an excess of heavy drinkers among patients, a significantly elevated mean consumption among regular drinkers, and the relative risk of having an orthopaedic admission at consumption over 21 units/week is 1.79 (95% confidence limits 1.05, 3.03). These associations are not evident in other age groups (Table I).

'Regular drinkers' comprised 71% ($n = 263$) and these were the men who were interviewed in more depth (Table II). This revealed an incident which led the interviewer to conclude that alcohol had been the main cause in 71 cases, that is, 19% of the whole sample. Other common 'causes' of accident as classified by the interviewer, in the regular drinkers, were sports injuries (19%), injuries at work (23%), and deliberate self-injury (12%).

Of the 71 individuals for whom the interviewer thought alcohol had contributed to the accident, 54 (76%) met the problem drinker criteria. Forty-nine men (13%) themselves said alcohol contributed to the accident. Of these, 41 (84%) met the problem drinker criteria. In the whole cohort, irrespective of whether the accident was deemed attributable to alcohol, 34% of men met the problem drinker criteria. Previous alcohol-related accidents (reported by 21%), arguments due to drinking with friends or family (reported by 40%), and other social problems commonly contributed to the problem drinker criteria being met in this sample. Problem drinking was commonest in the 31–50 years age group (39%) and in the 17–30 years age group (44%).

Twenty-six men said their accident had led them to think about changing their drinking habits; that is, one-half of those who considered alcohol contributed to the accident (one-third of those in whom the interviewer considered alcohol to have played a part in the accident).

Table I. Alcohol consumption in patients and general population

(a) *Percentage of men in different age categories*

	17–30 years		*31–50 years*		*51–65 years*	
	Patients n = 190	*Survey n = 180*	*Patients n = 89*	*Survey n = 215*	*Patients n = 47*	*Survey n = 137*
Abstainers or less than weekly	24	15	21	15	32	27
1–10 units per week	14	25	19	38	21	33
11–20 units per week	22	19	19	19	19	18
21–50 units per week	29	27	26	20	17	12
>51 units per week	10	13	15	8	9	7

(b) *Mean consumption in regular drinkers (drinking at least weekly)*

	n = 144	*n = 155*	*n = 71*	*n = 183*	*n = 29*	*n = 99*
Units/week	31.06	27.60	38.18	18.80	28.59	18.80
SE	3.73	2.10	6.56	1.50	6.26	2.10
SE (difference)	4.20		4.73		5.13	
t	0.82 (NS)		4.9 ($P<0.001$)		1.91 ($P<0.10$)	

(c) *Odds ratio for orthopaedic admission in regular drinkers for consumption of 21 units/week and over relative to consumption below 21 units/week (with confidence limits)*

0.84 (0.44, 1.5) 1.79 (1.05, 3.03) 0.57 (0.28, 1.2)

Discussion and conclusions

In the 30–50 years age group, consuming 21 units of alcohol a week or over increased the relative risk of an orthopaedic admission. Perhaps the frequency of sporting injuries, plus the likelihood that sportsmen drink less than their peers, reduces the proportionate contribution of alcohol to orthopaedic injury in younger men. However, among orthopaedic admissions, some young problem drinkers can undoubtedly be identified.

This study was conducted away from the seasons of the year when British consumption of alcohol peaks.

Table II. Prevalence of problem drinking

Population interviewed	*n = 369*
'Regular' drinkers	71%
'Problem' drinkers	34%
Patient thought alcohol contributed to accident	13%
Interviewer thought alcohol contributed to accident	19%
— % 'problem' drinkers	76%
Accident led patient to consider changing drinking habits	7%

Together with the probable under-reporting of consumption in such a study due to fear of medical disapproval or jeopardising insurance claims, this suggests that our estimate that 19% of admissions were alcohol-related is likely to be low rather than high if extrapolated to an annual figure.

Serum gamma glutamyl transferase tests in drink driving offenders show that many are regular heavy drinkers, rather than occasional drinkers who have been detected by chance *(18)*. The same applies to the men in this study whose accident was contributed to by alcohol: 76% could be classified as problem drinkers according to their self-reported consumption in the previous year and previous alcohol-related problems. Only 1 in 4 is a man whose drinking has not regularly been excessive or at times problematic.

Besides individuals who admitted an alcohol-related accident, the simple, brief interview used here reveals other problem drinkers. One-third of all subjects met criteria for problem drinking, a higher rate than the 27.1% obtained in medical wards in the same hospital *(11)*.

One-third of those in whom alcohol was deemed to have contributed to their accident said that this had led them to consider changing their drinking habits. However, it is clear from the degree of co-operation obtained in this hospital sample that many acute male

orthopaedic admissions are at least prepared to discuss their drinking and the problems it causes.

In a 3 month period, simple questioning revealed 26 patients who said their accident had led them to think about changing their drinking habits, and a further 28 were identified as problem drinkers according to their self reports. An offer of counselling about alcohol reduction may well be taken up by such men. A study in the USA showed that trauma patients with established alcoholism can be recruited into alcoholism treatment, especially if the family are involved *(19)*. In controlled studies, counselling has been shown to have a detectable effect in excessive drinkers detected in orthopaedic and surgical wards in a New Zealand hospital *(20)*, medical wards in Edinburgh *(12)* and in UK general practice *(21)*. It would be worthwhile to establish brief counselling aimed at safer drinking in an orthopaedic service.

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Assessor's comment

The results presented by Dr Chick *et al.* give further useful insight into the accident risks taken by heavy drinkers. The paper contains useful discussion of the age distribution of those most at risk, and speculates on the causes of injury. Presumably by reason of the available sample size, little is said that relates directly to road traffic accidents; it may therefore be appropriate to quote some results of a recent study carried out over a 2-year period at the John Radcliffe Hospital, Oxford, under contract to TRRL. Of 515 road casualties treated as inpatients, and on the basis of breath tests carried out in the accident and emergency department, over 20% were known to have been drinking alcohol, while over 14% were over the legal limit for driving (35 μg/100 ml

BrAC). However, consideration of all road casualties who attended the accident and emergency department (the majority of whom had less severe injuries not requiring further hospital treatment) indicated rather lower evidence of alcohol involvement—14% had been drinking, 8.4% over 35 μg/100 ml BrAC. Within this group, however, the incidence of heavy drinking was much greater among pedestrian casualties, the proportion having a Breath Alcohol Concentration in excess of 35 μg/100 ml BrAC being 27%. Considering again casualties among all road users, the age group found to have been drinking most heavily were those in their late thirties—a result which compares well with Dr Chick's results.

This Study will be published shortly as a Research Report (RR311) of the Transport and Road Research Laboratory, Crowthorne, Berks.

J T Everest
Trauma and Road Research Laboratory
Crowthorne, Berkshire

Notes on books

Atlas of Ear, Nose and Throat Pathology by L Michaels. 119 pages, illustrated. Kluwer Academic Publishers, Dordrecht. 1990. £80. ISBN 07923 8934 4

An atlas designed as a bench manual for pathologists who report biopsies taken from the deeper recesses of the ear, nose and throat. There is extensive supporting text; otolaryngologists should find much of great value within its pages.

Outpatient Anesthesia edited by Paul F White. 520 pages, illustrated. Churchill Livingstone, New York. 1990. £47.50. ISBN 0 443 08437 8

This volume reflects the greater use of day case surgery in North American practice as compared to that in the UK. It is a book written largely by anaesthetists, but has emphasis on organisation and economic factors which take up the first 100 pages. Later chapters deal with surgical considerations, nursing matters, different patient groups and different anaesthetic techniques. Complications, including pain, are discussed and the final chapter is devoted to controversial issues. There are 28 contributors, 26 from various centres in the USA, one from Helsinki and one from Melbourne.

Anaesthesia edited by R D Miller. 2 Volumes. 3rd edition. 2420 pages, illustrated. Churchill Livingstone, New York. 1990. £115. ISBN 0 443 08594 3

This large and popular American-based textbook has been completely revamped to enable the 3rd edition to reflect the increased knowledge in the subject that has accumulated since the first edition in 1980. There is thus greater emphasis on monitoring, and the increasing importance on legal and economic issues. Special chapters have been devoted to autotransfusion, haemodilution, patient-controlled analgesia and epidural narcotics, with a special focus on postoperative analgesia. Surgeons will be interested in these chapters and in those devoted to operating room management and environmental hazards. There are comprehensive chapters on cardiovascular, hepatic, renal, cerebral, and neuromuscular physiology, all of which would provide useful reading for both surgical and anaesthetic disciplines.

The chapter on anaesthetic risk and the anaesthetic implications of concurrent diseases should be read by practising surgeons as well as anaesthetists. The former includes discussion and such questions as: 'Does anaesthetic risk depend on who administers the anaesthesia?'! while the chapter on the latter is a wide-ranging and helpful account which should be read by all medical practitioners involved with surgical and anaesthetic management.

In the second volume the section on Perioperative Fluid Therapy and Resuscitation of the Newborn will appeal to both disciplines, as will the chapter on Outpatient Anaesthesia. The section on Critical Care Medicine includes interesting chapters on Nutrition and Cardiopulmonary Resuscitation.

In summary, this large, multi-author, well-referenced book should be one of the main texts available for reference in all major medical centres.

The Story of Thoracic Surgery—Milestones and Pioneers by Andreas P Naef. 157 pages, illustrated. Hogrefe & Huber Publishers, Toronto. 1990. $19.80 ISBN 3 456 81809 4

The development of surgery of the lung, oesophagus and heart is traced in this well-illustrated, easy-to-read book written by a distinguished Swiss cardiothoracic surgeon. The development of open heart surgery is particularly well covered as Dr Naef himself participated and knew personally most of the pioneers in this field. There is a useful bibliography giving important references. The volume can be recommended as a good introduction for the general reader.

Counselling the Coronary Patient and Partner by David R Thompson. 121 pages, paperback. Scutari Press, Harrow. £11.95. ISBM 1 71364 42 6

The author provides evidence that a programme of inhospital counselling reduces anxiety and depression and increases knowledge and satisfaction in patients with coronary artery disease and also their partners. Proposals are made for a change in customary practice and recommendations are given for the direction of future research.

Addiction (1994) 89, 1613–1617

RESEARCH REPORT

Trends in alcoholism among male doctors in Scotland

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Abstract

Alcohol abuse within the medical profession has long been an issue of concern. Recently, the General Medical Council reported that half of the doctors reported for health difficulties liable to affect professional competence were found to have an alcohol problem. This paper examines how rates of alcoholism among male doctors in Scotland have changed over the last three decades. Admission and discharge rates for doctors to psychiatric inpatient beds with diagnoses of alcoholism are compared with non-medical professions, for the years 1963–87. The results, assessed in the light of changing Standardized Mortality Rates for liver cirrhosis for the medical profession, suggest that doctors as a group remain at a higher risk of alcoholism compared to other professionals, but that this increased risk appears to be largely accounted for by a cohort of heavy-drinking doctors over the age of 45 years.

Introduction

The 1990 Annual Report of the General Medical Council states that half of the doctors reported for health difficulties liable to affect professional competence were found to have an alcohol problem. Explanations as to why doctors may be heavy drinkers have been plentiful. Doctors' incomes being above the national average make alcohol relatively cheap for them. Strong peer pressure on medical students and doctors may encourage heavy drinking. Many doctors work relatively free of close supervision and so can conceal their drinking more easily.[1] Social expectations, availability of alcohol and tolerance among the profession have also been blamed.[2] The British Medical Association note that high stress in the medical profession may contribute to alcohol problems.[3] Murray[1] compared alcoholism among male doctors in Scotland with other social class 1 controls by investigating first admissions to and discharges from Scottish psychiatric inpatient beds for diagnoses of alcoholism. For the period 1963–72 the rates were found to be over two-and-a-half times higher among doctors. Over half of all psychiatric hospitalizations of male doctors between the ages of 45 and 54 years were attributed to alcoholism.

The Standardized Mortality Rate (SMR) for deaths from cirrhosis of the liver in England and Wales from 1970–72 showed doctors to have three times the rate of the "average worker".[4] However, the SMR has recently fallen from 350 in 1962 and 311 in 1970–72, to 172 in 1979–80 and 115 in 1982–83.[5]

The present study investigates whether this fall in SMR might indicate a decline in alcoholism among doctors. Two recent studies indicate that the rate of alcoholism in the medical profession may be becoming closer to that of the general

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population. Alcoholism rates among doctors in the United States are reported to be little different now from that of the general population.[6] Alcohol consumption among British male medical students showed little difference from that of the general population when matched for age.[7] The present study compares data on first admissions to and discharges from Scottish psychiatric hospitals with diagnoses of alcoholism from 1973–87, with data from 1963–72 from Murray's earlier study. The Scottish Health Service (unlike the Service in England) routinely collected information on the occupation of patients (until 1987), which allows for a comparison between rates among doctors and other professional groups.

Methods

The study population included all social class 1 males, medical and non-medical, resident in Scotland. The numbers of first admissions to Scottish psychiatric inpatient beds for male doctors aged 25 years and over were obtained for the International Classification of Diseases (ICD 9) diagnoses of Alcoholic Psychosis (ICD 291) and Alcohol Dependence Syndrome (ICD 303). In this study the term alcoholism is used to refer to both these diagnoses.

The data from Murray's study[1] included first admissions and not total admissions to hospital. To allow a direct comparison of rates obtained from that study first admissions, rather than total admissions, were included in the present study. It is possible that over the study period the average number of repeat admissions required for treatment has changed. Data on total admissions, therefore, gives a less clear indication of trends of alcoholism. Admissions to private institutions were not examined but for the period under study, 1973–87, private care for alcoholism was not the custom in Scotland.

Admissions and discharge data, like cirrhosis mortality, are only indicators, not absolute measures, of rates of alcoholism. For the present comparison over time and between occupations, they are an adequate marker, because although patterns of inpatient vs. outpatient treatment may have changed over time there is no reason to believe that these have changed differently for different occupational groups. Outpatient attendance data by diagnosis was not available.

Female doctors were excluded from the study, as a potential inaccuracy arises from the recording of the occupation of a married woman as that of her husband.

Information was obtained for the 15 years from 1973–87. (Murray's study examined figures from 1963–72.) Identical data on non-medical social class 1 (NMSC 1) males aged 25 years and over were obtained for the same period to provide a control of similar social and economic level.

The numbers and age distribution of all male doctors in Scotland aged over 25 years were obtained from the General Medical Practitioners Census and the Medical and Dental Census for the years covering the period under study. The numbers and age distribution of social class 1 males in Scotland over the age of 25 years were obtained from the 1971 and 1981 Census figures.[8,9] Social class 1 category consisted of the professional occupations. Their numbers and age distribution over the period of study were calculated assuming population changes to be distributed equally over these years and the same trends projected to 1987.

Results

First admissions

During the 15 years studied from 1973–87 a total of 131 male doctors and 413 non-medical social class 1 (NMSC 1) males aged 25 years and over were admitted for the first time to Scottish psychiatric inpatient beds with a primary diagnosis of Alcoholic Psychosis or Alcohol Dependence Syndrome. This represents a mean annual first admission rate for alcoholism of 142 per 100 000 for doctors and 41 per 100 000 for NMSC1 controls. This difference is statistically significant (z value 13.6, $p < 0.01$).

Figure 1 shows the age-specific first admission rates for alcoholism. The rates are virtually the same for both doctors and other social class 1 controls under the age of 45 years. From 45 years onwards there is a dramatic increase in rates for doctors, whereas the increase for other social class 1 professionals is much less marked. The rate for doctors becomes approximately three times the rate of other social class 1 males over this age. In Murray's study the first admissions were not analysed according to age groups, so a comparison between the present trend for 1973–87 with the 1963–72 figures is not possible.

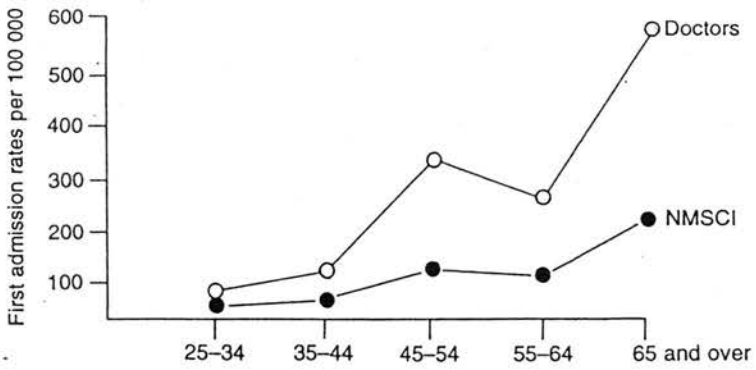

Figure 1. *Age-specific first admission rates for alcoholism per 100 000 population.*

All discharges

During the 15 years 1973–87 there were 359 discharges of male doctors and 1450 discharges of non-medical social class 1 males aged 25 years and over with a primary diagnosis of alcoholism. These figures account for 20% of the total discharges for male doctors and 25% of the total discharges for other social class 1 males from inpatient psychiatric beds in Scotland.

Figure 2 shows the age-specific discharge rates for alcoholism. The discharge rates for 1973–87, as with the first admission rates, dramatically increase for doctors more than 45 years old. The discharge rates for other social class 1 males increase only slightly at this age. The results of Murray's study for years 1963–72 are shown. Here there is a peak in discharge rates at age 45–54 years. Results form 1973–87 show no peak; rates continue to increase after 54 years old. The 1963–72 figures show that, of the total 218 discharges of male doctors between the ages of 45–54 years, 127 (58%) were due to alcoholism. In the present study the 1973–87 figures show the proportion to be lower; of the total 426 discharges, 121 (28%) were due to alcoholism. This proportion rises slightly in the older age group (55–64 years); of the total 351 discharges, 117 (31%) were due to alcoholism.

Discussion

The first admission rate for alcoholism from 1963–72 was 165 per 100 000 for doctors and 60 per 100 000 for other social class 1 males. The figures for 1973–87 of 142 per 100 000 for doctors and 41 per 100 000 for non-medical social class 1 males suggest that male doctors remain a high risk group for alcoholism. If anything, their relative risk appears higher, 2.7 times higher among doctors compared with other social class 1 professionals in the 1963–72 period, rising to 3.5 times higher for the 1973–87 period.

When age-specific rates are examined, the higher risk of alcoholism is only true for doctors aged 45 years and over. Doctors younger than 45 years have similar admission rates to other social class 1 professionals (Fig. 1). This is consistent with the finding that the fall in the SMR for cirrhosis of the liver in doctors has been chiefly in the younger age-band. The most recent age specific data available for Britain (1979–80 and 1982–83) show an SMR for liver cirrhosis of 208 for ages 55–64 (significantly different from 100 at the 95% confidence level), but an SMR of 40 for ages 35–44 and 25 for ages 45–54 (admittedly based on small numbers).[5]

It is possible that the cirrhosis mortality data and our Scottish data represent a cohort effect: that doctors practising in the 1960s were drinking more than average for their age group in social class 1 and continued into the next two decades, while the subsequent generation did not. The 1963–72 figures for psychiatric discharges for alcoholism show a peak of discharge rates for doctors aged 45–54 years. In the 1973–87 figures admission and discharge rates continue to rise in the over-54-year age-groups, suggesting an excess of older alcoholic doctors. The doctors aged 45–54 years in the 1963–72 period are now in these older age groups.

The cohort effect could be explained by

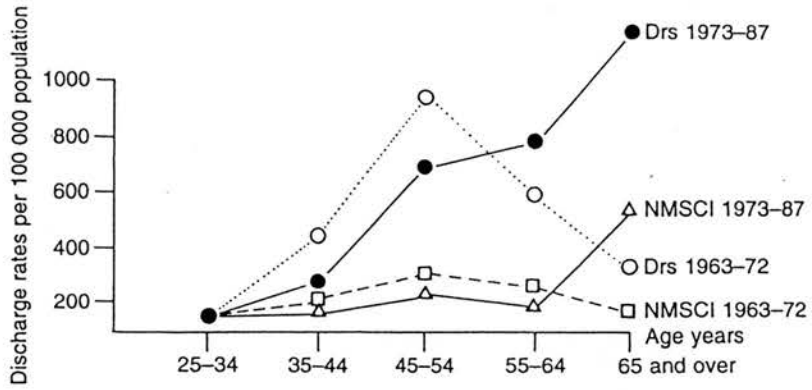

Figure 2. *Age-specific discharge rates for alcoholism per 100 000 population.*

younger doctors becoming aware of the risk of long-term alcohol abuse. This explanation is supported by the finding that the drinking habits of male medical students in the 1980s were in line with their non-medical contemporaries.[7] A precedent has been set with the change in doctors' smoking habits. Education about the risk of bronchial carcinoma resulted in decreased smoking and a subsequent SMR for lung cancer among doctors much lower than the general population.[10] The increased emphasis on the dangers of alcohol and the widespread effect it has on health has hopefully contributed to an increased awareness among doctors of their personal consumption. In contrast to this, during the period studied, per capita alcohol consumption in the United Kingdom (separate figures for Scotland are not available) was increasing, apart from a slight dip in 1980–82, until 1987.[11]

It can also be asked whether the improved SMR for cirrhosis in doctors has been in part because of improved outcome of alcoholism in the profession. Noble *et al.*[12] have put forward readier access to treatment as a possible explanation for falling cirrhosis mortality in the USA during a time when consumption did not fall. The Scottish data presented here show that despite a slight increase in the relative risk of admission for alcoholism compared to other social class 1 males, the number of discharges did not rise: for the years 1963–77 there was an average of 27 discharges per annum and for 1973–87, 24 per annum. The proportion of total psychiatric discharges (all diagnoses) attributable to alcoholism also fell for male doctors in the past 25 years, from 40% for the 1963–72 period to 31% for the 1973–87 period. These data may indicate a reduction in repeat admissions reflecting improved procedures within the profession[13] and a growing support network.[14]

Acknowledgements

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ORIGINAL PAPER

Mental health, alcohol and drugs: constructing a neighbourhood profile

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Keywords:
Community profiling
Health needs assessment
Mental health
Rapid participatory appraisal

A coherent, practical and explicit local approach is required to assess the needs that individuals and the wider community have with respect to mental health problems. A community psychiatric nurse (CPN), general practitioner and psychiatrist together applied four approaches within a council estate of 670 homes in Edinburgh. Data were collected by rapid participatory appraisal, postal survey, analyses of routinely available small area statistics and collation of practice-held information. Different methods yielded complementary insights into the needs of individuals, their carers and the wider community with respect to mental health, alcohol and drugs problems, and into current and potential service provision in the community, primary and secondary care. The neighbourhood profile built up by integrating different perspectives, utilizing quantitative and qualitative data, was more reliable and informative than concentrating time and effort on one method alone. Many residents and community workers were concerned at the high concentration of people with mental health problems who lived in the area. A change in housing policy was considered to be the most useful intervention. CPNs in primary care should have specific skills and apply interventions of proven efficiency, but may also have a valuable role as part of an expanded primary health care team, doing work which is currently undertaken by less appropriately trained (and frequently more costly) members.

Introduction

General practitioners in an increasingly primary care-led NHS are becoming more involved in the process of defining and measuring health needs, considering how these needs might best be met, and monitoring some aspects of the performance of providers. In England the "Health of the Nation" set as a key target "to improve significantly the health and social functioning of mentally ill people" [1]. The Scottish Needs Assessment Programme has estimated that 30% of the adult population of Scotland suffer from a mental health problem at some point in their lives, and that nine out of 10 mentally ill patients are treated in general practice [2]. If mental health needs could be assessed in primary care, targeted health promotion and support in the community could be given for people with mental illness.

Commissioning of health services led by primary care requires consideration of social services, education, employment and housing since all these affect mental health status [3]. Much work has been done to assess mental health needs using single methods such as surveys of mental health status [4], practice-based data [5] or data based on hospital attendances and admissions. Community-based studies are rare [6]. Little has been done to bring together these approaches to create an overall picture and to examine which approaches are most informative for which purposes with respect to mental health. Slade concluded that no single mental health assessment instrument integrates user and professional perspectives of need, and that methods should be developed to take account of both user and medical views [7]. Shanks advocated a multi-method approach for health needs assessment generally in primary care [8].

The setting of our study was a post-war council estate, Dumbiedykes, of 670 households in central Edinburgh. It is served mainly, but by no means exclusively [9], by the general practice where the study was based. Four complementary approaches to assessing general health and health service needs had previously been applied within the same neighbourhood [10]. Each

method had yielded particular information. At the suggestion of a local psychiatrist, a community psychiatric nurse (CPN) was recruited, based in the local practice for 1 year, and the same four methods were reapplied this time focused on mental health, alcohol and drugs. The methods were applied simply, such as might reasonably be carried out by an individual general practice in order to inform the commissioning of mental health services and also to inform local mental health advocacy work.

Methods

Practice-held information

Information was obtained concerning the 538 adult residents of Dumbiedykes registered with the practice using the following methods.

- A random sample of 100 medical records of adults was analysed. The following marker conditions were noted: drug abuse, alcohol abuse, schizophrenia, other psychoses, dementia, anxiety and depression.
- The general practitioners were presented with a list of the residents of Dumbiedykes who were registered at the practice. They were asked to indicate which patients had problems relating to mental health (covering all aspects from mild anxiety to psychotic episodes), alcohol and drugs.
- The practice register of drug addicts was examined for past or present residents in Dumbiedykes.
- Doctors, district nurse, health visitor, practice nurse, practice manager and receptionists were informally interviewed about their perceptions concerning mental health, alcohol and drugs in Dumbiedykes.

Rapid participatory appraisal

A rapid participatory appraisal was carried out to gain insight into the community's own perspectives of its priority needs. A CPN temporarily based in the practice, a local GP and a local psychiatrist collated data from three sources:

- existing documents about the neighbourhood;
- interviews with a range of informants;
- direct observations made in the neighbourhood and within homes.

A profile was built using information collected on 10 aspects of the community. These were brought together to form an information pyramid (Fig. 1), which was adapted to include specific blocks for mental health, alcohol and drug problems and their related services.

The validity of this approach depends on the concept of triangulation, with data collected from one source being validated or rejected by checking it with data from at least two other sources. Key informants, selected for their potential knowledge about the issues under study, included people with professional knowledge about the community, community leaders and people who were centrally placed because of their work (see Appendix 1). Twenty-six residents of Dumbiedykes were selected to represent various age groups, mental health, alcohol and drug problems. A semi-structured interviewing schedule was devised and piloted on residents and (with minor alterations) on local professionals and workers. Participants were interviewed in their homes or at work by the CPN, and occasionally in groups. The most "information-rich" informants were interviewed first. Data were extracted from the questionnaires using a thematic analysis where answers relevant to the different information blocks were grouped together. Subsequently, two focus groups of

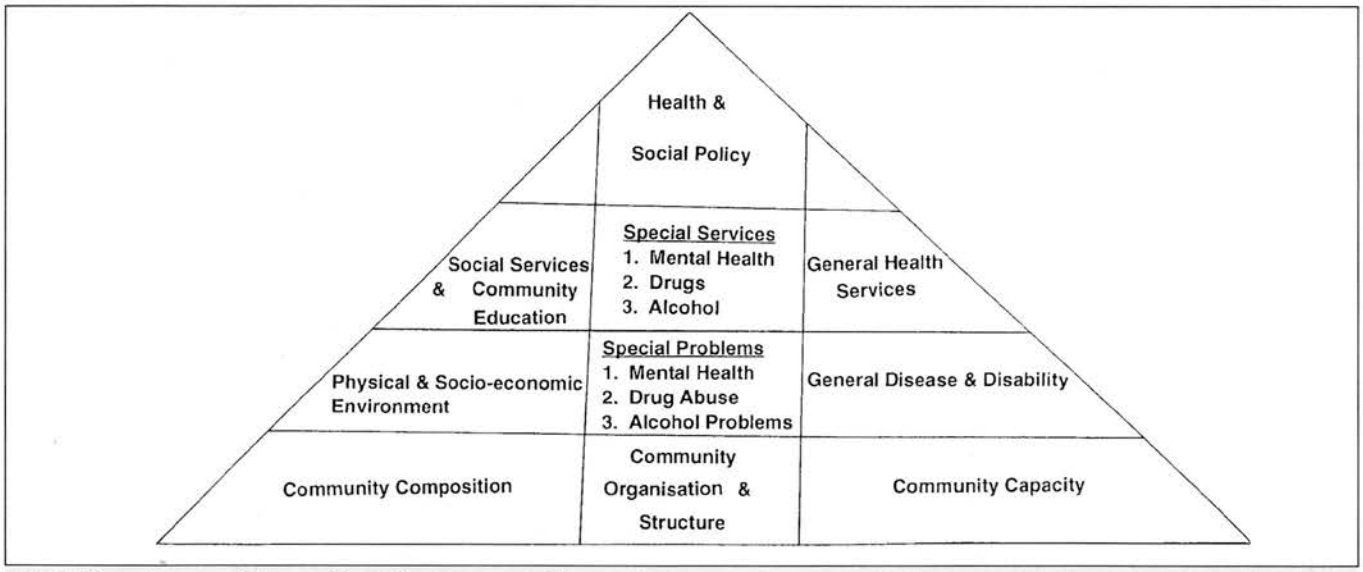

FIG. 1. Information pyramid for rapid participatory appraisal.

members of the community were set up to discuss and allot priority to the problems identified and to explore potential interventions. The process took the CPN 3 months, spending 15 hours/week.

Routinely available small area statistics

Edinburgh Health Care NHS Trust provided hospital-based morbidity information (out-patient attendances and admissions) collected by the PSYMON data system relating to the 19 postcodes for Dumbiedykes (population 1185), residents of South East Locality of Edinburgh in which Dumbiedykes is situated (population 117 000), and for the city of Edinburgh (population 402 670) for comparison. Census data on demography were available.

Postal survey

A postal survey had been carried out in 1993 on all residents of Dumbiedykes registered at the study practice (435 of the 993 adult residents of Dumbiedykes), with a response rate of 62% [10]. A mixture of lay concepts and medical diagnoses had been used. It covered the following areas:

- chronic illness;
- acute illnesses;
- health status: the Nottingham Health Profile, a standard multidimensional measure based on lay concepts to assess both functional and emotional distress using six subscales;
- use of health services over 6 months: perceived need for current and potential services;
- social and demographic characteristics of the respondents.

Thus postal survey information was available for comparison with data from other sources.

Results

General findings from the rapid participatory appraisal

Community composition, organizations and capacity. There was a relatively stable elderly population. Their pride in their home environment was matched only by a growing sense of unease towards the "incomers" to Dumbiedykes, some of whom they perceived as bringing with them alcohol and drug problems, and general antisocial and sometimes criminal behaviour. Their feeling was that they, as a stable community, were expected to cope with (and care for) incomers with problems, difficulties and needs, and they were unable to do this. Residents did not have many relatives living nearby. There was little sense of community identity. People felt unsafe, especially at night.

Environmental, socio-economic and disease profile. Many informants complained about dampness, poor windows and inadequate heating in the houses. Action had been undertaken by individuals, residents committees and their political representatives, but the Housing Department Maintenance Programme was perceived to be ineffective. A high unemployment rate (26% among males) plus a growing number of elderly people receiving basic pensions indicated that there were people with financial difficulties. Numerous comments about pigeon dirt and dog fouling all combined to suggest an area where people had little pride in where they lived. There were hints of violence, and of feeling unsafe. A small number of incidents were spoken about, and house breaking was increasingly common, where valuables and tablets were stolen. Drugs users were frequently blamed. Graffiti relating to a specific drug addict had been sprayed on the side of a house. Most residents knew the location of the local social work office, but few had had knowledge of what community education could offer.

Health and social policy. All key informants were positive towards the concept of care in the community, but all felt a need for better planning. The notion of quality care required money, and capable personnel in the community to provide a co-ordinated, well-resourced community care programme, distributed so that services did not depend unfairly on where the individual lives. But while increased support in the community was desired, greater possibility of relevant and regular employment was regarded as a high priority to improve the lot of those with mental health problems. Informants considered that mental health services should become more community focused. They suggested that small, specialist, residential units might be needed, dependent on the severity of the individual's problem, but the primary focus of care should be at home.

Mental health

Practice-held data. The random sample of 100 medical records revealed the current or previous diagnoses shown in Table I. Thus a psychosocial problem had been recorded in 51 of 100 records. However, the GPs could only actively identify 80 (15%) out of 538 patients as having the problems in Table I.

Routinely available small area statistics. Table II lists the diagnoses of new out-patient contacts (1991–1994) seen at the psychiatric hospital serving the area, by place of residence. The total contact rate for Dumbiedykes was three times that of the locality (South East Edinburgh) of which it is part. Organic psychosis, schizophrenia, other psychoses and neurotic conditions were all more common in Dumbiedykes residents. Neurotic conditions were responsible for most contacts for both areas. Table III lists the frequency of admission diagnoses of patients by place of residence for 1991–1994.

TABLE I. Current or previous mental health diagnoses from medical records

Depression	18
Anxiety	16
Alcohol	5
Drugs	4
Social problems	3
Psycho-neurosis	3
Schizophrenia	1
Others (multiple)	1
Total	51

TABLE II. Diagnosis of new out-patient contacts (1991–1994) by place of residence

	Dumbiedykes residents		SE locality residents		Edinburgh residents	
	n	Rate/1000/year	*n*	Rate/1000/year	*n*	Rate/1000/year
Organic psychoses	17	3.6	991	2.1	3756	2.3
Schizophrenia	14	3.0	601	1.3	1702	1.1
Other psychosis	11	2.3	702	1.5	2038	1.3
Neurotic conditions	84	17.8	4069	8.7	13217	8.2
Alcohol abuse/dependence	33	7.0	1171	2.4	3479	2.2
Drug abuse/dependence	26	5.5	563	1.2	1656	1.0
Learning difficulties	0	0	105	0.2	255	0.2
Total episodes	246	52.1	8103	17.3	25848	16.0

TABLE III. Frequncy of admission diagnosis of patients for 4-year period (1991–1994) by place of residence

	Dumbiedykes residents		SE locality residents		Edinburgh residents	
	n	Rate/1000/year	*n*	Rate/1000/year	*n*	Rate/1000/year
Organic psychoses	20	4.2	1009	2.1	3662	2.3
Schizophrenia	37	7.8	635	1.3	1683	1.0
Other psychosis	29	6.1	787	1.6	2431	1.5
Neurotic conditions	7	1.5	807	1.7	2263	1.4
Alcohol abuse/dependence	24	5.1	379	0.78	1157	0.72
Drug abuse/dependence	2	0.4	65	0.13	173	0.11
Total episodes	119	25.2	3692	7.6	11369	7.1

Episodes of non-organic psychoses occurred at five times the rate for Dumbiedykes than the locality. Psychotic episodes accounted for most admissions for both areas, especially from Dumbiedykes. The figures were relatively steady from 1991 to 1994. Census data revealed many indicators of social disadvantage and potential stresses: high unemployment rate (26%, compared with 11% in Lothian), owned housing 20% (66% in Lothian) and 47 lone parents bringing up 70 children. Twenty per cent of residents, compared with 12% of Lothian, suffered from a limiting long-term illness.

Rapid participatory appraisal. There was a perceived increase of people with mental health, drugs and social problems being "moved into Dumbiedykes", and that these same people were receiving little medical or social support. There were a large number of isolated individuals, both elderly and young. Mental health, alcohol and drug problems were perceived as breaking up relationships, causing financial difficulties, crime and violence, and further depression and anxiety. Within this spiral, incidents have frightened and antagonized neighbours, leading to a lack of tolerance and increasing separation and isolation between individuals with mental health problems and their neighbours. The GP was perceived as being a key figure in providing a service for those people with mental health problems, either as a means of access to more specialized help, or in actually providing the treatment and support. The emergence of a local community psychiatric day service for the south-east of Edinburgh was welcomed by those working in this field, but after 1 year it was still unknown to most residents. The psychiatric hospital serving Dumbiedykes invoked strong feelings. Clients, relatives and other key infor-mants had perceived a pressure on almost all aspects of the hospital service leading to frustration, disillusionment and anger, and uncer-tainty as to where to channel these emotions. Consultations appeared rushed. The constant activities of staff, the changes of personnel and an allocated keyworker system added to delay when a client requested help. Quick discharges were possible, but quick admissions were not so easily arranged. A local social worker reported inadequate arrangements for the transferring of patients from the hospital to the community, and a general lack of resources. There were many calls for mental health workers to be available and accessible in the community. The reduction in size of the large psychiatric institution was welcomed, but the need to create smaller residential units was also stressed. Inaccessibility and inflexibility were causing concern. Both clients and workers had experienced difficulties in contacting the appropriate service: "mental illness doesn't stop at 5 o'clock". Some service providers for those with mental health problems had themselves found difficulties with inter-agency communication, leading to the thought that a "one-door" approach, where different service providers were based in the same premises, could provide a more efficient and ultimately a more effective approach to care in the community.

Postal survey. In the postal survey, 18% of the total respondents (rising to 26% of females age 44–60 years) complained of anxiety, depression or "bad nerves". In the preceding 6 months, 28% had had difficulty sleeping and 16% claimed to have taken tranquillizers, antidepressants, or sleeping tablets in that period. The Nottingham Health Profile results showed that residents aged 16–44 scored highly on the emotional reaction and social isolation subscales. Seventy-two per cent of respondents indicated that advice about coping with stress would be helpful, and 63% had a perceived need for advice about benefits. A helpline was suggested.

Drug abuse

Practice-held data. The GPs reported they prescribed for a number of drug users in Dumbiedykes who tended to join and leave the practice list with a high turnover. Drug users frequently failed to utilize support offered by statutory and voluntary agencies, and sought to be certified unfit for work. Domestic violence and unplanned pregnancies occurred. Injecting in these users had become less common in the past half decade, but several children had been treated for needle stick injuries. Some drug addicts considered that moving out of the area was a solution for their drug problems, while others were evicted due to non-payment of rent.

Routinely available small area statistics. The admission rate for drug dependence for Dumbiedykes was three times greater than Edinburgh (Table II). The new out-patient contact rate was four times greater (Table III).

Rapid participatory appraisal findings. Drug addiction tended to be seen as a desire by younger people to escape from reality. A wide variety of drugs were being used: cannabis, methadone, ecstasy, dihydrocodeine, diazepam and temazepam. Neighbours complained about incidents of violence, intimidation, burglaries, noise disturbance and an influx of unwelcome non-residents visiting the drug users. In general, informants reported favourably on the community services for drug problems and their collaboration with GPs. Residents considered that the benefits of prescribing methadone probably improved the quality of life for the addicts and the community in which they lived. A need was identified for more support for young people at "street level", and the provision of more appropriate residential places.

Postal survey. Six per cent of respondents indicated they wanted help or advice about illegal drugs, and 26% wanted advice about HIV infection.

Alcohol problems

Practice-held data. From the 100 medical records examined, alcohol abuse was identified in five cases. Only seven patients were identified as having alcohol problems from the list of Dumbiedykes residents. However, practice-based staff commented on the amount of disturbance which a relatively small group of individuals can cause. The only shop on the estate sold alcoholic beverages but not low-alcohol beer.

Routinely available small area statistics. Alcohol dependence was responsible for three times more out-patient new contacts and six times more admissions from Dumbiedykes than would be expected in comparison with locality data (Tables II and III).

Rapid participatory appraisal. The closure of the local pub had made little difference to the perceived problems related to excessive drinking. Groups noted were men in their forties and fifties, younger people, and women drinkers. Dumbiedykes was not an area where drinkers were seen, although empty cans and bottles were visible in some public areas. Drinking was done in isolation, or in "drinking dens". These heavy drinking sessions were seen as causing damage to individuals' health and were detrimental to community cohesion.

Alcoholics Anonymous was the service most commonly recognized. Two other voluntary agencies, the city's NHS alcohol problems clinic and the GP and CPN were also mentioned. There was a mixed response as to whether or not this help was sufficient. An increase in detoxification facilities, either home-based support or residential places, was proposed, and again the theme of accessibility to the services was highlighted.

Postal survey. Thirty-two per cent of respondents to the survey indicated that they would value help or advice about reducing their alcohol intake.

Interventions suggested by key informants to address mental health, alcohol and drug issues in the community

The residents suggested the following: nursery provision in the community room; home visiting of the isolated; help for unemployment and financial problems; improved shopping; development of a community centre such as a cafe "drop-in"; improved liaison among health and other workers; and a change in allocation procedures for council housing. Local workers suggested: improved access to care, perhaps provided by a single allocation procedure; improved communication channels between residents, GPs, social workers, CPNs, the housing department, community projects, community education and community centres; recruitment of more CPNs; and increased resources for the community facilities. A number of these suggestions were facilitated by the CPN and the GP in the second 6-month period of the study, and will be reported elsewhere.

Discussion

Methods

Rapid participatory appraisal encouraged a broad multi-disciplinary approach to assessing health need. The

role of selected users, community leaders and workers in prioritizing and planning care was developed. A neighbourhood profile was generated which detailed broad needs, available resources and suggestions for change. The process in itself facilitated change in that, for example, a drop-in club for the socially isolated was commenced during the period of the study.

The postal survey yielded detailed information about perceived mental health status, and perceived need for existing and potential services for both users and non-users. Census statistics indicated a high frequency of socio-economic risk indicators for psychiatric problems and allowed comparison with regional norms. Hospital statistics revealed a high usage of out-patient and in-patient facilities. In the practice data, there was considerable evidence of mental health problems in medical records, and GPs could remember many such patients from memory. For alcohol problems, there appeared to be an under-identification in the practice data compared with the postal survey. Due to the small numbers involved and as no generalization from this very local study was sensible, no quantitative analyses of the findings were made. The statistics were used descriptively alongside more qualitative data.

Community profiling

In developing countries a number of formal assessment procedures have been developed to profile communities and to assess the needs, wants, demands and resources in a community. These procedures seek optimal methods of obtaining information about a community while including some type of community involvement in the information-gathering process. Health visitors have community profiling skills, but due to lack of time and lack of homogeneous practice areas have generally been unable to do this work. Profiling communities utilizing information from different sources may form a basis for needs-led purchasing with considerable public input, as is currently being advocated by the NHS Management Executive [11].

Role of the community psychiatric nurse in health needs assessment

This study has explored the role of a practice-based CPN in the assessment of the needs of individuals, their families, and the communities in which they live. With knowledge of services gained in community profiling, the CPN can initially assess patients with mental health problems and refer to various appropriate agencies, whether specifically for mental health problems or not. Practice-based CPNs may also be able to support primary health care teams by providing primary mental health care where the public perceive it is under-provided.

Implications

1) Practical strategies for assessing local mental health needs are required.
2) Possible methods may utilize:
   - practice-held data;
   - routinely available local statistics;
   - rapid participatory appraisal;
   - postal surveys.
3) A method mix may yield more information than one method alone.
4) Many locally important mental health needs cannot be met by health services alone.

Conclusion

Caution must be exercised when using only a single method to assess need. Practice data may understate the prevalence of disease in the community. Postal surveys may not be returned by mentally ill respondents. Rapid participatory appraisal will not yield statistics for service planning. Results are likely to be more widely relevant and accurate if data from different sources are built up to describe mental health needs. A locally appropriate method mix could utilize data from various sources according to ease of access, potential utility and possible resources, to paint a detailed picture. Similar methods could be used for larger neighbourhoods within localities, or for localities within districts for larger scale planning.

By adopting a comprehensive approach to mental health appraisal, this study provided broad information about the needs of people with mental health problems and of their relatives, neighbours and the community in which they live. Many significant social and environmental as well as medical needs were identified, implying that mental health services alone cannot meet the needs of the mentally ill. A change in housing policy was the intervention that most residents requested, to limit the large number of incomers who had mental health problems. GPs, CPNs and psychiatrists can be involved together in identifying mental health needs. Relatively inexpensive methods such as used here are applicable.

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Appendix 1: Key informants in the participatory appraisal

1. Community Development Worker
2. Mental Health Development Worker
3. CPN General Psychiatry
4. Project Worker, Canongate Youth Project
5. Social Worker, Mental Health
6. Home Care Organizer
7. Chair, Holyrood/Lochview Residents' Association
8. Charge Nurse, Psychiatric Day Hospital
9. Social Worker, Community Care
10. CPN, Community Drugs Problem Service
11. Housing Department Officer, Edinburgh District Council
12. District Nurse
13. CPN, Care of the Elderly
14. Community Police Officer
15. Project Leader, Canongate Day Centre
16. Co-ordinator, Dumbiedykes Children's Centre
17. Health Visitor
18. Senior Registrar, General Psychiatry
19. Pharmacist
20. District Councillor
21. General Practitioner
22. Councillor, Lothian Region
23. Consultant Psychiatrist, Alcohol Problems
24. Consultant Psychiatrist, Community Drugs Problems Service
25. Chair, Dumbiedykes Residents' Association

Twenty-six residents were also interviewed using a slightly different questionnaire. They were chosen to represent the following categories.

- People with mental health problems—six residents.
- People with drug problems—four residents.
- People with alcohol problems—four residents.
- People with a combination of the above problems—four residents.
- Elderly people—four residents.
- Young adults—four residents.

Short Communication

Evidence Suggesting Increasing Health Damage in Scotland Related to Alcohol

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Abstract

General hospitals in Scotland have experienced a steep rise in discharge rates for alcohol-related diagnoses. This cannot fully be explained by changes in drinking in the general population, a cohort of heavy drinkers, changes in diagnostic practice, or the closure of beds in psychiatric hospitals. Moreover, there has been an increase in deaths from alcoholic liver disease, not easily explained by change in diagnostic practice or a putative cohort of polysubstance abusers with viral hepatitis. Changes in society such as greater income disparity and greater social isolation may contribute and have not been off-set by improvements in availability or outcome of treatment.

Objective

There was a rise in discharges for alcohol dependence and alcoholic psychoses in Scottish general hospitals from 1980 to 1988. Discharges from general hospitals, and deaths, from alcoholic liver disease also rose.[1] This paper examines the continuation of these trends up till 1995, occurring in the already overstretched acute services, and examines possible explanations.

Data presented

(a) Population consumption of alcohol

Per capita consumption of alcohol estimated from UK Excise Duty rose from 1945. A peak of 10.00 litres of alcohol/adult/year was reached in 1980. From 1981–94 annual *per capita* consumption plateaued (minimum 8.93 litres in 1983, maximum 9.72 litres in 1988). Excise data are not published for Scotland separately but self reported consumption data are available for Scotland two-yearly.[2] Rates of men reporting weekly consumption above 21 units have remained on a plateau and for women reporting above 14 units have only increased slightly. (One unit is 8g ethanol.) The proportion of the population drinking above these levels, sometimes called the 'limits of sensible drinking' (men >21 units/week; women >14 units/week) were for men 27% in 1986 and 24.2% in 1994 and for women 7% in 1986 and 8.9% in 1994.* However, a continuous telephone interview survey over the period 1988 to 1995 of 34,247 Edinburgh and Glasgow residents aged 18–60,[3] which *inter alia* touched on self-reported consumption of alcohol, found there had been an increase in the rates of people reporting heavy drinking *on occasion*. This was defined as '5 or more drinks' in a session, and its occurrence increased significantly in both men (by 4.9%) and women (by 6.5%) during the years 1988 to 1995.

(b) Morbidity[4]

Figure 2 shows that, for the diagnosis alcohol related liver disorder, discharges from general hospitals, for males and females, rose from 1983 to 1995 continuing the trend noted by Findlay.[1] Discharges from general hospitals for alcoholic psychosis, alcohol dependence and alcohol misuse likewise rose during this period, for both genders (Figure 1).

On the other hand, admissions to psychiatric hospital for alcoholic psychosis and alcohol dependence decreased

*These were the 'upper limits' used during the 1980s, in connection with the term 'sensible drinking' and endorsed in 1995 by the Royal Colleges of Psychiatrists, of Physicians and of General Practitioners.[21] In 1995 a Government Interdepartmental Working Group[22] stated that for men regular drinking of up to between 3 and 4 units per day and for women up to between 2 and 3 units per day represented a 'sensible benchmark', though this was slightly higher than the Colleges' recommendation.

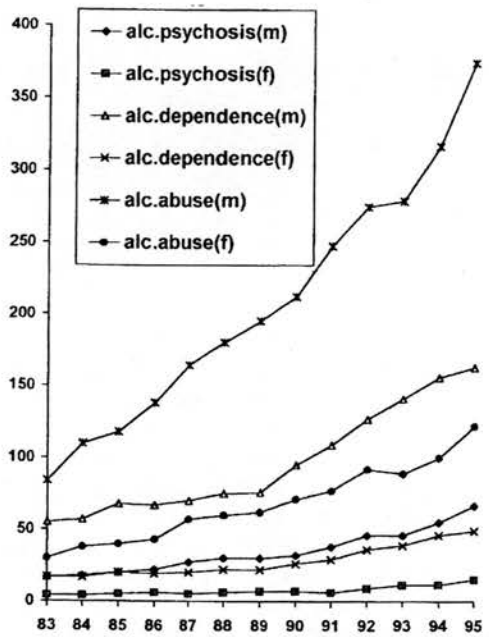

Figure 1. Discharges from Scottish General Hospitals (per 100,000 Population) 1983–1995.

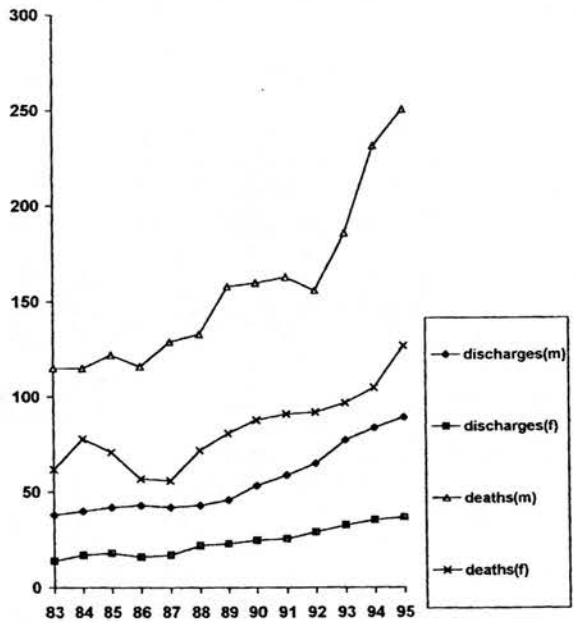

Figure 2. Alcohol Related Liver Damage: Total Number of Deaths; General Hospital Discharges/100,000.

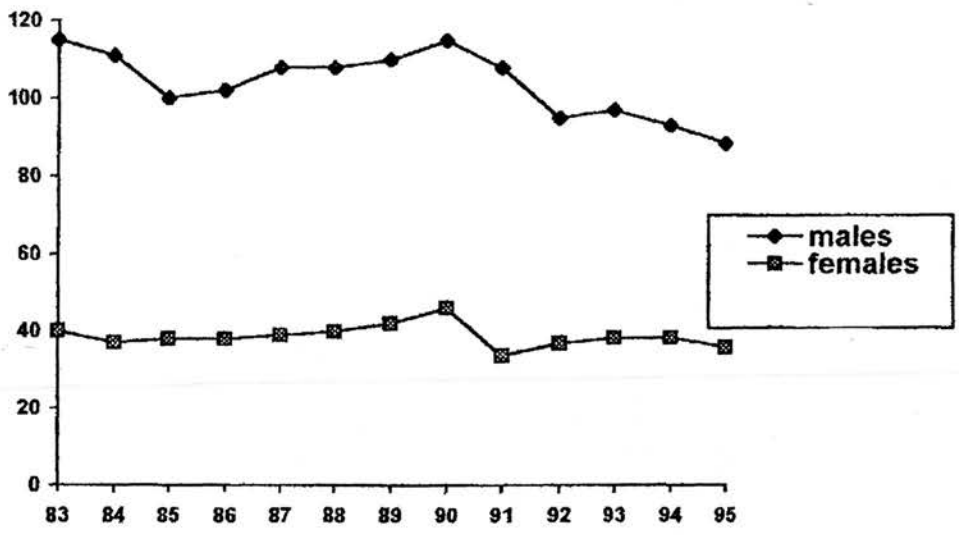

Figure 3. Admissions/100,000 to Psychiatric Hospitals for Alcoholic Psychosis or Dependence.

somewhat in males and remained fairly stable in females (Figure 3). (The coding system used for these, and other data below, was the International Classification of Diseases, 9th edition—ICD–9; 1995 data are provisional; the accuracy of the Scottish Morbidity Record (SMR) is regularly reviewed[5] and is impressive.)

(c) Mortality[6]

Deaths certified as due to alcohol-related liver disorder rose from 1983 to 1995 (Figure 2), also continuing the trend noted by Findlay.[1]

Possible explanations

Is the rise in problems due to a rise in per capita consumption? It is well grounded in 50 years' of studies in many societies that a rise in *per capita* consumption is often associated with a rise in health problems related to alcohol.[7] However, the rising rates of alcohol related mortality and morbidity shown in the Figures 1 and 2 have occurred during a period when *per capita* consumption was apparently on a plateau.

Mortality from alcoholic cirrhosis has usually risen when *per capita* consumption rises, but sometimes with a lag.[8] A lag might explain why Scottish rates of alcohol-related disorders continued to rise in the 1980s after general population alcohol consumption had stabilised. However, such lags have tended to last less than a decade, so it might be expected that a plateau in health damage from alcohol would have been reached by the 1990s. On the contrary, Figures 1 and 2 show a rise continuing into the 1990s.

Threshold for admission may have fallen. The threshold for emergency admission to general hospitals in the UK seems have fallen in the past decade.[9] This may explain in part the rise in discharge rates that have occurred for a number of diagnoses. Heart disease is an example: discharges for heart disease rose from 1,093/100,000 in 1985 to 1,630/100,000 in 1994–5.[4] However, the rise in general hospital discharges for alcohol-related disorders has been even steeper than that for heart disease. The fact that, at least for alcohol-related liver disorder, deaths have also risen argues

against the rise in discharges being merely a lower threshold resulting in milder cases being admitted, or the same cases being more frequently readmitted.

Closure of psychiatric beds may have diverted alcohol-related admissions to general hospitals. The fall in male admissions to psychiatric hospitals for alcohol-related conditions (Figure 3) may indeed result from a combination of planned bed closures plus greater confidence (hopefully not misplaced) in out-patient treatments. However, the reduction in psychiatric admissions is far less than the increase seen in general hospital activity. It appears unlikely, therefore, that the rise of alcohol problems seen in general hospitals is accounted for merely by a shift in practice, from admitting to a psychiatric hospital to a general hospital instead, although this may have been occurring in some regions. Furthermore, there has been no fall in female alcohol-related psychiatric admissions.

Diagnostic practices may have changed. Doctors may have relaxed their criteria for diagnosing alcohol disorders. This seems unlikely to be the full explanation of the increasing indices because:

(a) if doctors had begun to use the appellation 'alcohol' more freely for liver disorders or their alcohol detection methods had improved, then there would have been a redistribution of codings. That is, that the amount that 'alcohol-related liver disorders' rates rose would be the amount that rates for 'liver disorders—alcohol *not* specified' would fall. However, discharge rates for 'liver disorders—alcohol not specified' have been increasing rather than falling (from 1990 to 1994: 33.0 to 43.7/100,000(m), 17.4 to 22.7/100,000(f));[4]

(b) *total* deaths from chronic liver disease and cirrhosis have increased proportionate to the increase in deaths from alcohol-related liver disorder, rather than staying level[6] which would have been expected if the rise in alcohol deaths had been due to redistribution of codes;

(c) discharge rates for 'suggestive' diagnoses, alcohol not mentioned, are also increasing e.g. acute pancreatitis (from 1990 to 1994–5: 46 to 62/100,000(m), 34 to 59/100,000(f)).[4] This adds further support to the argument that the rise in rates of alcohol-related disorders is real and not merely an artefact of coding;

(d) doctors' thresholds for coding alcohol disorders seem still to be high: in 1995 an audit in ten wards of a Scottish general hospital found that in 46 records of patients treated for alcohol withdrawal, the discharge diagnoses mentioned alcohol in only seven (D. MacKenzie, personal communication);

(e) there have been no legal changes in Scotland to stimulate change in doctors' death certification. In the past decade in England and Wales, coroners' rules changed to make it more acceptable for alcohol to be mentioned on death certificates. There was reason to believe it had often been deliberately omitted, since previously it would lead to a coroner's enquiry.[10] This had not been the case in Scotland, which was sometimes given as an explanation of the higher Scottish recorded alcoholic liver disease mortality. While the Scottish procurators fiscal may have followed the English coroners in trying to ensure relevant recording of alcohol (albeit without there having been any legal artefact), the fact remains as stated already that records show an increase in *total* liver disease deaths, and not just the proportion coded as alcohol-related.

The rise in alcohol-related liver deaths may be due to increased drug abuse. Intravenous drug misuse increased 1970–1985.[11] It is possible that in this period some people destined to misuse alcohol had a period using drugs during which they contracted viral hepatitis. This could lead to higher rates of liver deaths in the heavy drinking population, which, if they had been drinking heavily prior to death might lead to their death certificate including alcohol misuse as a secondary cause of death. Antibodies to hepatitis C virus are frequently found in alcoholics with liver disease, and such antibody formation is related to the severity of liver damage.[12] According to the coding procedures of the Registrar General such deaths would be coded as 'alcohol related liver disorder'. Against this as a significant explanation of the rise in alcohol-related liver deaths are the following points:

(a) the increases in liver deaths are in all age groups, arguing against a cohort effect;
(b) there has been no rise in North American liver mortality[13, 14] following a similar period of increasing intravenous drug misuse;
(c) the rises in non-liver alcohol discharges are not explained.

There may have been a generation with many heavy drinkers. Perhaps there has been a specific cohort of people starting off as heavy drinkers in the 1970s and developing disorders in middle age, which could cause an elevation in indices, but a transient one. If so, as time passed we would see a rise in heavy drinkers in the age-band 45–65 with a change to less heavy drinking in the younger age bands. The General Household Survey data[2] do not show this for Scotland (though England and Wales data are suggestive and more years could perhaps reveal such a cohort effect). Also against a cohort effect is the fact that alcoholic liver deaths have increased in all ages.

There may be more people in recent years drinking in a risky pattern. The liver is probably affected more by regular heavy drinking, than heavy sessional drinking. The only sequential population data available for Scotland on patterns of drinking are the recent telephone survey results for Glasgow and Edinburgh,[3] but if anything these would suggest that it is heavy sessional drinking rather than regular drinking that has increased. This study was not principally aimed at specifying alcohol consumption and its results need replicating. The rising rates of many other types of general hospital 'non-liver' alcohol related admissions (e.g.trauma, with 'alcohol misuse') would implicate heavy session drinking rather than daily drinking. We do not seem to have an explanation thus far for the rise in alcohol-related liver mortality and morbidity shown in Figure 2.

Could *per capita* consumption have remained stable, but with a greater dispersion of drinking as the years passed: more light, fewer moderate, and more heavy drinkers (be it heavy sessional or heavy regular)? The General Household Survey does not show this, but surveys are insensitive at the heavy end (underestimating drinking compared to sales/excise data).[7] The explanation for the rise in recorded damage of all types therefore seems unlikely to be due to changing patterns or dispersion, but to more heavy drinkers.

Scottish alcoholism treatment services might have become less effective. Rates for liver deaths in Scotland have not followed the USA and Canada, where liver mortality fell in this period despite stable *per capita* consumption. Noble *et al.*[13] concluded that better treatments for cirrhosis could not explain all of the fall, but showed that the period corresponded with a burgeoning of alcohol treatment services and affiliation to Alcoholics Anonymous.[13, 14] During the past decade, some specialist alcohol treatment units have closed or been reduced in resource, though community services have grown. For the services that exist there has been no audit published which shows that they follow those approaches which have been demonstrated in randomised controlled studies to be effective. There is no data to show that treatment outcome is either getting worse, or that it is improving. A study which showed that the suicide rate in hospital-treated alcoholics in Scotland had decreased referred to 1974–83, the decade period prior to that discussed in this paper.[15] Doctors in Scotland, with the exception of an older cohort, have had a declining re-admission rate for alcohol dependence compared to other professions which could indicate improved outcome.[16] However, these findings are based on small numbers and are merely relative to other professions.

Comment

While increasing national consumption explained the post-war rise in alcohol problems, there is now a period of rising harm no longer driven by the increasingly liberal attitudes to drinking and fall in real price, which were influences in the 1960s and 1970s.[7] It is possible that surveys have been too insensitive to detect a growing number of problematic drinkers, and that these drinkers are also masked in national alcohol sales figures. A reason for the rise in their numbers might be because, in an era of relatively low real price and high availability of alcohol, other social changes have had an influence. Increasing disparity in income has been put forward as one social factor affecting health in the UK

and in Scotland[17] although there has been no link yet investigated between income disparity and problematic drinking. Another social change is increasing relative social isolation, as indicated by falling marriage rate and rising divorce rate[6] (the UK has the highest divorce rate in Europe[6]), rising rates of one person households[18] and doubling of the rate of lone parent families.[18] It appears to be increasingly easy in our society for women to leave their partners. Living alone and being divorced or separated are known to be related to regular and heavy drinking in Scotland[19] as in other cultures e.g.[20] The putative continuing rise in problematic drinking in the last decade appears not to have been offset by improvements in the availability or outcome of treatment.

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Conflict of interest

None.

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Counselling problem drinkers in medical wards: a controlled study

JONATHAN CHICK, GEOFFREY LLOYD, EVELYN CROMBIE

Abstract

Seven hundred and thirty one men admitted to medical wards were interviewed to identify problem drinkers who had not received previous treatment for alcoholism and who had some social support. One hundred and sixty one met the diagnostic criteria; 156 agreed to a follow up interview and were allocated to one of two groups. One group received a session of counselling about their drinking habits from a nurse while the other received only routine medical care. Both groups reported a reduction in alcohol consumption when interviewed 12 months later, but the counselled group had a significantly better outcome than the control group.

It is concluded that systematic screening for alcohol consumption and related problems should become a routine part of medical assessment and that advice on drinking habits is effective if given before irreversible physical or psychosocial problems have developed.

Introduction

Treatment of patients with alcohol problems is often unsatisfactory because many of them have developed advanced physical, psychiatric, or social complications before they present for medical help. Earlier detection has been recommended on the assumption that intervention will be more effective at an earlier stage in the illness,[1] but this has not yet been widely tested. Problems related to alcohol are common among inpatients in general hospitals,[2 3] and people subsequently identified as alcoholics have an excess of medical admissions for a wide range of conditions.[4] The extent of the problem, however, requires that the ideal treatment should be brief and readily available.

We report a study carried out in medical wards to determine the effectiveness of brief intervention in problem drinkers who had not received previous treatment and had at least some social support, which is an important influence on the outcome of treatment of alcoholism.[5]

Patients and methods

SCREENING

We studied a consecutive series of men aged 18-65 admitted for at least 48 hours to one of four male medical wards covering a wide range of specialties. The study was confined to men because the first six months of screening indicated a very low proportion of newly identified cases among women.[6]

Patients were excluded at the outset if they were of no fixed abode, their mental state precluded a reliable history, they were terminally ill, or they had already been referred to the department of psychiatry. A structured interview of proved interrater reliability was then given by a nurse with experience in treating alcoholism; this interview covered consumption, dependence, problems related to alcohol, recent and distant medical history, and social background. Patients were identified as problem drinkers if they acquired two or more points according to the criteria listed in the figure.

Patients were included in the study only if they met at least two of the following criteria: currently employed or employed for six of the past 12 months; married; had a "confidant" or close friend; or lived with at least one other person.

RANDOMISATION AND INTERVENTION

Patients who satisfied the above criteria were asked to participate in the study, which, they were told, was concerned with the relation between their health and drinking habits; they were also informed that they would be interviewed again 12 months later. Allocation was made to one of two groups: control and treatment. A compromise had to be made to the traditional method of random allocation of patients in a clinical trial. We wished to avoid a control patient being in the bed adjacent to a patient in the treatment group. Each ward therefore alternated every two or three months between being a source of controls and patients in the treatment group. This had the disadvantage that before the assessment interview began the nurse knew whether the patient, if recruited to the study, would be

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in the treatment group or not, but she endeavoured to keep the assessment procedure standardised. Patients in the treatment group received further counselling from the nurse. The session lasted up to 60 minutes, during which the nurse gave the patient a specially prepared booklet and engaged him in a discussion on his lifestyle and health, which helped him to weigh up the drawbacks of his pattern of drinking and to come to a decision about his future consumption. The objective was to help the patient towards problem free drinking, though abstinence was the agreed goal for some. Controls received no advice; no comment was made about the content of the screening interview. The physician in charge, however, may have advised the patient to modify his alcohol consumption, according to his normal practice. Mean cell volume and γ-glutamyltranspeptidase activity were measured in all cases as laboratory markers of alcohol consumption.

FOLLOW UP

Patients were approached again after one year. The interviewer was a senior nurse with experience of interviewing about alcoholism. He was unaware of the design of the study. The follow up interview included questions about general health and experience of problems related to alcohol (figure) in the 12 months since leaving hospital, and questions about alcohol consumption were repeated. Blood was taken to measure mean cell volume and γ-glutamyltranspeptidase activity.

During the year the patient might have received treatment for his alcohol problem from his general practitioner, from a hospital doctor, or at a treatment agency listed in the advice booklet. The interviewer did not ask about this as the information might have biased his observations.

DEFINING OUTCOME CATEGORIES

Patients were thought to be definitely improved if they reported no problems related to alcohol in the year to follow up. If the patient reported no problems at either interview he was considered to be improved if his consumption had fallen by 50% or more. In both cases improvement had to be supported by results of blood tests or a relative's report. If these criteria were not satisfied patients were regarded as not definitely improved.

γ-Glutamyltranspeptidase activity supported self reported improvement if it was 40 IU/l or below at intake and remained at that concentration, or if it had been above 40 IU/l and subsequently fell by at least 50%. Mean cell volume supported self reported improvement if it was 96 fl or below at intake and remained at that level, or if it had been above 96 fl and subsequently fell by at least 2 fl.

Consumption

Over 14 units* in a day on 10 or more occasions in past year
Over 50 units in typical week
Over 12 units in 24 hours in typical week

Problems related to alcohol

Current medical problems

Present illness potentially related to alcohol
Present illness definitely related to alcohol
Weight problem due to alcohol

Medical problems in past two years

Peptic ulcer aggravated by drinking
Liver disease due to alcohol
Accident due to drinking

Social problems in past two years

Antisocial behaviour
Problems at work (including absence)
Domestic arguments
Violence
Family rupture (threatened or actual)
Financial
Police

Dependence on alcohol in past two years

Difficulty in reducing consumption
Restlessness without alcohol
Tremor (over one day a week)
Morning relief drinking (over one day a week)
Hallucinations
Withdrawal seizure

Criteria for inclusion as a problem drinker. Patients scored one point for presence of any variable except for † presence of illness definitely due to alcohol, which scored two points.
*1 unit = 57 g (1 oz) of 40% (by volume) spirits; 13·7 ml (half pint) of 3·6% (by volume) beer; one glass of wine, etc—that is, roughly, 8 g ethanol.

Results

A total of 731 men eligible for inclusion were admitted during the study, of whom 161 met our diagnostic criteria. One hundred and fifty six agreed to a follow up interview, and 78 were allocated to each of the two groups. Control and treatment groups did not differ with regard to age, marital state, level of social support, occupational state, medical diagnosis, mean alcohol consumption in the week before admission, or mean cell volume and γ-glutamyltranspeptidase activity (table I). Symptoms of physical dependence were uncommon and did not differ between the two groups. The groups differed, however, with regard to the total mean problem score, which was higher in the group given counselling than in the controls ($p = 0{\cdot}014$). When patients were divided into those who did and those who did not admit to problems related to alcohol at intake the two groups were still matched on medical, sociodemographic, and dependence items and blood tests.

We interviewed 133 patients after one year. Data on γ-glutamyltranspeptidase activity and mean cell volume were available at both interviews in 124 cases. Three patients had died during the intervening period, and 20 could not be contacted or refused to be seen. This indicated poor outcome[7] and applied to more controls than patients given counselling.

Table I shows measures of outcome, from which it can be seen that both groups significantly reduced their mean weekly alcohol consumption. Patients who had been counselled did not reduce their consumption more than the controls, but 44 (64%) of these patients claimed that they had reduced their consumption by at least 50%, compared with 31 (48%) of the controls ($p = 0{\cdot}07$). The patients given counselling showed significant improvements in their score for problems related to alcohol and γ-glutamyltranspeptidase activity. Because they had a higher mean problem score at intake, however, the change in problem score was calculated as a percentage of the initial value. This showed a greater mean fall (41%) for the patients given counselling than the controls (14%) ($p = 0{\cdot}03$). At intake 23 (30%) of the patients given counselling and 30 (39%) of the controls did not acknowledge any problems, whereas at follow up the numbers were 40 (58%) and 33 (52%), respectively.

A significant difference between the groups was found when global categories of outcome were examined. Of the 124 interviewed for whom complete blood tests were available, 34 (52%) of those given counselling and 20 (34%) of the controls were categorised as definitely improved ($p = 0{\cdot}038$) (table II). Thirteen (19%) of the patients given

TABLE I—*Mean values (SEM) at intake and follow up for patients followed up at one year*

	Consumption in past week (units)		Problems related to alcohol		Mean cell volume (fl)		γ-Glutamyltranspeptidase activity (IU/l)	
	Intake	Follow up	Intake	Follow up	Intake	Follow up	Intake	Follow up
Patients given counselling	69 (5·2) (n = 69)	32 (5·1)** (n = 69)	2·4 (0·3) (n = 69)	1·1 (0·2)** (n = 69)	92 (0·6) (n = 65)	92 (0·6) (n = 65)	151 (44) (n = 65)	89 (23)* (n = 65)
Controls	69 (5·7) (n = 64)	35 (4·6)** (n = 64)	1·4 (0·2) (n = 64)	1·2 (0·2) (n = 64)	93 (0·8) (n = 59)	93 (0·8) (n = 59)	126 (43) (n = 59)	99 (24) (n = 59)

*$p < 0{\cdot}05$, **$p < 0{\cdot}001$ compared with values at intake.

TABLE II—*Outcome after one year*

	Dead	Refused or no contact	Blood tests incomplete	Blood tests complete	
				Definitely improved	Not definitely improved
Patients given counselling (n = 78)	1	8	4	34*	31*
Controls (n = 78)	2	12	5	20	39

*Patients given counselling v controls: $\chi^2 = 4{\cdot}26$, $p = 0{\cdot}038$.

counselling and 15 (23%) of the controls were admitted to hospital during the follow up period; four (6%) and 11 (17%), respectively, were admitted for eight days or more.

Discussion

Many patients showed a substantial improvement during the 12 months after the index admission to hospital. The experience of being ill, advice from various doctors treating them, and increases in the price of alcohol[8] may all have had a beneficial effect. There may also have been a "regression to the mean" effect: some patients were admitted with illnesses related to alcohol after a period of heavy drinking, and it is to be expected that at an arbitrary point in the future the consumption and associated problems of such patients would be reduced. Nevertheless, those who received additional counselling achieved a significantly greater improvement than those who received only routine medical care.

In defining outcome we gave precedence to improvements in self reported problems related to alcohol over improvements in self reported consumption because we believe that it is harder for a man to prevaricate about whether he has lost a job through drinking, for example, than about how much he drank in the previous week or in a typical week. Furthermore, our strategy of treatment was aimed at helping men achieve problem free drinking and not necessarily complete abstinence.

Our groups were not matched for the number of alcohol related problems at intake, though they were matched on every other variable at intake that we measured. We believe that this lack of matching can only have occurred by chance. In view of the difference in alcohol related problems we specified definite improvement as complete freedom from problems at follow up. This might have weighted our analysis against finding an effect of counselling because it would be harder for patients with several problems related to alcohol (of whom there were more in the counselling group) to become completely free of them than for patients with few problems.

The effectiveness of treatment for established alcoholics continues to be a matter of debate. A controlled study of intervention in early cases has yielded promising results[9]; even self help booklets, such as *Drinking Problems: Information and Advice for the Individual, Family and Friends*,[10] have proved successful.[11] The effect of treatment may well persist if brief intervention is repeated at intervals.[9] Our study shows how important early detection is, and our results are sufficiently encouraging for us to recommend that similar studies should be conducted in other general hospitals with inpatients or outpatients. Patients may be especially receptive to counselling when recovering from a medical illness. Screening for alcohol problems should become a routine part of nursing assessment and the medical history so that advice can be given before irreversible physical or psychosocial problems have developed.

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Secondary Prevention of Alcoholism and the Centres D'Hygiène Alimentaire

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Summary
France has invested in a mode of secondary prevention for alcoholism, the Centres d'Hygiène Alimentaire (C.H.A.). Early problem drinkers detected in industry, general hospitals, by social services, and drinking/driving offenders are referred for assessment and advice. The approach is medical. Among drinking/driving offenders in Soissons, a majority attend the C.H.A. and a majority of attenders return for follow-up. A randomized, controlled outcome study has not been performed, but the results of the Soissons C.H.A. are promising, as are some early results in two other projects.

The secondary prevention of alcoholism – detecting and intervening in the early case so as to prevent the development of addiction or serious social or physical harm – has been advocated in several policy documents [1, 2]. Although research on early detection has been widely published [e.g. 3], there is little yet in the literature on early intervention except in the drinking/driving area, where to date programmes have not demonstrated unequivocal success [4].

In France, considerable resources have been allocated to a programme of secondary prevention – the Centres d'Hygiène Alimentaire – but it is hard to find any objective evaluation of this investment.

The development of the Centres d'Hygiène Alimentaire

For 20 years before his death in 1979, Dr P.-M. Le Go developed a method for detecting early alcoholism and intervening. He worked in the French Railways where in 1957, 23 per cent of the many hundreds of workers screened by physical examination had been diagnosed as 'third degree alcoholics'. In 1965 only four per cent were so diagnosed [5]. He felt that this could be attributed to his intervention though it is not known whether recruitment policies altered during this period.

His approach to the excessive drinker was to educate him about the adverse effects of excessive drinking, and set this in the context of his daily diet. Unlike the classic alcohol programmes in French clinics, moderate drinking rather than abstinence was advised. The doctor reviewed his patient at intervals, giving practical advice and providing feedback about improvements – or deterioration – in general health. Emphasis was on the physical signs of excessive drinking – complexion, colour of the tongue; tremor of the tongue, mouth and hands; size and consistency of the liver. Blood tests, mean cell volume and gamma glutamyl transpeptidase, have since been added to the assessment. In France, where daily drinking is common, these blood tests correlate more highly with consumption [6] than has sometimes been the case further north in Europe [7].

Modelling themselves on the work of Le Go, some 140 Centres d'Hygiène Alimentaire (C.H.A.) have been created throughout France. The euphemistic appellation is an acknowledgement that heavy drinkers do not wish to be seen as alcoholics and need not be forced to. Typically, a C.H.A. has a receptionist (the key figure in ensuring that the initial contact is friendly and informal). a nurse, perhaps a dietician and/or a social worker, and general practitioners or general physicians with an interest in the field give several sessions per week.

The typical consultation takes less than 30 minutes; is concerned almost exclusively with present medical and to some extent social and psychological problems; sets short term drinking goals for reduction of drinking; gives practical advice on managing life with less alcohol and probably includes a brief medical examination. The patient may see the nurse for an informal chat prior to the doctor's consultation. The offices may be in a health centre, in down-town premises in a shopping area or perhaps next to the gastrointestinal unit in a general hospital.

Many C.H.A. have moved away from preventive

work to meet the pressure of the needs of established alcoholics. My impression, after visiting 11 rather different C.H.A., is that some staff find it easier to respond to the sick alcoholic than to win over the individual who is the target of preventive medicine and rightly or wrongly feel it is effort better spent. Thus, some C.H.A. have become out-patient alcoholism treatment centres. For example, in a C.H.A. in down-town Marseilles, 72 per cent of cases in 1981 could be classed as already dependent on alcohol. Nevertheless, some still concentrate on their original goal. At Soissons, for example, a small town 60 miles north-east of Paris, less than half the clients were, even on the loosest criteria, termed alcohol dependent.

Babor and colleagues [8] have commented on the paucity of evidence that the C.H.A.s are effective in preventing or retarding the development of alcoholism. This paper presents data from the Soissons C.H.A. (the 'model' centre) that I collected in an attempt to find evidence that might go towards answering whether a C.H.A. can claim to be effective.

Recruitment of cases to the C.H.A.

The C.H.A. based in a general hospital, for example in an office suite adjacent to the Gastroenterology Department, receives a high proportion of its referrals from hospital physicians, such as patients with upper gastrointestinal symptoms, liver abnormalities, a first attack of pancreatitis. However, as Table 1 shows, there is one source of clients which many C.H.A. have in common – those referred by the Direction Départmentale des Affairs Sanitaries et Sociales (DDASS).

Drinking/driving referrals

All the drinkers referred by the DDASS have been charged by the police for driving while intoxicated. There is a procedure in many regions whereby, since 1978, the Préfecture refers such individuals to the C.H.A. In Soissons since 1978 my analysis shows that 76 per cent of such offenders are seen at the C.H.A. (some non-attenders are individuals who were only temporarily in the area and reside far away; others decline the invitation). At other C.H.A. I studied, for example Nice and Marseilles, the estimated percentage is much lower, between 20 and 50 per cent attending. The initial approach to clients in Soissons is made by the C.H.A. not the Préfecture as in some other areas. In these areas individuals fear that the appointment is to enable the licensing authorities to label them as chronic alcoholics and ban them permanently from driving. However, in Soissons, the letter from the C.H.A. to the individual is carefully worded so as not to be threatening. The Préfect in Soissons at a special commission for reviewing driving licences notes whether or not individuals have taken up the invitation to attend the C.H.A. and may persuade them to do so. A further factor which may explain why the Soissons Centre has a greater attendance is that evening and Saturday morning consultations are available.

The C.H.A. has no officla role in deciding when or if a driving licence is returned. However, every individual has to report to the commission before his licence is returned. In Soissons, where relations between the Préfecture and the driving licence medical authorities are good, the opinion of the C.H.A. may be sought. There is no law specifying what level of daily drinking is permissible amongst people who hold driving licences nor what degree of liver abnormality is allowable. But even if there was, it would not extricate the C.H.A. doctor from the ethical dilemma of being asked to divulge information about a patient, which may not be in the patient's best interest. The C.H.A. doctor has the same ethical obliga-

Table 1 Source of referrals to three C.H.A. services in 1981

	Départment de l'Aisne (community-based)	Toulouse (hospital-based)	Nice: Hôpital Cimiez
DDAS (drinking/driving offenders)	50%	40%	37%
Medical commission for driving licences	15%	1%	0%
Family doctor	2%	6%	5%
Industrial doctor	3%	6%	1%
General hospital	9%	45%	52%
Social services	8%	5%	1%
Other, including self-referral	3%	5%	2%
Total number of clients	818	146	111

ions to his patients as any other doctor whose patients onsult him freely. There is no law compelling the rinking/driving offender to attend the C.H.A. nor is here a law compelling the C.H.A. doctor to give inormation to the Préfect or the commission on driving cences. The C.H.A. doctors respect their patients' ights.

Do most driving offenders only attend once, for example out of curiosity or to please the authorities?

n some C.H.A. the majority of drinking-driving offenders attend once, as a formality and do not return. Iowever, in Soissons, from 1978 to 31 July 1982, out of 11 cases, nine cases only attended once. All others ttended on two or more occasions. In the cohort ecruited in the 2 years to December 1980, out of 181 ases, 57 (31%) had made eight or more visits in the eriod from 1978 to the end of 1981. Presumably these ndividuals see a purpose in attending the clinic. Perhaps ome of them keep relapsing and have to attend because ney are doing badly? This may be true for some but nany appear to have a satisfactory outcome. Of the 302 rinking driving cases recruited from 1978 to July 1982, 41 were still being followed at the end of that period. The state of these individuals, based on information iven at the periodic visits supplemented by objective riteria such as blood tests and the relatively objective riteria of physical examination as coded according to ne 'Grid' method of Le Go [9], was as follows: 113 37%) 'abstinent or drinking without problems'; 70 23%) 'improved'; 9 (3%) unchanged; beginning treatnent 49 (16%). Assessment of outcome also takes into ccount information gleaned by the staff from their idely-based community contacts (Soissons is a small ommunity of 30,000). Fifty-seven cases had been disnarged, 29 (9%) as 'satisfactory', 15 (5%) because they ad been referred on or had left the district; 14 (5%) because they did not wish to continue, of whom four were known to be well. Four cases (1%) had died, one possibly of an alcohol-related cause. This yields an impressive 'improvement rate', but no independent evaluation has been made. Unfortunately it appears to be impossible easily to obtain accurate official data on recidivism rates for drinking/driving offences *per se*.

Are the people who attend truly at high risk for alcoholism?

Without a lengthy follow-up of an untreated group of drinking/driving offenders, we cannot answer this. Indeed, I do not know of such a follow-up in the international literature. But it is probable that the group seen contain many individuals at risk.

First, as Table 2 shows, both in Nice and in Soissons, three-quarters of attenders are either already damaged or are in the excessive drinking range (the classification used in Table 2 is based on the Grid method of Le Go, which depends largely on physical signs and has been compared with liver indices of alcoholism [9]).

Second, it is not the case that the C.H.A. fail to harvest the serious cxases. Attenders have the same age range and the same range of blood alcohols at the time of offence as those who do not attend (Table 3). (It seems likely that an individual who drives at a blood alcohol level above 2 g/l has an elevated tolerance to alcohol and is a regular heavy drinker.) Heavy drinkers do not specially avoid attending.

Discussion

The descriptive data presented here refer mainly to only one, albeit the major, type of recruit seen at the C.H.A., namely the drinking/driver offender. It is, incidentally, the type of recruit that many C.H.A. staff least prefer to

Table 2 Classification of attenders at two C.H.A. referred for driving while intoxicated*

	Occasional drinkers	Excessive drinkers probably drinking above 60 g (7 drinks) per day	Verging on dependent	Dependent already physically damaged
Nice-Cimiez 1978–July 1982 n = 229	60 (26%)	108 (47%)	34 (15%)	27 (12%)
Soissons Jan. 1978–July 1982 n = 311	84 (27%)	137 (44%)	73 (23%)	17 (5%)

*Classification according to Le Go [5] made by treating physician.

Table 3 Age and blood alcohol level at time of offence of individuals referred for driving while intoxicated to Soissons C.H.A. (Jan. 1978–July 1982): attenders v. non-attenders.

	Age				Blood alcohol g/l			
	20	20–30	30–40	40+	.80–1.00	1–2	2–3	3+
Attended C.H.A. n = 311	32 (10%)	132 (42%)	73 (23%)	74 (24%)	5 (2%)	124 (40%)	122 (39%)	29 (9%)
Did not attend C.H.A. n = 99	23 (12%)	44 (44%)	20 (20%)	23 (23%)	0 (0%)	50 (50%)	35 (35%)	14 (14%)

deal with. The data relate only to one C.H.A. and are uncontrolled. One can conclude no more than that the cases recruited are likely to be truly at risk and the treatment results are promising. One must not disparage the efforts of the C.H.A.: no-one, to my knowledge, has yet designed a treatment outcome study in drinking/driving offenders that could give information of value to the worker interested in preventing deterioration in the health and well-being of excessive drinkers.

Recidivism rates, which are not of interest to the health worker, have generally been the only outcome criterion in evaluations of treatment programmes for drinking/driving offenders [4]. In such evaluations randomization to treatment versus no treatment has been extremely difficult to arrange for administrative reasons. It seems unlikely that a design can be conceived where a control group accede to researchers wishing to collect detailed baseline and follow-up information on the group's medical and social state, drinking habits and problems. Clayton and colleagues (10), for example, obtained a research interview in only 36 per cent of 284 such offenders whom they approached.

There is greater hope of evaluating secondary prevention in a population who have come to medical attention already – visiting a family doctor or hospital – or even in the general population as Kristenson and colleagues have done in Malmo [11]. The Malmo study invited middle-aged men from the general population to a medical screening. Men whose self-reported drinking was heavy and where this was confirmed by elevated gamma glutamyl transpeptidase (GGT) were allocated to either (a) roughly three-monthly counselling and feedback about GGT levels, or (b) no intervention. About a quarter of the intervention group dropped out of treatment. In the first 5 years after intake to this study, the intervention group appears to have had a lower mortality, fewer sickness days and fewer days in hospital. In Edinburgh, male 'early problem drinkers' identified in general medical wards were allocated either to a counselling session with a nurse accompanied by a booklet, or no intervention. Here also, independent follow-up using objective criteria has begun to show better outcome in the treated than the control group [12, 13].

The possibilities for secondary prevention at this stage seem promising. However, if enthusiasm for secondary prevention is to be allowed to divert attention and resources away from the care of the established alcoholic or the imperatives of primary prevention, then it is necessary for the effectiveness of secondary prevention programmes to be properly established.

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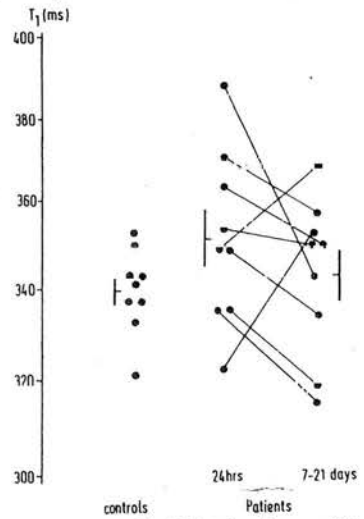
BRAIN WATER IN CHRONIC ALCOHOLIC PATIENTS MEASURED BY MAGNETIC RESONANCE IMAGING

SIR,—In magnetic resonance imaging (MRI) the T_1 relaxation time is related to the state of water in the tissue.[1] The T_1 value, measured in milliseconds, increases as the proportion of free to bound water increases. MRI is therefore a potentially valuable technique in the study of brain water during withdrawal of alcohol in chronic alcoholic patients. It has been used previously in such a study[2] which suggested that there was "decreased free water during intoxication and an increase in brain water during alcohol withdrawal", a somewhat surprising result that the authors admitted was "at variance with current clinical practice which emphasises the role of dehydration in the syndrome and encourages fluid replacement". We have repeated the study in a larger group of patients, since the result could have implications for the treatment of alcoholism.

The subjects were 9 chronic alcoholic patients (7 male, 2 female, aged 29–60 years, mean 46) voluntarily admitted to hospital for detoxification. They had been drinking at least 130 g ethanol per day (mean 180 g per day) before admission and had a 5–15 year history of alcoholism. None was clinically malnourished, or had physical disorders other than raised liver enzymes in serum. Over the first 5 days each patient received a normal diet, intramuscular vitamin B supplement, and decreasing doses of chlordiazepoxide. 9 normal controls, sex and age matched (range 26–62 years, mean 45), were chosen from hospital staff; their alcohol consumption ranged from total abstinence to the equivalent of 80 g ethanol per week.

Measurements were performed using a 0·08T resistive MRI system.[3] All patients were investigated on two occasions, at 24 h and at 7–21 days after cessation of alcohol consumption; controls were investigated once. Measurements of T_1 were made from a calculated T_1 image of a 12 mm thick transverse section 10 mm above the maximum diameter of the lateral ventricles. To define the T_1 in grey and white matter in the frontal, parietal, and occipital regions small regions of interest were defined—for grey matter 20 mm^2 and for white 69 mm^2—and the mean of similar regions in the left and right hemisphere was noted. In addition the T_1 value over the whole brain, excluding the cerebrospinal fluid (CSF), was measured. The precision of T_1 estimation was estimated from four repeated measurements on 3 normal volunteers over a period of a month. The T_1 precision of white matter was 2·8%, grey matter 4·9%, and the whole brain, excluding CSF, 2·6%.

At 24 h T_1 over whole brain was higher in alcoholic patients than in controls (see figure). It then falls over the next 7 to 21 days. The change in T_1 in the whole brain in alcoholic patients correlated with the time between abstinence and the second measurement ($r = -0·81$, $p<0·01$). The mean decrease in T_1 in alcoholic patients



T_1 values over whole brain of individual patients at 24 h and at 7–21 days after withdrawal of alcohol compared with age-matched normal controls.

Mean±1SE is shown.

in grey matter was 10·1 ms (SE = 6·9 ms) whereas the decrease in white matter was only 0·6 ms (SE = 4·0 ms). The decrease in T_1 in grey matter correlated with the duration of abstinence ($r = -0·76$, $p<0·05$). Though the decreases in T_1 over whole brain and in grey matter in alcoholic patients were not significantly different from zero, the reduction is significantly different ($p<0·05$) from the increase previously reported by Besson et al.[2]

The preliminary results of this study suggest that chronic alcoholic patients have a higher T_1 value in the brain than do normal controls. This raised T_1 probably reflects an increase in free water within the brain. During withdrawal from alcohol the T_1 drops, probably because of a decrease in the brain water content. Our findings contradict those of Besson et al[2] but are consistent with the generally accepted hypothesis that the brain becomes excessively hydrated during chronic alcohol consumption and that abstinence results in dehydration of the brain.

We intend to determine in more detail the differences between T_1 in alcoholic patients and normal volunteers, whether the subsequent reduction in T_1 is significant, and if so whether it returns to normal values with prolonged abstinence. A larger number of patients will enable the apparent difference in response between grey and white matter to be explored.

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Brain hydration during alcohol withdrawal in alcoholics measured by magnetic resonance imaging

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Twenty-seven patients had a first Magnetic Resonance Imaging (MRI) scan 1 – 3 days after stopping drinking and a second approximately 2 weeks later with no change in whole brain T_1 or T_1 in selected brain areas. Six patients whose first scan was over 36 h after the last drink underwent an increase in whole brain T_1 in the interval to the second scan. The later the first scan was performed the greater was the increase in T_1. These results are compatible with a very early fall in brain water immediately on cessation of drinking (perhaps due to a rebound increase of vasopressin activity) with a return to 'baseline' after two weeks. A third scan after discharge from hospital in 23 individuals who had abstained from alcohol or drank very little did not reveal any further significant change in brain T_1.

Key words: brain hydration; alcohol withdrawal; magnetic resonance imaging

Introduction

Water retention within the brain has been postulated as a contributant to some of the clinical features of alcohol withdrawal in chronic alcoholics [1]. In magnetic resonance imaging (MRI), T_1 relaxation time is related to the state of water in the tissue [2]. The T_1 value, measured in milliseconds (ms) increases as the proportion of free to bound water within the tissue increases. In vivo T_1 values have been shown to correlate with the level of brain water [3 – 5] and so may enable a study of brain water during withdrawal of alcohol in chronic alcoholics.

MRI was first used for the investigation of chronic alcoholics by Besson and colleagues [6]. These authors suggested that brain water is diminished during intoxication and increased during alcohol withdrawal. Acute intoxication in occasional drinkers results in a fall in whole brain T_1, compatible with the dehydration which follows acute intake of alcohol [7]. Eisenhoffer and colleagues [1] suggest that such an effect, if chronic, might result on alcohol withdrawal in a rebound increase of vasopressin activity, followed by a return to baseline.

It was therefore hypothesised that whole brain T_1 in alcoholics would be seen to fall from the level at 24 – 48 h following cessation of drinking to a lower level ('baseline') some 2 weeks later. We were unable to perform T_1 measurements in the present study in intoxicated alcoholics immediately prior to admission and thus unable to study the early part of the postulated pattern of changes (that is, the putative rise in brain water and T_1).

Patients and Methods

Chronic alcoholic patients who were about to be voluntarily admitted as inpatients for detoxification to the Alcohol Problems Clinic, Royal Edinburgh Hospital, were fully informed about the study and invited to participate.

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Twenty-seven patients (18 men, 9 women), were admitted to this study. Their mean age was 44 years (range 26–63, S.E.M. 5.2). They were to be scanned within 48 h of admission (day 1) and again approximately on day 15. However, the timing of scans varied according to the availability of the scanner and the requirements of the patients' participation in the ward programme.

In connection with a separate study [8] of cognitive impairment and MRI parameters, results of a scan performed at approximately day 15 were available in a further 42 patients. These patients had not been scanned at or near admission.

Patients had been drinking at least 130 g ethanol/day before admission and had a 5–15 year history of alcoholism. No patients were included if they had a history of drug abuse, or were clinically malnourished, or had physical disorders other than raised serum liver enzymes. Over the first 5 days each patient received a normal diet, intramuscular multivitamin supplements and decreasing doses of chlordiazepoxide to control withdrawal symptoms.

Our procedures for measuring whole brain T_1 and T_1 in regions of interest in the brain have been described [9]. The inter-operator reliability of our T_1 measurements has been reported [8]. Differences in T_1 values between groups of patients at different times were

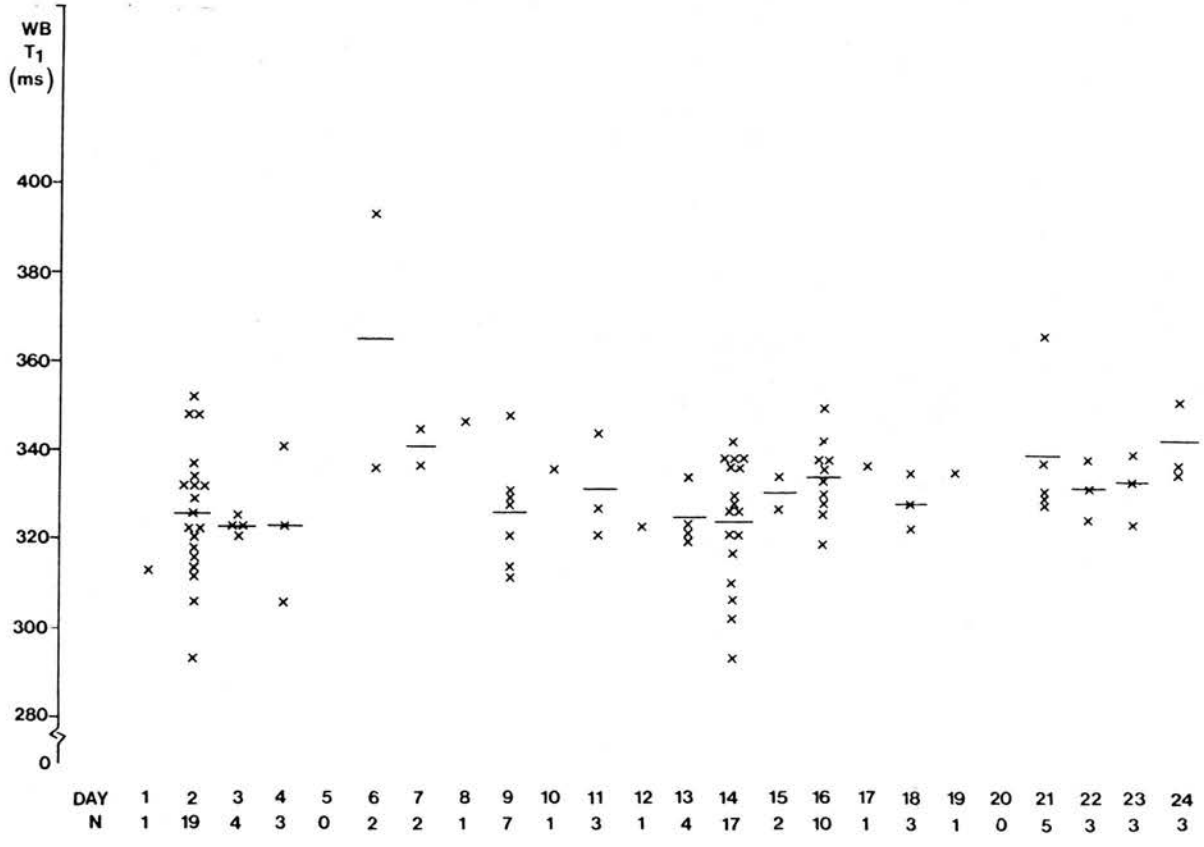

Fig. 1. Whole Brain T_1 measurements with means according to length of time since last drink.

Table I. Mean change in T_1 from Scan 1 to Scan 2 ($\Delta = T_1$ (Scan 2) $- T_1$ (Scan 1)).

	All subjects	Scan 1 within 36 h of last drink	Scan 1 36–84 h after last drink
Δ Frontal White	1.83 ± 9.46	−0.39 ± 2.04	8.50 ± 3.77
Δ Frontal Grey	0.50 ± 17.51	−1.833 ± 4.26	7.50 ± 6.08
Δ Parietal White	0.83 ± 9.17	−0.39 ± 2.12	4.50 ± 3.90
Δ Parietal Grey	−6.75 ± 22.21	−11.17 ± 5.09	6.50 ± 8.17
Δ Whole brain	0.75 ± 8.89	−1.78 ± 2.01	8.33* ± 2.04
n	24	18	6

*Significantly greater ($P = 0.012$) than in those whose first scan was within 36 h of last drink.

compared using Student's *t*-test. Changes in T_1 in individual patients were assessed using a paired Student's *t*-test.

Results

Three patients were unavailable for their second scan. The mean whole brain T_1 at the first scan in the 24 patients who had a second scan was 314 ms (range 283–338, S.E. 2.71). At the second scan the mean T_1 was also 314 ms (range 283–334, S.E. 2.69). T_1 measurements in small areas of interest likewise showed no significant change between scans. Figure 1 illustrates all our available data on whole brain T_1 in the withdrawal period. It includes the subjects on whom only the first scan was done, and subjects from our other study scanned only at day 15 approximately. No trend suggestive of a fall in whole brain T_1 is visible.

Lest the hypothesised fall in T_1 had been early and had been followed by an early 'return to baseline', an analysis of the change in T_1 between the first and second scan was made, comparing those patients who had their first scan within 36 h of the last drink to those whose first scan was later. The 18 patients scanned within 36 h had their second scan at a mean of 13.6 days later (range 9–16 days, S.E. 0.43) and the six whose first scan was up to 48 h later had their second scan at a mean interval of 12.3 days since the first (range 9–16, S.E. 1.15). This interval was not significantly different ($P = 0.33$).

In those whose first scan had been within 36 h of the last drink, the difference between whole brain T_1 on the first and second scans was insignificant (mean difference −1.78 ms – a fall – range −15 – +9, S.E. 2.01). A significant increase occurred, however, in those whose first scan had been up to 48 h later (mean 8.33 ms, range +2– +14, S.E. 2.04; $t = 4.08$, d.f. 5 $P < 0.01$). The difference between the changes in these two groups of patients, (between those scanned within 36 h of admission and those scanned later), is

Table II. Correlation of TIME OF SCAN 1 (post admission) with CHANGE IN T_1 from Scan 1 to Scan 2.

R-values (* – $P < 0.01$) $n = 24$

	Δ WB	Δ FW	Δ PW	Δ FG	Δ PG
TIME OF SCAN 1	0.4048*	0.2434*	0.1080*	0.4076*	0.4242*

significant (t = 2.73, d.f. 22, P = 0.012) (Table I). The trend was visible but not significant in each of the T_1 measurements made in areas of interest. The later the first scan was performed after the last drink, the greater the change between the first and second scans, as shown by the correlation coefficients given in Table II.

In case our timing of the scans had resulted in our missing any later changes in T_1, another comparison was made. Four patients had the second scan on the 9th or 10th day and 20 patients beyond the 10th day. There was no significant difference when these groups were compared in the mean change between the first and second scans (2.25 ms, S.E. 5.28, range −11 — +13 and 0.45 ms, range −15 — +14, S.E. 1.97, respectively; t = 0.36, d.f. 22, P = 0.72).

We had some further data after patients had been discharged from the 2-week ward programme. Seventeen patients from the present study had a further scan 2 months after discharge. There was also a scan at that point in 38 patients in the collateral study already mentioned. The difficulty in using this data is that we were not always certain whether or not an individual had continued to abstain from alcohol during that period. We examined the T_1 values in 23 individuals who had been scanned at about day 15 and had a repeat scan at a mean of 102 days and who as far as we could tell had abstained during that period or drunk very little. No significant change in T_1 in any of the regions of interest or in the whole brain was noted. However, the trend in these apparent abstainers in all our T_1 measures was for a slight increase, but with considerable individual variation (for example, the mean increase in whole brain T_1 was 2.39 ms, range −11 — +19, S.E. 1.55 ms, n = 23).

Discussion and Conclusions

The only possible way in which our data would support the notion that there is a fall in brain water following withdrawal from alcohol is using the sparse data comparing the changes in those scanned within 36 h of the last drink with those whose first scan was later. Our data would support a fall in T_1 between 36 h and 84 h, with a subsequent return to 'baseline' during the next 10 days approximately. It would have to be postulated, however, that individual differences in 'baseline' T_1 prevented this from emerging in the data on the whole sample as illustrated in Fig. 1.

Our data do not uphold the provisional result which we obtained on our first 9 patients [9]. In that paper, we reported a fall in whole brain T_1 which correlated positively with the length of abstinence prior to the second scan. In our present sample, the correlation between change in whole brain T_1 and interval to the second scan was insignificant (−0.09). Neither were there significant correlations between the change in T_1 in the areas of interest and interval to the second scan.

Further studies should comprise daily measurements beginning on the day prior to admission, when the patient is still drinking, and continuing for 2 weeks.

Acknowledgements

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The relationship of cerebral atrophy and T_1 in alcoholics: an MRI study

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There was a significant correlation between two measures of cerebral atrophy (the ventricle to brain ratio and the relative cerebral volume) and T_1 in 19 detoxified alcoholics. This provides further evidence that T_1 is a marker of structural damage in alcoholics although the partial volume effect of CSF may contribute to this finding. This has implications for studies comparing alcoholics to normal controls and suggests that better ways of excluding CSF need to be found.

Key words: alcohol; cerebral atrophy; magnetic resonance imaging

Introduction

In magnetic resonance imaging (MRI) the T_1 relaxation time is related to the state of the water in the tissue [1]. The T_1 time increases as the proportion of free to bound water within the tissue increases. Raised T_1 times have been shown in alcoholics [2], which decrease transiently during the first 48 h of detoxification [3], but show little change after 6 months abstinence. Hospitalised Korsakoff's patients still have significantly raised T_1 times after 5 years [4].

Despite these changes the exact physiological basis of the raised T_1 time is still unknown. It could be caused by an increase in intra- or extracellular water content of the tissue or by a change in the ordered structure of water around macromolecules, perhaps related to changes in phospholipids [5]. Indeed its relative stability suggests a permanent structural change. T_1 times show a significant correlation with age [6] and this provides further evidence that structural change is a factor since brain water levels do not change appreciably after the age of 20 [7].

Interpretation is theoretically confounded by the presence of CSF which has a high T_1. If it was not successfully excluded during measurement it could cause a spurious increase in T_1 Because alcoholics suffer cerebral atrophy [8], and therefore have proportionally more CSF present in an MRI scan, this might contribute to the differences between patients and controls.

This study was undertaken to examine the relationship between cerebral atrophy and T_1, and to determine the effects of CSF.

Method

Nineteen alcoholics (15 males), mean age 46.2 ± 9.3 years (range 32 – 63), who had been abstinent for a median of 4 days (range 3 days to 2 years), had an MRI scan using a 0.08T resistive system. A transverse T_1 scan was obtained 10 cm above the maximum diameter of the lateral ventricles. Ten contiguous proton density serial coronal scans were also obtained. All sections were 12 mm thick with a pixel size of 2 mm^2. Measurement of mean T_1 of the entire area of the transverse section (the grey and

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white matter together but not the CSF) was made. The area of each hemisphere to be sampled was delineated separately using an irregular region of interest; a cursor was used to draw the boundary of the area to be measured directly onto the image of the section as it was displayed on the monitor. The mean T_1 within the region of interest was calculated and displayed. CSF has a high T_1, and is white on the coloured display. It is therefore possible to try to exclude sulcal CSF by ensuring that it is not included within the boundary of the area to be sampled. Therefore an estimate of T_1 for brain tissue in the entire section ('whole brain T_1') was obtained.

The relative Cortical Volume (rCV) was also estimated from the transverse T_1 image. The area of brain tissue was divided by the intracranial area, identified by the MRI silent skull (which appears black on the coloured display).

The Ventricle to Brain Ratio (VBR) was measured from the serial coronal scans which were available for 16 patients (13 males). Two areas were measured on each scan and summed: the intracranial area (ICR) bounded by the superior edge of the cerebellum and the skull; and the ventricular area (VA), again easily identified because the proton density image highlights the CSF, since it is red against the yellow background of the brain tissue. The VBR is then given by VA/(ICR − VA). These measurements were made blind to the T_1 results and the areas to be measured were identified with the help of a radiologist.

In order to assess whether our method excluded the partial volume effect of CSF, a histogram of the T_1 results was produced. This estimated the percentage of pixels within each of 17 T_1 bands between 250−1000 ms. All results were given ± standard deviation.

Results

A significant correlation existed between rCV and age ($r = -0.65$, df 17, $P = 0.002$) and that for VBR and age just failed to reach significance ($r = 0.48$, df 14, $P = 0.06$). Hence the technique of partial correlation, holding age constant, has been used in the data analysis [9].

Table I. An example of the distribution of whole brain T_1 values in the transverse MRI section.

T_1 (ms)	Volume (%)
0−249	2
250−297	8
298−344	17
345−391	15
392−438	13
439−485	9
486−532	7
533−579	5
580−626	3
627−673	3
674−720	3
721−767	2
768−814	2
815−861	2
862−908	2
909−955	1
956−999	7

The mean T_1 was 381 ± 15 ms, the mean VBR was 4.0 ± 1.5 and the mean rCV was 80 ± 7%. The measures of cerebral atrophy were significantly correlated with each other ($r = 0.47$, df 13, $P = 0.03$), and both were significantly correlated with T_1 ($r = 0.62$, df 13, $P < 0.02$, and $r = -0.57$, df 16, $P < 0.02$, respectively).

Table I shows an example of the distribution of T_1 values for one of the patients. If partial volume effects had been totally excluded a clear discontinuity between brain tissue (T_1 approx. 200−400 ms) and CSF (T_1 >700 ms) would be expected. There was no discontinuity for this and four other patients in the study.

Discussion

The significant correlation between T_1 and the measures of cerebral atrophy is at variance with our previous report using linear measures of cerebral atrophy [2]. However, this is probably explained by the evidence from CT studies that have shown that area measurements are more accurate [8]. Two explanations for this relationship seem plausible: (1) An effect on some intracellular structures that increased their T_1 into the range 400−700 ms and simultaneously caused atrophy or cell shrinkage. This would imply that the association was indirect and due to the severity of alco-

holism. (2) Measurement artefact caused by the 'partial volume' effect of CSF. Although obvious CSF was excluded during the measurement process, the imaged tissue slice is 12 mm thick and a sulcus may therefore occur just below the surface which is not obvious to the investigator but which will affect the T_1. This is more likely to occur in alcoholics because they have atrophied brains with increased sulcal widths and ventricle to brain ratios [8]. The lack of a discontinuity in the T_1 results for some of the patients could be interpreted to mean that the partial volume effect has not been excluded. Nevertheless we believe that this is unlikely to be a major confounding factor since 75—80% of the tissue at the level being measured is white and not likely to be substantially influenced by CSF. In addition, Christie et al. [4] in their study that included control subjects, patients with Alzheimer-type dementia and Korsakoff's patients hospitalised for over 5 years found that the latter had significantly raised T_1 values which were approximately 4% higher than those of the Alzheimer's patients, whose values in turn were no different to the controls. They argued that this finding was unlikely to be a measurement artefact of cortical atrophy since it was identical in the two patient groups.

There is evidence of structural change affecting T_1 in rats. Greentree et al. [10] have used ethanol-tolerant rats to study the relationship of T_1, water content and phospholipid (PL) composition. Different classes of PL are distributed asymetrically within biological membrane bilayers. Phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI) composition determine the degree of order in the inner lipid layer and therefore influence the degree of structure in intracellular water close to the cell membrane and hence the T_1 time. They found a reduction in T_1 time in the cortex while tissue water content remained unaffected. Increased proportions of saturated fatty acids and a reduction in the proportion of long chain, polyunsaturated fatty acids were detected in the PE fraction. This suggested to the authors that MRI changes in alcoholics could be attributable to altered membrane composition and structure which in turn influenced the nature of intracellular water. However, there is currently no explanation why phospholipid changes, which are thought to increase the rigidity of cell membranes with chronic exposure to alcohol [10], should lead to an increase, rather than a decrease in T_1 in patients [2]. Similarly, the increase in fluidity of cell membranes in response to acute ingestion of alcohol would be expected to increase T_1 but the opposite has been shown in volunteers [11]. The interpretation of the T_1 changes is therefore problematical although it has been known for over 40 years that the brains of alcoholics at post mortem are oedematous [12,13] and this would lead to an increase in T_1. It is of course entirely possible that a structural effect other than that known to occur in lipids could be responsible for these results.

The findings of this study support the hypothesis that T_1 is a marker of structural change in alcoholics, but future work must find effective methods of excluding the effect of CSF from the field of measurement. By choosing appropriate pulse sequences it should be possible to obtain a CSF map and estimate its T_1. This could perhaps be used to obtain a T_1 image corrected for the presence of CSF.

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Magnetic Resonance Imaging of the Brain in Alcoholics: Cerebral Atrophy, Lifetime Alcohol Consumption, and Cognitive Deficits

J. D. Chick, M. A. Smith, H. M. Engleman, D. M. Kean, A. J. Mander, R. H. B. Douglas, and J. J. K. Best

Magnetic resonance imaging of the brain in 69 detoxified alcoholics revealed that relaxation time (T_1) in whole brain and in grey matter and parietal white matter was greater than in age-matched controls. In 48 patients, data on cognitive function and lifetime alcohol consumption were available. With age-controlled, lifetime consumption, and impairment on performance in the cognitive test (a Category Sorting Test) correlated positively with T_1 in whole brain and in selected regions. Impairment in the cognitive test correlated with increased T_1 in whole brain and white matter independently of cerebral atrophy. Alcohol consumption patterns in the following 6 months were unrelated to changes in T_1. The excess water implied by the elevated T_1 values may be intra- or extracellular. It is uncertain whether or not T_1 elevation in alcoholics is a marker of neuronal damage. T_1 elevation appears to be a marker of one type of alcohol-related cognitive impairment.

EXCESSIVE DRINKING is associated with impaired cognition.[1] There is evidence in some drinkers that a defect in cognition predates the heavy drinking.[2] However, improvements in cognition occur in some alcoholics who become abstinent.[1,3] Also indicators of predrinking intelligence such as early academic attainment and retained verbal skills suggest that the excessive drinking is at least as much a cause of certain types of cognitive impairment as a consequence thereof.[1,2]

Brain shrinkage is also well established,[4,5] and modest correlations between measures of shrinkage (especially central shrinkage) and cognitive impairment have been found.[1,3] The cause of this shrinkage is unknown. However, the cerebellar atrophy of alcoholism is due at least in part to neuronal death.[6] Neuronal death may contribute to the cerebral shrinkage of the alcoholic, a possibility that was raised over 80 years ago.[7] Animal studies have shown that ethanol consumption can cause nerve cell dysfunction and death.[8-11]

A potential marker of nerve cell death in alcoholic patients is, of course, the shrinkage visible in computer tomographic (CT) scans. However, a search for another marker seems justified since the correlations between cognitive impairment indices and CT measurements is, as mentioned, modest at best. An alternative marker might be provided by magnetic resonance imaging (MRI) of the brain. Furthermore, the observation that the histology of neuronal death may show *oedematous* cells[12] suggests a particular importance for MRI.

In magnetic resonance imaging of living tissue the parameter known as T_1 relaxation time is related to the state of water in the tissue.[13] The T_1 value, measured in milliseconds, increases as the proportion of free to bound water within the tissue increases. MRI scanning of brain in the intact patient before neurosurgery has shown that in vivo T_1 measurements predict the degree of brain hydration.[14] Besson et al.[15] were the first to report brain T_1 measurements in a small group of alcoholics but reported only on change in the phase immediately after cessation of alcohol intake.

The present study had four hypotheses: (*a*) that the detoxified alcoholic brain some 2 weeks after the last drink would be overhydrated compared to age and sex matched non-alcoholics; (*b*) that in detoxified alcoholics the degree of overhydration in the brain would be related to the total lifetime consumption of alcohol; (*c*) that this overhydration would predict cognitive impairment; (*d*) that extended abstinence in the posttreatment phase would be associated with reduction of overhydration and improvement in cognitive functioning.

SUBJECTS AND METHODS

Alcoholic patients admitted for detoxification to the Alcohol Problems Clinic at the Royal Edinburgh Hospital were fully informed about the purpose and procedures of the study and invited to participate. Signed consent was obtained. The project was approved by the appropriate Ethics of Research Committee.

Hypothesis 1

Sixty-nine patients (46 males, 23 females) were scanned at the end of detoxification—a mean interval of 14 days after the last alcoholic drink. These 69 patients had a minimum of 5 years of recent heavy drinking. Their mean age was 44 years (range, 22–70; SE, 1.16). None had the clinical features of Wernicke-Korsakoff syndrome, had a history of drug abuse, were clinically malnourished, or had physical disorders other than raised serum liver enzymes. They had all been drinking at least 130 g of ethanol per day during drinking episodes. In Britain, a "standard drink," i.e., a half pint of beer, a glass of wine, or a single measure of spirits, contains 8–9 g ethanol. They spanned the range of socioeconomic

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backgrounds, and though half were unemployed none were without a fixed address.

Hypotheses 2, 3, and 4

A subgroup of 48 of the above patients (32 males 16 females) was invited to have cognitive testing and to attend for repeat MRI scans and cognitive testing at 6 months, (though in the event only 26 patients kept the following appointments for both scans and testing). These patients were selected on the basis of their willingness and likely ability to attend for further testing. Their mean age was 44 years (range, 22–70; SE, 1.36). They had mean red cell volumes ranging from 88 to 111 fl (mean, 98.9; SE, 0.98; $n = 42$) and serum γ-glutamyl transpeptidase (GGT) values ranging from 5 to 1000 units (median, 100; mean, 217; SE, 42; $n = 43$). The consumption pattern of this group was studied in more detail. They were asked to give anchor dates throughout their adult lives and commencing with the year in which they first drank alcohol, to reconstruct their typical pattern of drinking month by month during each of the succeeding years. The method is based on that of Skinner and Sheu.[16] Thus an estimate was obtained of cumulative total lifetime alcohol consumption. Inter-rater reliability of this method in 10 patients whose responses were rated by two independent assessors showed an average agreement between assessors of 87%. (Taking the past year's consumption enabled some of the relationships of interest to be analyzed using a recent, rather than a lifetime consumption measure. However, to reduce the total number of tests of significance made, it was decided to concentrate on our cumulative lifetime measure of consumption).

Normal MRI values were available from a group ($n = 26$) recruited from hospital staff and patients' relatives. Their usual alcohol consumption ranged from nil to 80 g ethanol per week. Their ages ranged from 23 to 74 years with a mean of 42 years, and a similar distribution to that of the patients. The ratio of women to men in the normal sample was 14 males to 12 females, that is, a higher proportion of women than in the patients. However a two-tailed t test of the differences in the females and males of the control group found that there were no significant differences in their whole brain T_1 measurements ($p = 0.88$) so the differences in the proportions of the sexes in the control and the alcoholic samples are not considered to be of importance. They may have been of slightly higher mean socioeconomic status than the patients but this was not thought likely to bias the results, though no study of MRI and socioeconomic status has to our knowledge been reported.

Our index of cognitive function was the microcomputer-administered Maudsley Category Sorting Test.[17,18] This provides a measure of abstract reasoning ability and rigidity of thought processes and it is of interest because rigidity of thinking in alcoholics is a major impediment in the psychological treatment of the condition. The subject is required to deduce the categorization system being used by the computer program and to shift his or her set when the program changes. The program offers six different methods and the number of times out of six in which the subject correctly arrives at the solution is counted (CATEGORIES). The number of trials needed to achieve that number of correct solutions is counted (SORTS). The total number of errors made is summed (ERRORS). The number of perseverative errors (errors repeated despite feedback from the program) is totalled (PERSEVERATIONS). We have concentrated on the Category Sorting Test because it has been shown that deficits in this type of function correlate well with CT parameters of atrophy,[19] and are common to both older and younger alcoholics whereas impairments on tests of memory and general intellect tend to be seen only in older patients.[3]

Alcohol consumption in the follow-up period was estimated from the clinic treatment records, and interviews with the patient conducted by a research assistant at 3 months and 6 months. This information was corroborated where possible by an additional interview with a relative and by changes in the serum GGT in those patients who had an elevation of this marker[20] at intake to the study. For some patients only a qualitative report on consumption was available. Patients were categorized as follows for each of the 3-month period: total abstinence; "intermediate" drinking (1–40 g per day); "heavy" drinking (over 40 g per day).

MRI measurements were performed using a 0.08 Tesla-resistive MRI system.[21] Three or four transverse sections were obtained through the brain centered to the maximum diameter of the lateral ventricles. The slice thickness was 12 mm and pixel size was 2 x 2 mm. An interleaved saturation recovery and inversion recovery pulse sequence, with a repetition time of 1000 ms for both and a time from inversion of 200 ms for the latter, was used to obtain a calculated T_1 map of each section. Measurements of the patient's brain T_1 were made from a section approximately 10 mm above the maximum diameter of the lateral ventricles. The T_1 in grey and white matter in the frontal and parietal regions was measured from the T_1 map using small regions of interest generated by the computer. Different size regions of interest were used for grey matter (20 mm^2) and for white matter (69 mm^2) and the mean of similar regions in the left and right hemisphere was noted. Larger irregular regions of interest were also measured to attain mean T_1 values of each cerebral hemisphere. To achieve this an electronic cursor was used to delineate the border of each hemisphere directly on the computer reconstructed image of the brain as displayed on the monitor. Obvious areas of CSF (which have a very high T_1 and appear white on the coloured image) were avoided. As a further precaution to exclude CSF, the computer was programmed to display the mean T_1 for each hemisphere only for values within the range 60–600 ms. An example of a T_1 map in a patient including the regions of interest used for analysis is shown in Fig. 1.

The precision of the T_1 measurements was estimated from four repeated measurements on three normal volunteers over a period of a month. The T_1 precision of white matter was 2.8%, grey matter was 4.9%, and the whole brain 2.6%.[22] The poorer precision of the measurements of grey matter are due to the fact that it is generally of small volume and adjacent to CSF resulting in partial volume errors. In addition smaller regions of interest are used resulting in a larger error. The interoperator variation of our T_1 measurements was assessed in two independent operators in 20 sections from five different patients. The percentage differences between rates were: whole brain 1.9%; frontal, occipital, and parietal white matter 2.5%; temporal white matter 5.2%; grey matter (all areas) 5.5%. All ratings were blind to the clinical state of the patient, consumption measures, and cognitive test scores. However, control scans were identified as such, and dates of all scans were also known to the raters. T_1 maps were analyzed by three operators; results from the same patient were always analyzed by the same operator.

Atrophy Measurements

Commonly used indices of cerebral atrophy[23] were made by caliper measurement on MRI scans: (*a*) *Third ventricle*, widest diameter; (*b*)

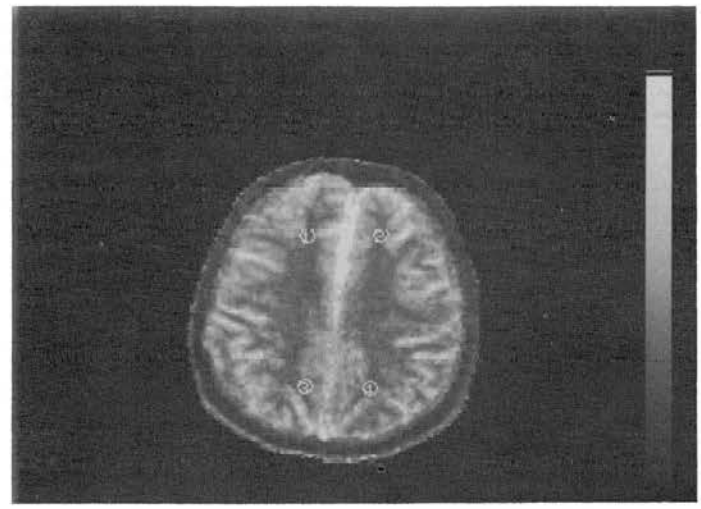

Fig. 1. An example of an MRI scan in a patient indicating region of interest marker.

The Ventricular Index, the distance between the choroid plexuses divided by the maximum width between the frontal horns; (*c*) *The Huckmann Index*, the sum of the maximum and minimum widths of the frontal horns; and (*d*) *The mean width of four cortical sulci* was measured on a slice 16 mm above the upper limit of the lateral ventricles, choosing the two widest sulci on each side.

As an attempt at assessing the reliability of these measures in our hands, we checked the correlations between the indices of internal atrophy. The Huckmann index correlated $r = 0.33$ ($p < 0.05$) with the ventricular index and $r = 0.47$ ($p < 0.01$) with "3rd ventricle" ($n = 46$).

Differences in T_1 values within groups of patients at different times were compared using Student's t test. Changes in T_1 were assessed using a paired Student's t test. The relationship between changes in T_1 values, drinking and changes in cognitive function were assessed using linear regression analysis. Partial correlation analysis was used to investigate the relationship between cognitive function and T_1 value and cognitive function and previous drinking history to control for the effect of age and atrophy.

RESULTS

The T_1 values obtained from the patients at 2 weeks and 6 months are given in Table 1 with the results from normal controls for comparison. The most pronounced differences between normals and alcoholic patients are seen in the whole brain and in grey matter T_1 values.

Relationship between T_1, Age, and Alcohol Consumption

In the subgroup studied intensively the mean lifetime drinking total was 775×10^3 g (SE, 104×10^3; range, 71×10^3–3329×10^3). The T_1 values at the time of the first scan correlated positively with the patient's age, significantly so in frontal white matter ($r = 0.49$, $p < 0.01$) and in posterior white matter ($r = 0.41$, $p < 0.05$). Eliminating the effect of age using partial correlation, a significant positive correlation was found between whole brain T_1 in the detoxified patient and the patient's cumulative total life's consumption $r = 0.36$, ($p < 0.01$). (The past year's consumption, which not unexpectedly correlated significantly with lifetime consumption, correlated positively with parietal white matter T_1 but not significantly with whole brain T_1). ($n = 47$).

Relationship between T_1 and Cognitive Impairment

In the alcoholics given cognitive testing, impairment in each of the scores on the Category Sorting Test was related to an increase in T_1 in all regions of the brain. The findings are shown in Table 2. The effect of age has been controlled for. Correlations of each of the test measures with whole brain T_1 and with frontal white T_1 were significant at either the 99% or 95% levels. The relationships remained significant when the sexes were examined separately. Both lifetime consumption and past year's consumption correlated significantly with each of the test measures with age controlled.

Role of Atrophy

Table 3 shows that internal atrophy as measured by the Huckmann index appears to be associated with increased T_1 in white matter, and with impairment in the number of categories achieved in the sorting test. However, by chance, in the 36 correlations shown in Table 3, two would be significant at the 5% level.

There is little evidence of a relationship between other measures of atrophy and either T_1 values or cognitive test impairment. However, the correlation of 0.26 between sulcal width and T_1 in frontal grey matter is probably meaningful in that when patients are divided about the median for sulcal width, the T_1 (frontal grey) is 10 points higher for those with sulcal width above the median than for those below the median ($t = 3.3$, $p < 0.01$). This supports the possibility that CSF in the subarachnoid space, increased in cortical atrophy, might tend to increase T_1 measurements in grey matter.

Can atrophy account for the relationships shown in Table 2 between T_1 increase and cognitive impairment?

Table 1. Mean ± SE (Range) of T_1 in Whole Brain and Regions of Interest and in the Whole Sample of Alcoholics at a Mean of 15.0 Days after Admission

	Whole brain	Frontal white	Parietal white	Frontal grey	Parietal grey	Timing (days after admission)
Control group ($n = 26$)	306 ± 1.69 (290–324)	268 ± 1.58 (252–283)	269 ± 1.97 (248–296)	341 ± 2.09 (326–371)	334 ± 1.50 (310–351)	
Patients—whole sample ($n = 69$)	321 ± 1.67* (283–383)	265 ± 1.49 (230–326)	276 ± 1.45 (230–326)	367 ± 2.28* (314–400)	360 ± 1.76* (321–392)	15.0 ± 0.06 (6–24)
Patients—subgroup with cognitive test ($n = 48$)	325 ± 1.81* (304–383)	266 ± 1.93 (230–326)	277 ± 1.81† (230–326)	373 ± 2.41* (315–400)	361 ± 2.25 (326–392)	15.7 ± 0.8 (6–24)
Patients—subgroup attending for follow-up ($n = 26$)						
First scan	322 ± 1.74* (304–383)	265 ± 1.89 (249–284)	276 ± 1.62 (256–288)	372 ± 2.99* (336–400)	366 ± 2.90* (335–392)	14.0 ± 0.9 (6–23)
Follow-up scan						
< 40 g ethanol per day	324 ± 1.31* (312–333)	266 ± 1.88 (254–285)	280 ± 2.71† (262–301)	373 ± 4.17* (349–406)	365 ± 296* (348–390)	192 ± 4.0 (147–258)
> 40 g ethanol per day	330 ± 5.55* (311–378)	270 ± 3.84 (251–298)	277 ± 3.18 (258–293)	374 ± 4.31* (346–393)	363 ± 4.04 (342–392)	

* Patients greater than controls, $p < 0.01$; †$p < 0.05$.

Table 2. Age Controlled Correlation Coefficients of T_1 Values and Estimated Lifetime Consumption with Scores on Components of the Category Sorting Test in Alcoholics at a Mean of 15.7 Days after Admission (*$p<0.01$; †$p<0.05$). (Impairment Results in a Lower Score on Categories, and a Higher Score on Sorts, Errors, and Perseverations).

Category Sorting Test scores [mean ± SE (range)]		Whole brain	Frontal white	Parietal white	Frontal grey	Parietal grey	Lifetime drinking total
Categories	5.42 ± 0.16 (37–136)	−0.44*	−0.50*	−0.42*	−0.24†	−0.17	−0.31†
Sorts	60.90 ± 3.42 (37–136)	0.33†	0.26†	0.19	0.21	0.14	0.37*
Errors	21.00 ± 3.02 (1–90)	0.38†	0.34†	0.30†	0.23	0.20	0.40*
Perseverations	6.33 ± 1.25 (0–35)	0.41* $n = 48$	0.34† $n = 48$	0.29† $n = 48$	0.21 $n = 48$	0.25 $n = 48$	0.40* $n = 47$

Table 3. Age-controlled Correlation Coefficients of Atrophy Indices, T_1 Values, and Cognitive Test Scores ($n = 46$)

	Huckmann	Ventricular	Third V	Sulcal width
T_1				
Frontal white	0.33*	0.27	0.14	0.09
Frontal grey	−0.13	0.04	−0.09	0.26
Parietal white	0.39†	−0.10	0.26	0.23
Parietal grey	0.10	−0.15	0.06	0.12
Whole brain	0.03	−0.04	−0.01	0.06
Categories	−0.30*	0.02	−0.21	−0.09
Sorts	0.16	−0.01	0.04	0.03
Error total	0.15	−0.01	0.06	0.07
Perseverations	0.11	−0.01	0.00	0.08

*$p < 0.05$; †$p < 0.01$.

Table 4. Correlation Coefficients of T_1 Values (White Matter and Whole Brain) with Cognitive Test Scores, Controlling for Age and Huckmann Index ($n = 46$)

	Whole brain	Frontal white	Parietal white
Categories	−0.43*	−0.55*	−0.44
Sorts	0.32†	0.40*	0.30†
Errors	0.36†	0.47*	0.40*
Perseverations	0.38*	0.46*	0.40*

*$p < 0.05$; †$p < 0.01$.

Table 5. Correlation Coefficients of T_1 Values in Whole Brain and Grey Matter with Cognitive Test Scores, Controlling for Sulcal Width and Age ($n = 46$)

	Whole brain	Frontal grey	Parietal grey
Categories	−0.43*	−0.21	−0.20
Sorts	0.33†	0.20	0.17
Errors	0.37†	0.21	0.23
Perseverations	0.40*	0.19	0.27

*$p < 0.05$; †$p < 0.01$.

Table 4 shows that internal atrophy did not account for the relationship between raised T_1 in white matter and cognitive impairment. Table 2 showed, as already mentioned, correlations in the expected direction though in general not significant between T_1 in grey matter and cognitive impairment. Table 5 shows little alteration in the size of these correlations when cortical atrophy as measured by sulcal width is controlled for. T_1 in whole brain also remains significantly related to cognitive impairment despite the possible confounding effect of atrophy.

The relative lack of importance of atrophy in this study may partly reflect our measurements. We used indices previously used in CT scans, and by comparison MRI scans lack definition. Our measurements were made by caliper rather than by computer.

Changes in T_1 and Cognitive Function in Relation to Degree of Abstinence

There were 26 patients who reattended for the repeat scan and on whom we had data on consumption of alcohol in the interval (Table 1).

Whether or not patients were deemed to have resumed drinking heavily, the trend was for whole brain T_1 to rise slightly over the 6-month period. Whole brain T_1 measurements at 6 months in those 15 patients who had been abstinent or who had drunk on average less than 40 g of ethanol per day had risen by a mean of 2.33 ms (range, −11 to 29; SE, 2.87) (see also Fig. 2). The mean serum GGT of this group was within the normal range (21 IU/liter, $n = 14$). In those 11 patients who had drunk more than 40 g per day on average during the 6-month period the mean rise in whole brain T_1 was 6.27 ms (range, −15 to 60; SE, 5.94) (see also Fig. 2). This was not a significantly greater mean rise ($p = 0.56$) than in those drinking less than 40 g/day. The mean serum GGT of this group was elevated (178 IU/liter, $n = 10$). The two patients with the highest T_1 values at follow-up were in this group. They were men who had severe long-standing dependence on alcohol for many years and were once again drinking in excess of a bottle of spirits per day (280 g ethanol per day) up to the time of the scan.

There were only nine patients in whom we could be sure that abstinence or near abstinence had been achieved for the whole of the 6-month period. The mean change in whole brain T_1 in these patients was −0.78 ms (range, −11 to 10; SE 2.85). Figure 2 illustrates the pattern of whole brain T_1 changes in individual subjects from the initial scan to the 6-month scan showing abstainers, "intermediate" and "heavy" drinkers separately. Analysis of variance to compare the changes in T_1 values in whole brain and regions of interest over the 6-month period across these three groups defined by increasing posttreatment consumption did not reveal a significant trend for any of the T_1 measurements (frontal white, $F = 1.65$, $p = 0.21$; frontal grey $F = 1.06$, $p = 0.36$; parietal white, $F = 1.92$, $p = 0.17$; parietal grey, $F = 0.26$, $p = 0.77$; whole brain, $F = 0.67$, $p = 0.52$; in each test $df = 2/23$).

There were 25 patients who repeated the Category Sorting Test in a sober state at the time of the 6-month scan. The mean changes in these individuals' scores were: CAT-

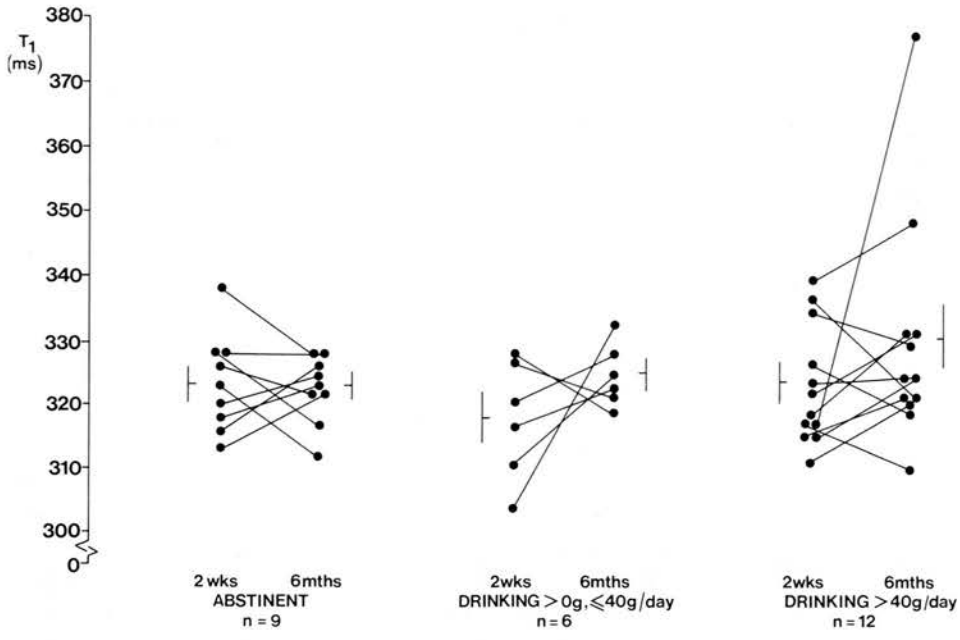

Fig. 2. Whole brain T_1 measurements, separately for those patients who abstained, drank 40 g ethanol per day or less, and who drank over 40 g ethanol per day, to illustrate change between scan at 2 weeks after admission and at approximately 6 months later.

EGORIES, +0.44 (range, −1 to +3; SE, 0.17); SORTS, −5.2 (range, −44 to +18; SE, 3.4); ERRORS, −5.2 (range, −32 to +16; SE, 2.5); PERSEVERATIONS, −0.8 (range, −15 to +7; SE, 1.0). However despite this trend towards amelioration, no significant correlations were found between these changes and changes in T_1.

DISCUSSION

The findings of a raised whole brain T_1 in newly detoxified patients and of a significant relationship between T_1 measurements and both cognitive impairment and the possible cause of that impairment, total lifetime consumption, suggest that T_1 measurements have both potential clinical utility and a neuropathological significance. Cognitive deficits were also linked to increased T_1 in white matter, but not grey matter. The finding that is not corroborative is the lack of difference between controls and patients in frontal white matter T_1, given that cognitive deficits appeared to relate to that measure. Grey matter T_1 measures, while they did distinguish alcoholics from controls did not relate (significantly) to cognitive impairment. This raises the question that our T_1 findings are artefacts due to cerebral atrophy (which would be expected to affect grey rather than white matter T_1 measurements). However, the only T_1 measurement which we made which was significantly related to atrophy was that in frontal grey matter. Thus, while noting that frontal white matter T_1 measurements did not distinguish alcoholics from controls, we feel we have found a relationship between T_1 in whole brain and in white matter that relates to alcohol consumption and to cognitive impairment, and that this is independent of atrophy. We note that Harper et al.[4] have stressed that it is loss of white matter, rather than grey matter, which is most important in alcoholics.

Previous workers have attempted to estimate total lifetime consumption[1,16] but its reliability remains in some doubt. Although we have little confidence in the absolute accuracy of the estimates, the rank ordering that the method yields is possibly more reliable. This is supported by our finding a correlation of this estimate with T_1 values, and with cognitive test scores (Table 2). Measures of more recent consumption might be thought to be more reliable. However, while more reliable because the memory is fresher, patients' recent consumption often poorly reflects longer standing patterns of drinking: for example, the patient coming to a clinic has often been trying recently to abstain for periods; or, he has presented for treatment because of one or two especially heavy recent binges. Thus in the general working population, where patterns of drinking are fairly stable over time, a marker such as the serum GGT may correlate well with a measure of recent drinking[20]; while in patients admitted to clinics no apparent relationship is found.[24]

In the "Subjects and Methods" section we explained some of the reasons for our choice of the Category Sorting Test. In addition, its microcomputer-assisted administration makes it an inexpensive and convenient test to perform and reduces tester-induced bias; it tests a psychological function of clinical relevance; previous (unpublished) work in some 150 patients had led us to conclude that among a range of tests it was sensitive to increasing severity of alcoholism. It is not a widely used test in the literature, but it is closely based on the better known Wisconsin Card Sorting Test.[25] Category Sorting Tests are believed to reflect frontal lobe functioning.[17,25] It is notable therefore that the largest correlations between test scores and T_1 in the region of interest measurements were found in frontal tissue. Unfortunately, over a period of 6 months, we believe that a subject who had mastered the test could later recall his method of doing it and so we hesitate to

interpret changes in scores in this test during the follow-up period.

The associations which have been found by other authors between CT changes and cognitive tests suggest that it is central atrophy (i.e., loss of white matter), rather than cortical atrophy (loss of grey matter) which best predicts cognitive impairment, albeit only explaining less than 20% of the variance in cognitive performance overall.[3] Central changes appear to regress less quickly with abstinence than cortical changes.[3] Thus, our failure to find significant correlation between T_1 in grey matter and cognitive impairment is consistent with Bergman[3] and also Ron.[1]

Only slightly over half of the patients invited for a 6-month scan attended, despite repeated arrangements being made in some cases. Only very occasionally did the patient give as a reason that he or she found the enclosed space of the scanner unpleasant. Nonattenders were mostly patients who had resumed drinking and wished to break off contact with the clinic. It is difficult to obtain reliable information on drinking in the follow-up phase without, for example, incorporating at the outset specific monitoring by relatives, or urine, blood, or sweat testing at frequent intervals. It would be premature to conclude that our lack of T_1 reduction in our small number of supposedly abstinent patients indicates that elevated values are permanent in the established alcoholic. However, other follow-up studies of abstinent alcoholics have failed to show improvements in cognitive function[26] and the classic alcohol-related deficit, Korsakoff's syndrome, is marked by persisting permanent alterations in brain cells and persisting cognitive impairment despite abstinence. On the other hand, cortical shrinkage as identified by cerebral tomography sometimes resolves with abstinence.[3] Also, cerebral perfusion, diminished in the newly detoxified alcoholic by comparison to controls, appears to improve with abstinence.[27]

A number of neuropathological processes may occur simultaneously in the alcoholic. An increase in the measured T_1 is a marker of overhydration or oedema of either intra- or extracellular tissue. It remains speculative whether an elevated T_1 is a marker of damaged neurones. Christie et al.[28] have shown that frontal and parietal grey and white matter T_1 values are not elevated in patients with presenile Alzheimer-type dementia when compared to age-matched controls whereas patients with Korsakoff psychosis, abstinent for 1–14 years, (mean, 5 years), have raised cortical T_1 values when compared to age-matched normal controls and to frontal grey and white matter in patients with Alzheimer's disease. (Christie et al. were able to distinguish increased T_1 measurements from atrophy in this study of dementia, supporting our conclusion in the present study that our findings are independent of atrophy). Measurements of T_1, like cortical atrophy, increase with age as also found in a previous study[29] as well of the present study.

In conclusion we believe we have shown that MRI T_1 measurements, especially in white matter, are elevated in alcoholics proportionate to their cumulative alcohol intake and to the degree of impairment on a Category Sorting Test of cognitive function. These findings are analogous to those of ageing. The precise location of the extra water which is presumed to underly this change, and its cause, is unknown. Potentially, MRI T_1 is of clinical value as a marker of alcohol-related brain damage.

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COMPARISON OF TWO BENZODIAZEPINES IN THE TREATMENT OF ALCOHOL WITHDRAWAL: EFFECTS ON SYMPTOMS AND COGNITIVE RECOVERY

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SUMMARY

Forty newly admitted alcohol-dependent patients were randomly allocated to equivalent 6-day regimes of either lorazepam or diazepam, to compare involvement in physical, emotional and cognitive state during the first 8 days in hospital. Diazepam provided a more comfortable withdrawal period and was associated with slightly better cognitive functioning on the eighth day.

Key words: Alcohol withdrawal — Treatment — Diazepam — Lorazepam

INTRODUCTION

The abstinence syndrome amongst patients suffering from alcohol dependence is characterised by well known physical signs of tremor, restlessness, insomnia and increased central nervous system excitability with, on occasions, epileptic fits. Anxiety is also a significant component of this syndrome. Tranquilisers are commonly prescribed to alleviate these symptoms. The present study aimed to contrast the efficacy of two benzodiazepines, diazepam (Valium®) and lorazepam (Ativan®). Both drugs are widely used, but it was felt that lorazepam, because of the absence of active metabolites, might be associated with quicker recovery of cognitive functioning than diazepam for a given degree of control of withdrawal symptoms. Cognitive impairment experienced during the early stages of treatment for alcohol dependence may well diminish a patient's capacity to enter into psychological treatment, by impairing recall, by rendering thinking inflexible and by retarding new learning.

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SUBJECTS AND METHOD

New patients who were alcohol-dependent requiring withdrawal medication and had been admitted to the Alcohol Problems Clinic were invited to participate in the study. Specifically excluded were patients who had current active hepatocellular pathology, grossly disordered hepatic or renal function, were known to be sensitive to benzodiazepines, were psychotic or suffered from epilepsy, or had a history of withdrawal fits or psychosis, drug abuse or recent sedative usage.

Forty patients were enrolled in the trial. Identical tablets containing either lorazepam 1 mg or diazepam 5 mg were supplied in numbered bottles. Numbers were allocated at random and the trial was therefore double-blind. The patients were also given vitamin supplements according to the usual routine of the clinic. The basic regime of the two drugs is shown in Table I. Where clinically indicated medication was increased or reduced at the instigation of one or other author, the aim being to provide control of withdrawal symptoms without undesirable sedation. Such alterations were, however, kept to a minimum.

On the day of admission patients were given a physical and mental state assessment and measures made of their past drinking pattern and degree of alcohol dependence [1]. They were also assessed using the Bexley Maudsley Automated Psychological Screening and Bexley Maudsley Category Sorting Test on a number of cognitive tests administered by microcomputer [2,3]. Psychomotor accuracy was assessed by finger tapping and the peg board tests [4].

At the same time of each day throughout the trial patients completed a visual analogue scale giving a rating in millimetres of their self-perceived anxiety and depression. They also completed a 5-point scale estimating their craving for alcohol. Nurses rated the patients' clinical state after the

TABLE I

SCHEDULE OF DRUG ADMINISTRATION

Time (h)	Lorazepam mg				Diazepam mg			
	0800	1200	1800	2000	0800	1200	1800	2000
Day								
1	Admit	2	2	2	Admit	10	10	10
2	2	1	–	2	10	5	–	10
3	1	1	–	2	5	5	–	10
4	1	1	–	1	5	5	–	5
5	1	–	–	1	5	–	–	5
6	–	–	–	1	–	–	–	5
7	–	–	–	–	–	–	–	–

method described by Gross et al. [5]. On the eighth hospital day the patient was reassessed physically and psychiatrically, and cognitive and psychomotor accuracy tests were repeated, and a version of the Mill Hill vocabulary scale administered.

We have used the Ackers' automated testing in a context which is possibly novel and also outside the authors' intentions. Published work refers to their use in already detoxified alcoholics. The validity of each of the tests was not our concern — in non-detoxified patients the validity of these tests is unknown. We were only interested in change within a given patient. We required tests that would be convenient to administer and attractive to our subjects, and microcomputer administration was, therefore, ideal in this project.

RESULTS

Forty patients were recruited to the study, 20 in each drug group. In both groups there were 14 men and 6 women. The average age in the lorazepam group was 47.1 years (range 33–60) and in the diazepam group was 41.7 years (range 20–74). There was no significant difference between the two groups in physical condition, degree of alcohol dependence, the presence of concomitant anxiety state, depression or severity of withdrawal symptoms at the time of admission. Both groups reported drinking similar amounts of alcohol during the week preceding admission. (Blood ethanol concentration on admission was measured in 29 patients and within these patients there was no significant tendency for one group to have a higher mean.) Blood tests on admission, including mean cell volume and gamma glutamyl transpeptidase did not indicate that either group contained a predominance of more severely affected patients. Mill Hill vocabulary score on day 8 did not reveal a difference in verbal intelligence between the groups.

One patient from the lorazepam group was withdrawn because her symptoms were not controlled. The mean number of capsules consumed by the lorazepam group was 22.8 (S.D. 3.4) and by the diazepam group 23.0 (S.D. 3.5).

TABLE II

AVERAGE SELF-RATED MOOD DURING THE 7-DAY PERIOD

Drug	*N*	Anxiety		Depression		Craving	
		Median Interquartile	Range	Median Interquartile	Range	Mean	S.D.
Lorazepam	19	42*	23–56	33**	22–51	34	20
Diazepam	18	28	22–35	19	12–25	26	17

* P,0.05.
** P,0.01.

Self-reported anxiety, depression and craving was expressed as the average of each patient's scores over 7 days. These findings are summarised in Table II omitting two patients in the diazepam group whose daily ratings were incomplete.

Patients in the lorazepam group reported significantly more depression ($P < 0.01$) and anxiety ($P < 0.05$). There was no significant difference in craving experienced.

The patients' daily clinical state assessed on 18 variables showed that withdrawal symptoms were significantly less evident with diazepam ($P < 0.05$) (Table III). The mean daily pulse rate was significantly ($P < 0.05$) higher with lorazepam (mean 94 S.D. 10) than diazepam (mean 85 S.D. 9). A grand mal seizure occurred in one patient in the lorazepam group, on day 8.

All patients improved on the finger tapping test during the week. No significant difference was evident between the drug groups.

The principal changes on automated cognitive testing are summarised in Table IV (full details available on request). Three patients in the lorazepam group did not take the second test and 1 patient in the lorazepam group did not complete the first test—all 4 were excluded from further analysis.

In the capacity to make right/left discrimination elicited by the 'Little Men' test there was a significant improvement in the percentages correct in the diazepam group ($P < 0.05$) and no significant change with lorazepam. There was a highly significant reduction ($P < 0.001$) in both groups in the reaction time in the symbol digit test with no significant change in the number of mistakes. In Visuo-spatial analysis there was a significant ($P < 0.01$) increase in the diazepam group only, mainly attributable to a lower starting value. There was a significant reduction in the number of mistakes ($P < 0.01$) and the reaction time ($P < 0.05$) for both groups in the verbal memory forced choice lists.

In most of the parameters of the Maudsley Category Sorting Test there was a significant improvement. Neither the pattern nor the degree of improvement distinguished the groups.

It is of note that in this group of severely addicted patients blood ethanol level at admission did not significantly relate to performance on any of the cognitive tests, though higher levels impaired psychomotor accuracy measured by the tapping test.

TABLE III

MEAN OF CLINICAL STATE RATINGS OVER 7 DAYS

$P < 0.05$, t-test.

Drug	N	Mean	S.D.	Range
Lorazepam	19	15.6	8.4	3–40
Diazepam	18	9.4	5.3	2–22

TABLE IV

RESULTS ON BEXLEY MAUDSLEY AUTOMATED TESTING AT START AND FINISH OF TREATMENT

Significance of the change: $*P < 0.05$, $**P < 0.01$.

	Lorazepam $N = 15$		Diazepam $N = 20$	
	Mean	Range	Mean	Range
Test 1 Visual Spatial Ability ('Little men' test)				
Percentage correct				
Start	82.5	(55–100)	79.4	(53–100)
Finish	85.1	(47–100)	86.3	(59–100)
Change	2.6	(−19–36)	6.9*	(−12–34)
Reaction time (s)				
Start	3.4	(1–6)	3.6	(2–7)
Finish	3.1	(1–6)	3.2	(2–7)
Change	0.3	(2–3)	−0.4*	(−2–2)
Test 2 Symbol Digit				
Start	2.9	(2–7)	2.4	(2–4)
Finish	2.2	(1–5)	1.9	(1–3)
Change	−0.7	(−2–0.1)**	−0.5	(−2–0.4)**
Test 3 Visuo-spatial Analysis				
Start	11.2	(9–12)	10.4	(6–12)
Finish	11.3	(9–12)	11.4	(9–12)
Change	0.1	(−1–3)	1.0**	(−1–6)
Number correct (4 different)				
Start	11.0	(8–12)	11.2	(9–12)
Finish	11.8	(11–12)	11.2	(8–12)
Change	0.8	(0–3)**	0	(−4–3)
Test 4 Verbal Memory forced choice				
Start	28.6	(14–36)	32.4	(24–35)
Finish	32.8	(17–36)	32.1	(29–36)
Change	4.2	(−2–20)	1.7	(−1–8)
Maudsley Category Sorting Test (number of categories achieved)				
Start	4.5	(3–6)	3.8	(0–6)
Finish	5.1	(2–6)	4.8	(2–6)
Change	0.6*	(−1–3)	1.0**	(−1–5)

DISCUSSION

As anticipated both groups improved physically and mentally during the withdrawal phase. The patients receiving diazepam had a significantly more comfortable withdrawal phase and in some respects showed a more rapid improvement in cognitive skills as measured on the test battery.

One possible explanation for this observed difference may be that the extended half-lives of diazepam and its active metabolites gives a smoother control of symptoms. With the shorter acting tranquiliser break-through

symptoms of the abstinence syndrome were more evident, a phenomenon mentioned by Cohn [6]. It may be argued that a different more frequent dosage regime might have suited lorazepam better, but it is hard to see any clinical advantage in such a change.

Solomon et al.[7] compared lorazepam and chlordiazepoxide in predominantly black male patients and found no significant difference in severity of withdrawal phenomena, though 2 of the lorazepam group and apparently none of the chlordiazepoxide group had seizures. These authors make the point that hepatic conjugates of lorazepam, unlike those of diazepam and chlordiazepoxide, are excreted in the urine, and suggest that liver disease has little or no effect on lorazepam pharmacokinetics. We agree that it may therefore be the drug of choice for alcoholics with severe liver damage.

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THE SECCAT SURVEY: II. THE ALCOHOL RELATED PROBLEMS QUESTIONNAIRE AS A PROXY FOR RESOURCE COSTS AND QUALITY OF LIFE IN ALCOHOLISM TREATMENT

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Abstract — An interview was obtained with 212 patients who had, at a point 12 months previously, been in contact with an alcohol problems clinic. Quality of life (SF-36) was measured and for the preceding 6 months the cost of health and social service resource use was estimated, together with the total abstinent (or controlled drinking) days accrued. Alcohol related health, personal and social problems experienced during that period were elicited using a brief 11-item questionnaire, the Alcohol Related Problems Questionnaire (ARPQ). The estimate of costs correlated more strongly with the ARPQ score ($r = -0.32$, $P = 0.0001$) than with abstinent days ($r = 0.03$, n.s.) or controlled drinking months ($r = -0.21$, $P = 0.002$). The lack of relation of total abstinent days to cost is partly because abstainers tended to use considerable alcohol problems clinic resources. ARPQ scores indicating more problems were associated with lower quality of life. The ARPQ can serve as a proxy for resource use and quality of life in alcoholism treatment.

INTRODUCTION

For some clients and for therapists in some situations, abstinence is the chief goal of treatment for alcohol problems. For other therapists and clients, reduction or cessation of problems related to alcohol is the chief goal, though it is often the case that abstinence or reduction in consumption, or at least reduction of the frequency of heavy drinking, is the route to achieve that.

Self-reports of drinking in people who are dependent on alcohol are sometimes at variance with data from interviews with relatives, alcohol analysis in breath or urine, and blood test markers such as mean cell volume and serum gamma-glutamyl transferase (Fuller *et al.*, 1988; Keso and Salaspuro, 1989). It is possible that measures of alcohol related problems may be more valid than measures of consumption. It is presumably as easy to lie about an occurrence such as an injury or a conflict at work as about the quantity of alcohol consumed. But recall may be better about a specific event than how much alcohol was taken.

Although including information from relatives or other collaterals may improve reliability of consumption data (Midanik, 1988), this may not apply to data on alcohol related problems. For example, during follow-up after treatment, Loethan and Khavari (1990) found that patients identified more alcohol related problems than collaterals. Outcome measured in terms of problems that may have social and medical costs are, of course, not only relevant to patients and their families but also, perhaps more than changes in alcohol consumption, to purchasers of health and social services.

This paper reports data from a 1-year follow-up study which among other goals attempted to find a convenient proxy measure for health and other resource costs. We compared the traditional outcome measure in alcohol treatment studies, alcohol consumption data, with a measure of problems, the Alcohol Related Problems Questionnaire (ARPQ). As well as cost, another dimension of social and personal relevance is quality of life, and we tested ARPQ as an indicator

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Table 1. Alcohol Related Problems Questionnaire (ARPQ) items

	Yes	No
1. Has the patient been in hospital (or casualty department) related to drinking?	1	2
2. Has he/she retched or vomited in the morning connected with drinking the day before?	1	2
3. Has he/she had diarrhoea connected with heavy drinking?	1	2
4. Has he/she been in an accident, (partly) due to alcohol, which came to medical attention or should have?	1	2
5. Has the patient been depressed due to drinking?	1	2
6. Has the patient tried to harm him/herself, deliberately taking an overdose?	1	2
7. *Complete section (a) or (b)*		
(a) The patient has had a job in the past month.		
Has he/she been off sick or absent from work due to drinking?		
or Has he/she had any trouble? (e.g. warning about lateness or performance)		
or Has he/she been dismissed from work (due to drinking)		
(b) The patient has had no job in the past month.		
(i) Has he/she been unable to fulfil a commitment?	1	2
8. Have there been arguments at home about drinking in the past month?	1	2
(If he/she has no home, explore living arrangements and family contacts and include any arguments with friends or general public arising out of his/her drinking)		
9. In the past month, have there been any times when the patient has become so violently angry that he/she hit someone in the family, flat etc.	1	2
(Living alone — include violence to others, including general public)		
10. *Complete section (a) or (b)*		
(a) The patient is married		
(i) Has had arguments which led to his/her partner threatening to leave, or created such an unpleasant atmosphere that he/she thought of leaving		
(b) The patient is not married		
(ii) Has had arguments which led to friends and relatives threatening to leave, or led them to ask the patient to leave, or created such an unpleasant atmosphere that the patient thought of leaving	1	2
11. Trouble with police — police involved because of his/her drinking (not necessarily leading to charge)	1	2
TOTAL SCORE:		

of health status as measured by the SF-36 (Ware *et al.*, 1992).

METHODS

Subjects' characteristics

The cohort of the Study of Socio-Economic Consequences and Costs of Alcoholism and its Treatment (SECCAT) is described in a recently published paper (McKenna *et al.*, 1996). It comprised all those patients diagnosed on DSM-III-R criteria (American Psychiatric Association, 1987) as alcohol dependent (n = 447), alcohol abusers (n = 125), alcohol intoxicated (n = 10) and four patients with an alcohol problem in whom DSM-III-R diagnosis was not specified. All subjects had been in contact with an alcohol problems clinic (APC) at a point 12 months previously and gave a home address within the region. Following a protocol described by McKenna *et al.* (1996), an invitation for interview was posted to 586 patients and 212 were interviewed, of whom 55 (26%) were female, and 102 (48%) were still in contact, even if occasionally, with the clinic. Currently, 97 (46%) were living alone, 51 (24%) were in full-time employment and 57 (27%) gave their marital status as married. Their mean age was 48 (range 21–70).

The ARPQ

A scale used in a previous outcome study (Chick *et al.*, 1988) and modified following further experience (Chick *et al.*, 1991), the ARPQ (Table 1), consists of 11 questions on physical and mental health, problems at work (if unemployed, failure to keep to commitments) and at home (if living alone problems with acquaintances or others), and police trouble. It is completed by the interviewer. The total score ranges from 11 to 22, a higher score indicating a better outcome, that is, fewer problems, for

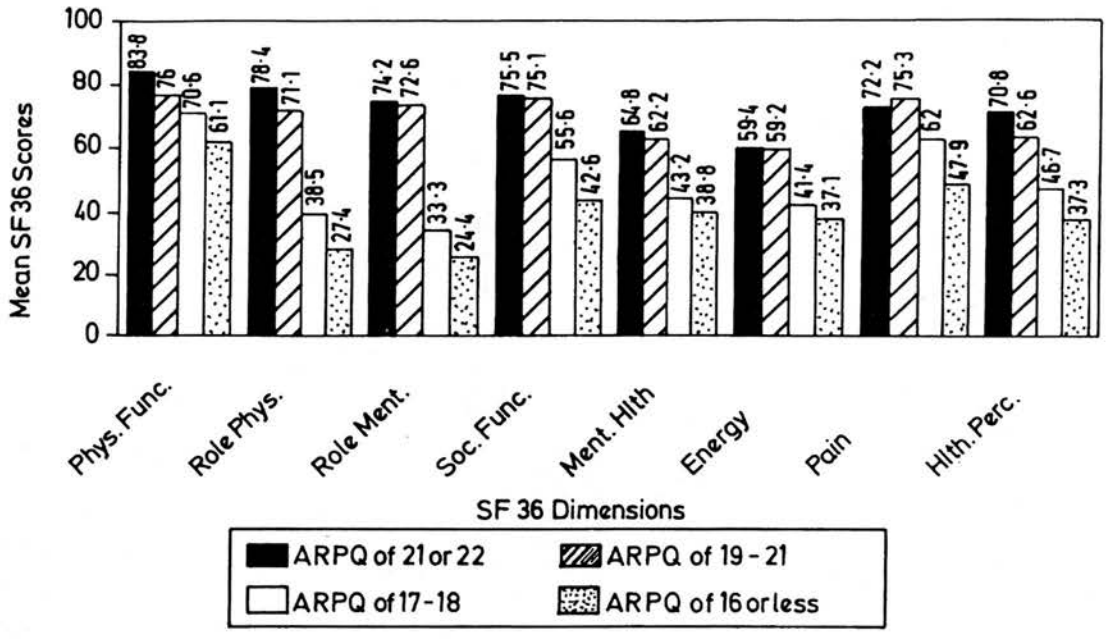

Fig. 1. SF-36 dimensions (mean scores) by ARPQ score

example 'Tried to harm him/herself deliberately taking an overdose': 'yes' would be scored as 1 point, 'no' as 2 points. The time frame used for this study was the 6 months prior to the interview (Table 1).

The SF-36

The SF-36 is an easily administered, psychometrically sound, short measure of subjective health status according to eight dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, general mental health; energy/vitality, bodily pain, and general health perceptions. A score is derived for each dimension of between 0 (poor health) and 100 (good health). The time frame used was either the present, or the past 1 month, depending on the question. Analysis of SF-36 data in our study followed the users' manual (Ware *et al.*, 1992). Our internal validation of the instrument in this population showed acceptable validity on all dimensions (M. McKenna *et al.*, unpublished).

Indicators of alcohol consumption

In addition to the commonly used proxy for alcohol consumption, the total of abstinent days, we used an additional measure, controlled drinking months. This was defined as the total of completed months when drinking occurred but in a controlled way, defined as less than an average of 5 units (45 g ethanol) per day for men and 3 units (27 g ethanol) for women with no days on which consumption exceeded 8 units (72 g) for men and 6 units (54 g) for women.

Resource use

Hospital and general practice records supplemented information from patients about the following, which were each costed: APC: number of individual or group sessions, number of home visits from APC staff, number of inpatient stays; GP: visits to or from the GP, to or from the practice nurse; other: number of counselling sessions at voluntary agencies, weeks in residential treatment units (social work or non-statutory), general hospital outpatient visits or inpatient stays, visits to casualty departments, and cost of drugs

Table 2. Correlation matrix of total cost, abstinent days, controlled drinking months and ARPQ score

	Total cost	Abstinent days	Controlled drinking months	ARPQ score
Total cost				
r	1.0000	0.0344	−0.2147	−0.3245
P	0.0	0.2334	0.0020	0.0001
n	212	212	212	212
Abstinent days				
r	0.0344	1.0000	0.4870	0.5488
P	0.2334	0.0	0.0001	0.0001
n	212	212	212	212
Controlled drinking months				
r	−0.2147	0.4870	1.0000	0.5209
P	0.0020	0.0001	0.0	0.0001
n	212	212	212	212
ARPQ score				
r	−0.3245	0.5488	0.5209	1.0000
P	0.0001	0.0001	0.0001	0.0
n	212	212	212	212

prescribed. (The basis of these resource use estimates is described by McKenna *et al.*, 1996.) Costs incurred in work accidents or absenteeism, or to the police, courts or social services were not estimated.

RESULTS

Proxies for cost

Spearman correlation coefficients were calculated to ascertain which clinical parameters were the best proxies for cost, that is, cost of total health service contacts. First, alcohol consumption measures were examined. The link was fairly weak: abstinent days $r = 0.03$ (n.s.), controlled drinking months $r = -0.21$ ($P = 0.002$). A stronger correlation was observed with ARPQ score: $r = -0.32$, $P = 0.0001$) (more problems associated with more cost). Table 2 is the matrix of correlations between these predictor variables.

Table 3 shows the fall in mean resource use costs by quartiles of the ARPQ distribution. There was no *a priori* reason to expect that alcohol abuse would differ from dependence when the relationship between ARPQ and cost was examined — a problem is a problem, whether caused by a dependent or non-dependent pattern of drinking — and so it was decided not to pursue such subanalyses.

Scattergrams were examined to clarify the relationship between ARPQ and cost. The distribution is indeed somewhat scattered despite the significant overall correlation. Outliers are: (a) individuals who had ARPQ scores of 22 (i.e. free of problems) but who had used resources regularly, perhaps to help them stay sober or recover from relapses before going on to develop problems: (b) some individuals with low ARPQ scores (i.e. many problems accrued) who had managed or chosen to keep away from the health services.

Relation of ARPQ to SF-36

Figure 1 shows SF-36 scores with the improvement in the scores by quartiles of the ARPQ distributions. There is a steep gradient in the values on all dimensions, and with the exception of 'pain', the gradient is entirely consistent in direction for each quartile. SF-36 scores are very high (indicating good quality of life) among those who report no alcohol related problems, and are in fact higher than UK SF-36 norms for the general population, for all dimensions, except 'role physical' (see Brazier *et al.*, 1992; Jenkinson *et al.*, 1993).

DISCUSSION

To examine further the relationship between ARPQ and costs, a post-hoc search for a suppressor variable was made using multiple regression, regressing total costs against abstinent days, controlled drinking months, age and ARPQ,

Table 3. Comparison of average total cost of health service use (£) by score on Alcohol Related Problems Questionnaire (ARPQ)

	ARPQ 1–16 $n = 56$	ARPQ 17–18 $n = 48$	ARPQ 19–20 $n = 64$	ARPQ 21–22 $n = 44$
APC	651	588	336	108
GP	69	61	42	38
Hospital	1029	700	299	227
Drugs	72	102	82	74
Total	1823	1451	759	447

Costs are in £ and given by quartiles of the ARPQ.
APC = alcohol problems clinic; GP = general practitioners.

with the following as dummy variables: sex, marital status, living circumstances, housing situation and employment status. Backward elimination (and stepwise elimination) were conducted. Of these variables, all except controlled drinking months met the criteria of statistical significance. However, a suppressor variable could not be identified.

The lack of relation of total abstinent days to cost is partly because some patients achieving lengthy abstinent periods used considerable APC resources, and this has been discussed in a recent paper (McKenna *et al.*, 1996).

There are some contexts where 'at risk' drinking is the target of treatment, for drinkers who have not developed problems, or not yet, for example, as identified in screening or opportunistic interview in general practice (Wallace *et al.*, 1988). A measure of 'problems' would not necessarily be a proxy for resource costs in that setting. The present study has looked at costs in the same period for which the ARPQ was completed. It would be important to examine the sensitivity of the ARPQ in a prospective study, to see whether ARPQ scores for the past 6 months would also predict future costs.

ARPQ scores and total cost are not strictly independent variables, because the questionnaire has one item about attending a hospital or casualty department. While this point diminishes the value of ARPQ as an independent construct, its practical value as a proxy for costs is not diminished. It would seem a useful outcome measure for service use, particularly because it is also a marker for quality of life.

It is probable that two other established measures of alcohol-related problems, the Alcohol Problems Questionnaire (Drummond, 1990) and the Addiction Severity Index (McLellan *et al.*, 1992) would perform in the same way, although they are more data-hungry than the ARPQ. All are considerably less elaborate to use than collecting data on costs, or even using the SF-36, which, although easy for patients to complete, does not generate immediate figures for the clinician to use. Whilst in a formal evaluation of one treatment versus another, it would be justified to use the methods of McKenna *et al.* (1996) and the SF-36, in audit or in routine practice the ARPQ can be recommended as a simple, convenient tool.

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Advice Versus Extended Treatment for Alcoholism: a controlled study

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Summary

One hundred and fifty-two attenders at an alcohol problems clinic were randomly allocated to one session of advice or extended in or outpatient treatment. Two years later, the group who were offered extended treatment were functioning better, in that over the year prior to the independently conducted follow-up interview they had accumulated less harm from their drinking than those only treated briefly. Abstinence was not, however, more common in patients offered extended treatment. In the group of 94 patients given advice only, no advantage in amplifying the session of advice could be demonstrated.

Introduction

In alcoholism treatment clinics, when two treatments of differing intensity have been compared, the less intensive has usually proved as effective as the more intensive (e.g. Ritson,[1] Edwards & Guthrie,[2] Edwards *et al.*[3]). Exceptions have been few (e.g. Azrin,[4] Chaney & O'Leary[5]). There may be some patients for whom an authoritative, concentrated, unequivocal session of advice may be effective, and have a greater impact than involvement in a drawn-out, complex alcoholism treatment programme.

Only in screening projects with less severe problem drinkers has it been ethical or practical to have a truly untreated control group.[6,7] The closest a controlled study has come to random allocation to no treatment in the setting of an alcoholism treatment clinic has been the London 'advice versus treatment' 1 year follow-up study in 100 married male alcoholics by Edwards *et al.*[3]. We report here a further comparison of brief versus extended treatment, and within brief treatment a comparison of very brief advice with more comprehensive advice such as that offered to the minimal treatment group in the London study. Our sample includes women and single people as well and thus is more representative of the total range of referrals. We used a 2-year follow-up period.

Method

The Sample

The study, which was approved by the local ethics committee, was conducted at the sole specialized alcohol problems treatment service for Edinburgh, a city of 500,000, and its surrounding area. Referrals come mainly from general practitioners, but some patients refer themselves or come via social workers or hospital specialists. All patients are asked to attend their initial appointment accompanied by a close friend or relative.

With the aim of obtaining a sample as representative as possible of the patients we see at our routine clinics, during a 12-month period in 1980/81 every second new patient was approached. Patients were asked to participate in a study into how they fared after contact with our clinic. They were asked if they would agree to a friend or relative being contacted every 3 months for information about

how they are getting on, and to an interview with us in 2 years. During the year of recruitment, four out of five patients approached named an informant and agreed to follow-up; those who had no-one close enough to fulfill the role, and the few who refused, were not taken into the study. Auxiliary addresses such as those of other relatives were noted for both patients and informants.

Excluded at the outset were patients who: were diagnosed as not having an alcohol problem; exhibited physical violence to family members; were mothers in charge of children under 11 years old; had cirrhosis or clinically evident brain damage; had a major medical or psychiatric disorder other than alcoholism; were suicidal; presented as emergencies requiring immediate medical intervention; had been seen at our clinic within the past 6 months; or lived more than 20 miles away. One man who was totally unwilling to discuss his drinking was also omitted.

The sample obtained differed from the remainder of patients seen in that period and not recruited to the study in that it contained a lower proportion of socially isolated individuals (two-thirds of our sample were married or cohabiting compared to half of the non-recruited patients) and a lower proportion of women (1 in 5 as opposed to 1 in 4).

The Randomization

After the patient and informant assessment interviewing and testing were complete, random assignment to treatment group was made, stratified by severity of alcohol dependence (high/low) and marital status (whether or not married or cohabiting). (For this purpose a clinical judgement of severity of dependence was made based on signs at examination, e.g. tremor, tolerance to a high blood alcohol level, and reports of early morning tremor and relief drinking.) Randomization was by drawing the top envelope from one of four piles of closed envelopes according to the patient's level of dependence and marital status. The procedure was predesigned so that the ratio of 'advice-only' to 'extended' interventions would be 3:2, and within the 'advice' group half would be given 'simple' advice and half 'amplified' advice. The final numbers were: advice-only $n=96$ (simple advice $n=41$; amplified advice $n=55$); extended treatment $n=58$.

The Nature of the Treatment Interventions

Simple advice was standardized and lasted no longer than 5 min. In the presence of the informant, the patient was told "You have an alcohol problem. The only treatment is to stop drinking". It was emphasized that the responsibility for this lay in the patient's hands.

Amplified advice was essentially the same but the psychiatrist was allowed 30–60 min during which he or she attempted to enhance the motivation of the patient by encouraging the patient and informant to reflect on the reasons why a radical change in drinking was necessary and discuss how that might be achieved. This did not specifically follow the method sometimes termed 'motivational interviewing'. Strategies were suggested and patients encouraged to see the positive aspects of life without alcohol. For married couples, advice was sometimes given on how the cohesiveness of the marriage could be improved.

'Extended' treatment consisted of the above advice given on the first day, but with the offer of further help according to the patient's needs, including detoxification, further appointments or inpatient or day-patient attendance at our 2–4 week milieu- and group-therapy based treatment programme. Group work, as well as aiming to educate the patient about alcohol problems and reduce denial and rationalization, used the techniques of social skills training to help patients identify situations when relapse was likely and develop better strategies for coping with these. Counselling tended to be either non-directive or cognitive in style. The inpatient programme was oriented towards abstinence, but for younger and less severely dependent subjects in outpatient treatment, retraining with a view to controlled drinking was occasionally the goal. Most patients including all those admitted were informed about Alcoholics Anonymous and the benefits of regular attendance. Deterrent drugs such as disulfiram were seldom prescribed. Thus extended treatment had much in common with other British alcoholism treatment programmes of the day, except perhaps for its shorter length of inpatient stay.[8] For patients who declined further treatment, the offer of treatment was kept open.

Follow-up Procedures and 'Safety Net'

At 3-monthly intervals one from a team of five research social workers interviewed the informant about his or her own well-being and that of the patient. The social worker knew the treatment to which the patient had been allocated. For 'advice' patients, she kept the interview strictly to the structured research schedule and the typical inter-

view lasted 30 min. The workers were rotated so that the informants of 'advice' patients were less likely to build up a therapeutic relationship with the research staff, a possibility that Edwards *et al.*[3] discussed in relation to the monthly social work visits in their study.

The purpose of the social work visits was to act as a safety net so that patients or families in serious difficulties could be reassessed by a psychiatrist. In some instances we found deterioration to be so severe that we felt ethically bound to urge intensive treatment. In this way 20 'advice' patients (21%) were deemed to have failed in the advice-only condition and will be referred to as 'failures of advice' (F/A). These 20 were taken out of the study and offered treatment at a mean of 33 weeks, 10 in the first 6 months and 10 between 6 and 18 months. The reasons for our intervening were: suicidal behaviour (3); repeated haematemeses (1); worsening antisocial behaviour causing severe family strain or risk to spouse (5); risk of harm to children (3); suspected developing Korsakov's syndrome (1); imminent dismissal from job (2); paranoid syndrome (1); repeated severe withdrawal syndromes with fits or hallucinations (4).

Measures Used

Intake and follow-up interviews included a *Scale of Alcohol-related Problems*. This was compiled both of items asked of the patient (a sub-scale of nine items about alcohol-related physical and mental symptoms, and a sub-scale of fourteen items about alcohol-related social problems in the areas of money, job, the law, marriage) and items based on the work of the London group[3] asked of the informant alone (a subscale of 12 items to do with disagreeable behaviour in the family ascribed by the informant to drinking, such as restlessness at night, poor personal hygiene, not taking part in family life, picking quarrels, violence, fear in the children, possessiveness). Heavy binges (a bottle, 750 ml, of spirits or equivalent in 24 h) scored points according to frequency. Positive response to some items yielded a score of more than one point depending on severity. For example, threatened rupture of marriage scored one point, and actual separation scored two. Each item was asked with respect to the past month, and to the past year. As a way of dealing with the issue of non-applicability of certain items to certain subjects (e.g. unmarried subjects cannot score on an item on marriage-rupture, the unemployed cannot be absent from work) sub-scale scores were converted to percentage scores, with the denominator being the number of possible items. The total problem score was the sum of the sub-scale scores.

Estimates of *Alcohol Consumption* were based on accounts, checked against relatives' views, of what the patient said he or she had drunk in the 7 days leading up to the interview, or if that had not been typical, in a typical week. This was elicited by going over each day in that week and asking the patient to recall his activities, the money he had spent, the company he had been in, and the quantities and type of beverage consumed. Conversion to grams of ethanol was made. The number of days of abstinence in the past month, and in the past year, was estimated by asking the subject to recall such periods.

Dependence on Alcohol was measured from responses to four items previously reported on[9] concerning restlessness without a drink, frequency of tremor, severity of tremor and frequency of morning relief drinking. The time frame was the past 3 months. Possible scores ranged from 0 to 16.

Blood Tests: measurements were made at intake and follow up of serum gamma glutamyl transpeptidase (GGT), which has an association with heavy drinking.[10]

An enquiry was made of the process of making the decision to attend the clinic, and of previous help obtained.

Assessment of Outcome

Follow-up was aided by our attempts to keep in touch with the informant during the 2-year period. The informant was the cohabitee/spouse in 67% of the sample. At the 2-year point an experienced psychiatric nurse not associated with the treatment team conducted a structured interview usually at the clinic with the patient and the informant always seen separately. The interview contained the questions that had been asked at intake, this time with reference to the past 12 months and past 1 month. Where patient and informant differed in their replies, guided by her clinical experience she adjusted her rating of the patient's responses taking into account the views of the informant whom she interviewed later in general resulting in her recording the more pessimistic of the two responses. Strenuous and successful efforts were made to keep this nurse blind to the treatment group of the patient and she was not told that the design involved a comparison of different treatments. Where informa-

tion about a subject was deficient and/or no contact could be made (16 cases), a search was made of records of local hospitals and enquiries made to general practitioners.

As shown in Table 2, seven patients had died and the cause of death was obtained for each. Two F/A patients died, each approximately 6 months after being offered intensive treatment. Follow-up information was available on 84 (87.5%) of the brief group and 53 (91.6%) of the extended group. In one 'advice' patient (case 145) who refused to be interviewed at the 2-year point we had detailed information from relatives in regular contact with the patient and confirmatory evidence from general practitioners. Since all reports were that his condition was worse than at intake, he was given a problem score at outcome equal to his intake score so that he could be included in the analysis.

When the 2-year assessment was complete, a psychiatrist saw each patient and where appropriate offered further treatment.

Analysis. Analysis of variance was conducted to compare the scores on continuous variables. In analysing differences in scores on the scale of alcohol-related problems and serum GGT, since these variables yielded skewed distributions the non-parametric Mann Whitney U test was also used. Chi-square tests were applied to the tables of outcome by categories.

Results

At Intake

Our three groups did not differ significantly in their previous treatment experience, or on any socio-demographic, clinical or drinking variable (Table 1), except the following. Patients given the 'extended' intervention had a significantly higher serum GGT (mean 138 i.u./l) than patients given advice only ($U=2097, Z=-.296, p=0.02$). Within the group of patients given advice only, the difference in serum GGT between those receiving 'simple' advice (mean 93 i.u./l) and those receiving 'amplified' advice (mean 59 i.u./l) was not significant ($U=967$, $Z=-0.766$, $p=0.44$). The 'extended' group had been abstinent for less days in the month before the intake interview than the combined 'advice' patients (7.9 days as against 11.3 days, $p=0.02$, 2-tailed). 'Advice' patients were more likely to have been referred as a result of a crisis, than patients allocated to extended treatment.

Treatment Received

For the 58 patients offered extended care, the treatment received was as follows. Fifty-six attended at least one further outpatient appointment, of whom 32 (55%) attended at least 10 appointments. Of the married patients, being seen with the spouse present was common: 32 of the 39 married or cohabiting patients (82%) had at least three joint meetings. Thirty-two (55%) had inpatient treatment with seven (12%) having one or more readmissions. The average total time as an inpatient among those admitted was 19 days. Fourteen patients also had a period attending the main programme as a day patient; for some this was in addition to an inpatient stay. In the initial phase a specific AA referral was made in seven patients and disulfiram or calcium carbimide was prescribed in 11 patients. Only one patient became a regular attender at AA. Two became faithful adherents of the Council on Alcoholism. Six continued in regular contact with their general practitioner. One received frequent counselling from another source. Some patients were still being seen occasionally as outpatients at our clinic into the second year.

At some point in the 2 years 'social drinking' was agreed by the therapist, albeit sometimes reluctantly and perhaps only for a short experimental period, in 28 (48%) of the patients offered extended care. Counselling was given on how to prevent this social drinking getting out of control. At the time of intake to the study 33 (57%) had said they did not wish to stop drinking completely.

Although patients allocated to 'advice only' were not referred to other agencies, six (6%) were known through our contacts with informants to be attending Alcoholics Anonymous regularly. Two (2%) were regular attenders at the local Council on Alcoholism and two patients were admitted to a general psychiatric hospital elsewhere in the region. Four obtained regular help from other sources (hypnotherapist, company doctor, health visitor at child's nursery, priest). During the 2-year period, 18 'advice' patients had regular contact (10 or more visits) with their general practitioners.

Outcome: combined 'advice' groups versus 'extended treatment'

In describing the patients at the 2-year point, we retain F/A cases in their original 'advice' category. All 3 'advice' patients who eventually died of alcohol-related causes were offered full treatment

Table 1. *Characteristics at Intake*

	Advice only		Extended treatment
	Simple advice $n=41$	Amplified advice $n=54$	$n=58$
Males (%)	78	70	84
Females (%)	22	30	16
Age mean ± SD	42 ± 11.5	38 ± 11.6	41 ± 10.8
Previous help (any agency) (%)	68	66	64
SE Status (%)			
Professional	2	7	7
Managerial	5	7	14
Technical	24	19	17
Skilled Manual	27	37	33
Unskilled Manual	39	30	28
Unclarified	2	0	2
Currently employed (%)	54	63	58
Serum GGT i.u./l mean ± SD	93 ± 103	59 ± 50	138 ± 185
Married or cohabiting (%)	56	72	69
Achieved 2+ months of abstinence in past year (%)	15	31	25
Attendance instigated because of a crisis (%)	63	77	44
Previous attempts to cut down (%)	77	85	91
Sees self as having drink problem (%)	93	84	97
'Full' social support (%) (see Ettore[8])	51	67	64
Dependence Score			
Low 0–3 (%)	12	27	32
High 10–16 (%)	63	50	49
Clinical diagnosis severe dependence (%)	68	65	53
Consumption in past week or typical week			
<1000 g (%)	39	48	34
1000–1600 g (%)	22	28	26
>1600 g (%)	39	24	40
Alcohol-related offences since aged 18 (one or more) (%)	54	48	52
Alcohol-related problems scale (past 1 year)			
Total (mean and SD)	45 ± 13	46 ± 16	44 ± 15
Physical/Mental symptoms: few (0–3) (%)	12	20	12
very many (8–15) (%)	44	41	31
Disagreeable behaviour to family: little (0–25) (%)	29	30	31
Much (51–100) (%)	24	24	19
Social problems: little (0–25) (%)	27	22	31
much (51–100) (%)	34	37	28

during the course of their deterioration though only two accepted it.

Outcome by Categories

Table 2 categorizes cases according to the findings based on the responses received by the nurse at the 2-year follow-up interview. Trouble-free drinking is defined as drinking of any quantity, but without incurring any of the alcohol-related problems on our scale. Total abstainers included two patients who each admitted one drink on one occasion. Abstainers also had to have a normal serum GGT. Abstension or drinking completely without problems for the full year or more prior to the follow-up was not common, and no more frequent in the 'extended'

Table 2. *Outcome at 2 years*

	Abstinent for more than past year	Drinking but without problems for more than past year	Abstinent, or trouble-free drinking, for past 1–12 months	Continuing problems	Total dead (alcohol-related deaths in brackets)	No information
Advice only $n=96$						
Simple advice ($n=41$)	4	2	5	20	4 (3)	6
Amplified advice ($n=55$)	8	2*	11**	27	1 (0)	6
Extended treatment $n=58$	5	7	18	21	2 (1)	5

*Includes one case (**two cases) who took up extended treatment offered following serious relapse.

Table 3. *Summary of Outcome in Patients Reassessed at 2 Years*

	No alcohol-related problems for at least preceding month	Continuing problems**
Advice only $n=82$	32* (39%)	50 (61%)
Extended treatment $n=52$	30 (58%)	22 (44%)
		$p=0.053$

*Includes 3 of the 20 cases who took up treatment offered after serious relapses.
**Includes deaths from alcohol-related causes.

group than either of the 'advice' sub-groups. 'Short-term successes' were cases who were problem-free for the past 1 to 12 months. Table 3 collapses the data of Table 2 to show outcome categorized only in terms of whether or not the patient has been trouble-free (either drinking or abstinent) for a minimum of the past month. Those dead of alcohol-related causes are grouped with the poor-outcome group. Those on whom no information was available, or who died of non-alcohol related causes are omitted. In the good outcome group there are slightly more 'extended' patients (58% of 52) than 'advice' patients (39% of 82) (Chi-square with Yates correction 3.74 d.f. 1, $p=0.053$).

Duration of Satisfactory Outcome in Short-term Successes

We did not attempt to obtain from patients exact dates of alcohol related problems, but asked them to specify only whether the problem had occurred within the past month or only within the past year. To reconstruct how long patients had been problem-free working back during the year, we only had two measures: (i) We asked when the last occasion was that the patient had had any alcohol. Of the 'extended' patients 14% had been abstinent for at least 3 months, and 12% for 6 months, compared to 17% and 13% in the 'advice' patients. (ii) We had some incomplete information from the social-workers' contacts with informants in the second year. The social worker was not blind to the treatment given. Out of 37 short term successes, there were data on 29 at the 24-month informant interview. This revealed that 12 of 14 'advice' patients had been problem-free for at least the preceding 3 months, and 10 of 15 'extended' patients. The 21-month interview offered data on 23 of these short-term successes. This showed that 10 of 12 'advice' cases were problem-free for at least 6 months whereas only 6 of 11 'extended' cases could be so classified. There is too much missing data to allow conclusions to be drawn. The numbers are anyhow small and the slight trend indicating that short-term successes in the 'advice' group had been doing well for longer did not reach significance (chi-square) at either point.

So far, in presenting data on the strict criterion of whether the patient is problem-free, or abstinent, it seems that extended treatment at best contributes to only short periods of recovery.

One-Year Scores on Alcohol-related Problems

At intake, the mean total score of alcohol-related problems experienced in the preceding year on our scale was not significantly different for patients offered extended treatment (43.8, $n=58$; SD 15.0) and 'advice' patients (45.2, $n=96$; SD 14.8). In calculating follow-up scores using the one-year window, patients who died during the study of a definitely alcohol-related cause were given a follow-up problem score equal to the highest follow up problem score in the sample. We found that patients offered extended treatment had a lower mean problem score at follow-up (22.5, $n=52$; SD 19.8, 95% confidence interval 17.0–28.0) than 'advice' patients (34.3, $n=82$; SD 27.1, 95% confidence interval 28.3–40.3) ($F=7.32$, $p=0.008$, 2-tailed).

In order to control for problem score at intake, a Mann Whitney U test was performed comparing the groups on the difference between intake and follow-up problem scores. The group offered extended treatment was superior to the 'advice' group when compared in this way ($U=1653$; $Z=-2.190$; $p=0.0285$, 2-tailed, $n=134$). If patients dying of alcohol-related causes are not included, the difference between the groups remains significant ($U=1576$; $Z=-1.988$; $p=0.0469$, 2-tailed, $n=129$).

This difference between intake and outcome problem scores was correlated with each of the variables which at intake had significantly differentiated 'extended' from 'advice' patients. Only the number of abstinent days in the month preceding the intake interview correlated significantly

($r=0.17$, $n=134$, $p=0.025$). Therefore, an analysis of covariance was performed to test whether, with that variable controlled, a significantly greater fall in the problem score was still found in the 'extended' group. This was confirmed: F (explained) 4.85, d.f. 2/131, $p=0.009$. To explore which areas accounted for the greatest improvement in the problem score in patients offered extended treatment, changes in individual items were examined. Looking at the outcome data (one-year window), a 'symptom' could be scored as now present where it had not been present at intake; still present but no worse; no longer present, or less severe; neither present at intake nor at follow-up. Grouping the last two categories together to represent good outcome, chi-square tests were performed on 21 individual problem items or combinations of related items. There was no item where patients offered extended treatment tended to have improved less than those only given advice, though there was little difference between the groups in alcohol-related physical symptoms, trouble at work or absenteeism, and police trouble. Significantly greater improvement was found in the patients offered extended treatment in their behaviour in the family (or with the people they lived with). They had improved more in the following: joining in family activities ($p=0.027$), threatened violence ($p=0.009$), breaking or damaging things ($p=0.028$), jealousy and possessiveness ($p=0.032$), causing fear and anxiety in the children ($p=0.0027$), being noisy and disturbing at night ($p=0.07$). Commensurate with this, there was a trend favouring 'extended' patients in the item on threatened or actual marital/cohabiting break-up ($p<0.2$). There was a trend for greater improvement also in the item on 'trouble with your nerves due to drinking' ($p=0.07$).

In terms of *alcohol consumption* Table 4 shows that there was a trend for those who received extended treatment to have been drinking at a lower consumption bracket in the 7 days before the follow-up interview; and to have been less likely to have had 20 or more days in the preceding year drinking more than a bottle of spirits per day or equivalent (200 g ethanol). Neither trend reached significance. In both groups 87% of patients reduced the frequency of such binges. No trend was visible when 'extended' and 'advice' patients were compared in the number of abstinent days achieved in the past year. The number of abstinent days was increased in 73% of the 'extended' patients and in 67% of the 'advice' patients.

In terms of *social stability*, there was a general decline over the 2 years, which was similar in all treatment categories (Table 5).

Table 4. *Problems and Consumption at the 2-year follow-up*

	Advice only		Extended treatment
	Simple advice	Amplified advice	
Alcohol-related problem scale (past 1 year) (Mean and SD)	36.4 ± 27.8 ($n=34$)	32.8 ± 26.8 ($n=48$)	22.5 ± 19.8** ($n=52$)
Past 7 days' drinking (g ethanol)			
<500 g (%)	56	61	71
500–1000 g (%)	29	25	13
>1000 g (%)	15	14	16
	($n=27$)	($n=44$)	($n=49$)
Frequency of drinking over 200 g ethanol per day (past year)			
never (%)	52	41	54
1–20 days (%)	10	22	18
>20 days (%)	38	37	28
	($n=29$)	($n=46$)	($n=50$)
Abstinence (past year)			
Less than 2 months (%)	70	54	59
2–6 months (%)	17	24	25
>6 months (%)	13	22	16
	($n=30$)	($n=46$)	($n=49$)

**Extended group significantly less than combined advice groups ($p=0.008$).

Serum GGT. There were 65 'advice' patients and 41 patients offered extended treatment in whom intake and follow-up measures of this enzyme were available. Serum GGT had decreased below the intake measurement, i.e. improved, in 24 (59%) of the 'extended' patients and 36 (55%) of the 'advice' patients. However, the mean remained higher, as it had been at intake, in the 'extended' patients (mean 127 i.u./1, SD 194, 95% C.I. 67–187, $n=42$) than in patients given amplified advice (mean 83 i.u./1, SD 160, 95% C.I. 34–132, $n=43$) or patients given simple advice (mean 93 i.u./1, SD 139, 95% C.I. 34–150, $n=24$).

Comparison of 'Simple' Versus 'Amplified' Advice

Collapsing the data in Table 2 and including alcohol-related deaths with 'continuing problems' reveals that abstinence or trouble-free drinking for at least a month was noted in 11 (32%) of those given simple advice and 21 (44%) of those given amplified advice (percentages expressed as a percentage of those on whom information available). This trend in favour of amplified advice is not significant (chi-square 1.09, d.f. 1, $p>0.1$). There is also a trend in favour of amplified advice when marital stability is examined (Table 5) but this also is non-significant (chi-square 3.04, d.f. 1, $0.1<p<0.05$).

The mean past year's problem score at follow-up for 'amplified' patients was 32.8 (SD 26.8, 95% C.I. 25.1–40.5, $n=48$) and for 'simple' patients 36.4 (SD 27.8, 95% C.I. 16.9—44.9, $n=34$). The mean fall in the problem score total between the intake and outcome assessments did not distinguish significantly between these two groups either when those dying of alcohol-related causes were included ($U=784$; $Z=-0.306$; $p=0.760$, 2-tailed, $n=82$) or excluded ($U=711$, $z=-0.179$, $p=0.858$, 2 tailed, $n=79$).

Problem-free drinking. Although Table 2 shows 11 individuals who continued to drink some alcohol in the year to follow-up and achieved this with no apparent problems, five had an elevated serum GGT at follow-up (of whom two relapsed into problematic drinking in the year following), and one refused to give a blood sample (and also subsequently relapsed).

Failure of Advice Cases. These cases differed at intake from the remainder of the sample in that proportionately more were female (half) and in that on average they had had more previous treatment. Seventeen of the 20 took up the treatment offered though with varying levels of perseverance. Two had an excellent outcome and a further three were clinically definitely improved. As mentioned, two died, despite being offered more help.

Help Acknowledged in Good Outcome 'Advice' Cases

Of the 16 'advice' patients who abstained or were free of troubles for the year to follow-up, one had received considerable help from a psychiatrist elsewhere and also from AA. Two others had attended AA. There were none who had sought regular help from the Council on Alcoholism. Two laid great store by the help, even though it was brief, at their intake interview. Two others were F/A patients given treatment with disulfiram, ingestion being supervised in one by the clinic as part of an agreement between himself and his employer.

Discussion

In terms of what is known of the predictors of outcome in alcoholism, our randomization gave us apparently well matched groups.

The need to take out the 'advice' group patients who were doing very badly, and offer therapy raises the question of whether they should be left out of

Table 5. *Employment and Marital Status of Patients in Whom Complete Follow-up Information Was Available*

	Advice only		Extended treatment
	Simple advice	Amplified advice	
Employed at intake	*n* 19	30	32
% still employed at 2 years	74	70	75
Living with spouse or cohabitee at intake	*n* 24	38	39
% still living with spouse or cohabitee at 2 years	58	79	69

the final analysis. To leave them out, removes from the 'advice' group some of its poorest prognosis cases. To keep them in, possibly weights the results against finding a positive effect of treatment. We chose to leave them in.

We believe that the follow-up interviewer remained blind to the treatment group of the patient. We did not assess after each patient whether or not she had guessed the group, because we tried, and succeeded until the end of the study, to keep her ignorant of the design itself.

There was a trend which did not quite reach significance suggesting that at the point of follow-up a higher percentage of the patients offered extended treatment were in a state of remission. Much of this comprises short-term abstinence, of the type shown in the Rand Report[11] often to be temporary. However, the data on accumulated problems in the longer one-year window demonstrates that extended treatment can result in a more sustained overall lessening of problems if not complete abstinence. This positive result in favour of treatment has been found in a population slightly weighted towards men, and towards married patients, in comparison to our total clinic population.

While the reduction in problems reached statistical significance, the accompanying trend towards less consumption of alcohol in the patients offered extended treatment did not. While a larger sample may have demonstrated a clearer reduction in consumption in that group, it may be that they were simply achieving a less hazardous style of drinking particularly as far as the family and spouse are concerned.

Only four patients offered extended treatment were readmitted during the year leading to follow-up, and each spent on average 20 days in hospital. If that occurred it counted in the score of alcohol-related problems. Thus, the lower aggregate problem scores at follow-up in the 'extended' group were not due to institutionally enforced sobriety.

It is likely that we had more complete admission by patients and their families of relapses and the ensuing problems in the patients offered extended treatment than in 'advice-only' patients, simply because we had maintained contact with so many of the patients during the follow-up period: it would be less easy for them to deny problems. This also weighs against finding a result in favour of extended treatment.

Our conclusion that extended treatment contributed to an overall lessening of harm hinges on our scale of alcohol-related problems. The items were not novel. Most had been used either in the London study,[3] or our previous clinical work[7] and survey work in heavy drinking occupational subcultures (Chick *et al.*[10]) and are of known reliability. However, this compilation was new and concurrent validation of the scale has not been attempted. Nevertheless, the face validity of the individual items is not in doubt. Furthermore, when improvements in individual items were examined there was the expected concordance among individual items in the domain of behaviour in the family related to drinking. We cannot ourselves conceive of how a property of our scale could lead to a biased result in favour of the extended treatment group.

In the London study,[3] 10 of the 46 'advice' patients had an admission, albeit usually short, to a psychiatric hospital during the year of the follow-up compared to only two of our 96 'advice' patients. Some of our 'advice' patients undoubtedly received other help, indeed 5 of the 15 who attained stable abstinence attributed their recovery to the help they had sought. However, as a group our minimally treated patients probably received less help overall than the 'advice only' group in the London study. This could have contributed to our obtaining a result showing an effect of extended treatment while the London study did not.

Despite its undoubted link with heavy drinking[10] the serum GGT in British alcoholism clinic samples correlates poorly with admitted consumption and other indices of severity.[12,13] In these samples, as in ours, there are bout drinkers whose consumption patterns fluctuate greatly. In this study we are dealing mainly with a population whose behaviour in response to alcohol rather than their tissue response is the presenting problem. Thus, we do not feel the lack of clear advantage in terms of improvement of serum GGT in the 'extended' group should detract from the indication that those patients had a somewhat better outcome. Of course, it would be desirable to have a marker of outcome that was purely objective. Without it, there remains the possibility that the patients offered extended treatment and their families minimized their reports of problems more than 'advice' patients because they wanted to please the clinic staff.

Some of the 'extended' group were still receiving outpatient support at the time of the follow-up interview. We cannot say whether the results for the 'extended' group might gradually worsen towards that of the 'advice' group if that support was withdrawn. We are aware of how short a period 2 years is in the span of a severe drinking problem.

For the 20 'advice' patients who were doing so badly as to necessitate removal from their study group, we cannot know what the fate would have been if they had been left untreated. It is worth repeating, however, that with treatment two had an excellent outcome. Substantial improvement was noted in a further three.

We have not addressed the question of compliance. There were, of course, patients offered extended treatment who did not take it. In the first 6 months of the study 16 of 47 patients offered extended treatment in whom the therapist was able to make a rating of compliance were said to be cooperating poorly with treatment. In 19, denial of their alcohol problem was rated as 'moderate' or 'marked'. However, it is our philosophy that dealing with denial and enhancing motivation are key ingredients of treatment.

The social work follow-up of all subjects may have had a therapeutic effect on the drinker via the family. This would have diminished the magnitude of the advantage of extended treatment.

Our finding that greater improvement resulted from extended than brief treatment supports the tentative conclusion of Emrick.[14] Emrick pooled the findings of several studies where the outcome of patients given treatment was compared with that of patients given none or only minimal treatment. He found that of 634 patients given no treatment or minimal treatment, 42% improved, whereas of 1774 who received more than minimal treatment 65% improved. However, in general these studies had not randomly allocated patients to the different treatment categories nor attempted to match patients on important prognostic characteristics. Nevertheless, it suggested that treatment was offering some advantage.

The Possible Value of the Advice-only Treatment

The finding that amplified advice was not more effective than simple advice suggests that in the study of Edwards *et al.*[3] that important ingredient was the unequivocal diagnosis and the injunction to abstain rather than the additional advice given with the London brief treatment. Or, indeed, the key factor may be the decision of the patient to do something about his drinking reflected in his coming for the appointment and whatever brief advice is given makes little difference. The assessment procedure was impressive and lengthy, involving computerized testing of cognitive function (to be reported separately). This may have enhanced the power of the advice-only treatment. We cannot say what the effect of our advice, either simple or amplified, would be in another setting, or with less attention paid to taking a detailed personal, medical and marital history. That 12 (12.5%) of 96 patients who received only advice were stable abstainers 2 years later should not be ignored. In the absence of a no-treatment control we cannot know whether this is merely the 'spontaneous remission rate'.

We will write elsewhere about the predictors of outcome and the matching of different types of patient to different intensities of treatment. We will also treat separately the question of whether our results lend support to the notion that a return to controlled, problem-free drinking is possible in such patients.

Conclusion

Extended treatment offered an overall lessening of the harm which accrues to problem drinkers, their families and society in the course of time. Extended treatment did not increase the likelihood of a patient achieving stable abstinence, or stable problem-free drinking, beyond that which could result from much briefer treatment. Nor did it improve the likelihood that a patient would remain in employment or in marriage. Larger samples in future studies may yield clearer results.

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To assess the efficacy of supervised disulfiram as an adjunct to out-patient treatment of alcoholics, a randomised, partially blind, six-month follow-up study was conducted in which 126 patients received 200 mg disulfiram or 100 mg vitamin C under the supervision of a nominated informant. In the opinion of the (blinded) independent assessor, patients on disulfiram increased average total abstinent days by 100 and patients on vitamin C by 69, thus enhancing by one-third this measure of treatment outcome. Mean weekly alcohol consumption was reduced by 162 units with disulfiram, compared with 105 units with vitamin C, and the disulfiram patients reduced their total six-month alcohol consumption by 2572 units compared with an average reduction of 1448 units in the vitamin C group. Serum gamma-GT showed a mean fall of 21 IU/l in patients on disulfiram but rose by a mean of 13 IU/l with vitamin C. Unwanted effects in the disulfiram group led to a dose reduction in seven patients and to treatment withdrawal in four (and in one vitamin C patient). Two-thirds of the disulfiram group asked to continue the treatment at the end of the study. There were no medically serious adverse reactions.

Disulfiram (Antabuse) is an agent which inhibits metabolism of alcohol, resulting in the unpleasant symptoms (flushing, headache, nausea, dizziness, tachycardia) of the disulfiram–alcohol reaction. Although it has been available for many years as an adjunct to counselling in the treatment of chronic alcoholism, and despite a dearth of therapies for this condition (Vaillant, 1983), disulfiram is not commonly prescribed in the UK owing partly to concern that the agent may cause hepatic damage (Peachey & Naranjo, 1983; Peachey, 1988). In addition, the early literature provided poor evidence of the efficacy of disulfiram, but these studies often lacked adequate controls (Bourne *et al*, 1966; Edwards & Dill, 1974; Bigelow *et al*, 1976) or supervision of patient compliance (Fuller & Roth, 1979). Compliance with the disulfiram regime, found to be as low as 20% in a study in the USA (Fuller *et al*, 1986), can be improved with supervision by the spouse or clinic (Gerrein *et al*, 1972; Robichaud *et al*, 1979; Azrin *et al*, 1982; Sereny *et al*, 1986).

We report here the first UK controlled study of supervised disulfiram as an adjunct to out-patient treatment of alcoholics, in which safety and acceptability were assessed in addition to the effect of the treatment on alcohol consumption and related problems.

Method

One hundred and twenty-six subjects entered the trial from among patients of either sex, aged 18–67 years, attending seven alcoholism treatment centres. Only patients who had already relapsed after previous therapy or other support were invited to participate, since we felt the memory of previous failure would aid their compliance with the study treatment. Pregnant women were excluded, as were subjects with cardiac disease, psychosis, or habitual drug abuse, and those showing abnormally high levels of serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

The protocol was approved by local hospital ethical review committees. All patients gave their written, informed consent to receive one tablet a day of disulfiram (200 mg, dispersed in water) or vitamin C (100 mg) for six months under supervision, and an informant was nominated, usually the spouse (occasionally another relative, colleague, or a member of the clinic staff, with whom they had contact at least once a week). Treatments were randomly placed against lists of numbers, supplied to the pharmacist at the various centres, who then allocated the numbers sequentially to patients entering the trial.

For ethical reasons the treatment codes were broken after allocation so that a thorough explanation of the use of disulfiram and the associated risks of drinking, to include written information and a pocket warning card, could be given to the patients and families concerned. If left blind, patients might have been tempted to test whether or not drinking could trigger a reaction.

The vitamin C group was included to control for the effects of receiving supervised medication and out-patient counselling, and patients were told this; if they asked further they were told that vitamin C was chosen for the control medication because alcoholics may have vitamin deficiencies, of which this is one.

Medication was usually supervised daily by the informant; where the informant was not the spouse the dose on a day when the informant and patient did not meet was either given the day before or given to take unsupervised at home. The informant was encouraged to telephone the clinic if

the patient refused the medication or lost touch, so that advice could be offered. No written contract, however, was involved, and no sanctions were invoked if the patient ceased taking the medication.

Patients were either already in, or were offered, a range of out-patient and community counselling and support, which varied between centres. A few patients were offered day-patient places. Marital therapy, relaxation therapy, attendance at Alcoholics Anonymous (AA), vitamin B supplements, and supportive group therapy were also used by some patients.

At intake, the clinican conducted a physical examination of the patient, which included blood tests, and took a medical and psychiatric history. During treatment the clinician monitored compliance (checking with the informant) and drug safety at each visit, recording any unusual symptoms reported by the patient, and reviewed patient progress at the end of the six-month trial. Blood tests (haematology and biochemistry, including liver function tests and blood alcohol, plus serum gamma-glutamyl transferase (GT) and mean red cell volume (MCV) as markers of regular alcohol consumption (Chick *et al*, 1981)) were repeated after one, three and six months of treatment.

Each centre appointed as an independent assessor to obtain follow-up data someone with previous experience with alcoholics: medical practitioners, nurses, or trained research interviewers. They were to stay blind to the medication received. Patients and informants were reminded at each contact not to give any information which could reveal the medication.

The assessor saw patient and informant at intake and again, separately, at weeks 2 and 4, and thereafter monthly until the final interview at six months. Interview questions concerned alcohol consumption, alcohol dependence (the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell *et al*, 1983)) and 13 alcohol-related health and social problems (Chick *et al*, 1988), all with reference to the period since the last visit (or the previous six months for the first and final visits).

'Typical week's consumption' was according to a retrospective diary of a typical week during which the patient drank. In addition, at each interview the assessor obtained an estimate of total consumption in the previous four weeks. These were aggregated in the analysis to give 'total units consumed in past six months'. At intake the assessor had obtained an estimate of the prior six months' consumption, with anchor dates to aid memory. Informants' information was included, and was evaluated by the assessor in making a judgement, because patients are known to report less consumption than informants (Fuller *et al*, 1988).

Statistical analysis

All data were used, on an 'intention-to-treat' basis, irrespective of patient compliance, attempts having been made to follow up all patients. Categorical data were analysed using Fisher's exact test for 2×2 tables and Pearson's χ^2 test for larger tables. Otherwise, the Mack Skilling's test (Mack & Skillings, 1980), taking account of the weighting at different centres, was used to test for significant treatment differences. Laboratory blood data were analysed by fitting an additive linear model of centre and treatment effects and using a t-test to compare treatments (Searle, 1971).

Where possible, differences from pre-treatment were analysed. All tests were two-tailed with a significance level of 5%.

Results

The two groups of patients commencing treatment (64 on disulfiram, 62 on vitamin C) had similar demographic and social backgrounds. The overall mean age was 43 years (range 18–67); 84% were male, 65% were unemployed, and 46% lived with a spouse or other cohabitee. The commonest illness suffered was gastrointestinal disease (21% of patients), of which 85% was alcohol-related. Two-thirds of the disulfiram group and half the vitamin C group had had in-patient treatment for alcoholism. Informants were mainly spouses (41%) or members of the clinic staff (33%).

Fifty-seven patients (28 on disulfiram, 29 on vitamin C) did not adhere to their allocated treatment, 45 through failure to keep appointments or by withdrawing consent. Follow-up interviews were not obtained in 20% (15 disulfiram patients, 14 vitamin C patients). Both initial and final blood samples were available in only 57%, because at follow-up some patients were interviewed by telephone, and at intake and follow-up some samples were not analysable because of delay or damage.

Four patients on disulfiram and one on vitamin C were withdrawn with adverse reactions: two of the former owing to allergic skin rash, one with suspected neuropathy, and one with dizziness and nausea, while the patient on vitamin C was admitted suffering left hemiparesis. A further two withdrawals from the vitamin C group were due to increasing problems with drinking. (Four of the patients on vitamin C who withdrew their consent did so because they wanted to take disulfiram; in addition, three initial recruits had withdrawn as soon as they heard they had been assigned to vitamin C and were thus excluded from the trial population.)

Unusual symptoms were reported equally in the two groups (e.g. depression: 4 disulfiram, 5 vitamin C patients; nausea: 2 disulfiram, 2 vitamin C patients) except for headache (11 disulfiram, 5 vitamin C patients), fatigue (12 disulfiram, 6 vitamin C patients), and skin rash (4 disulfiram patients only). Seven patients on disulfiram had their dose reduced because of side-effects. Disulfiram–alcohol reactions were reported on 29 occasions, but none led to a reduction of dose. Five patients had their disulfiram dose increased because the alcohol reaction was mild or absent, and one such patient refused to have the dose increased. There were no abnormalities of liver function during treatment.

Treatment effects are summarised in Tables 1–4. Both treatment groups achieved a reduction in alcohol consumption which by most estimates was greater with disulfiram, the treatment difference reaching statistical significance for values at 6 months (Table 1). However, at the final assessment the number of days since the last drink and alcohol consumption in the last month of the study revealed no significant treatment difference (Table 3).

The mean (s.d.) SADQ score at intake was similar in the two groups, and fell equally (disulfiram: intake 31.6 (13.8)

Table 1
Effects of trial treatment on estimated alcohol consumption: comparison of changes from intake values (means (s.d.))

Estimated consumption (change from intake)	Patient		Informant		Assessor	
	Disulfiram (*n*)	Vitamin C (*n*)	Disulfiram (*n*)	Vitamin C (*n*)	Disulfiram (*n*)	Vitamin C (*n*)
No. of abstinent days in last six months						
intake	58 (59) (63)	77 (53) (59)	54 (55) (57)	68 (51) (54)	55 (58) (63)	66 (50) (58)
change after treatment	+98 (68) (43)	+54 (79) (47)	+97 (68) (39)	+71 (70) (36)	+100 (70) (47)	+69 (67) (46)
Treatment difference:						
mean (95% confidence interval)	44 (14 to 79)		26 (−4 to 63)		31 (6 to 63)	
P value	0.004**		0.06		0.02*	
Typical consumption: units per week						
intake	207 (137) (63)	190 (153) (58)	214 (154) (52)	172 (160) (49)	224 (141) (63)	208 (166) (59)
change after treatment	−165 (173) (46)	−97 (148) (46)	−186 (158) (42)	−105 (136) (35)	−162 (172) (49)	−105 (147) (48)
Treatment difference:						
mean (95% confidence interval)	−68 (−132 to −5)		−81 (−144 to −10)		− 57 (−108 to 12)	
P value	0.05*		0.04*		0.14	
No. of units consumed in last 6 months						
intake	2573 (2549) (62)	2247 (2514) (57)	2911 (2767) (50)	2198 (2750) (47)	3001 (2735) (62)	2916 (3053) (58)
change after treatment	−2558 (2777) (43)	−856 (2442) (42)	−2807 (2677) (39)	−1171 (1562) (33)	−2572 (2708) (46)	−1448 (1753) (44)
Treatment difference:						
mean (95% confidence interval)	−1702 (−2016 to −290)		−1636 (−2052 to −238)		−1124 (−1620 to −84)	
P value	0.007**		0.011*		0.04*	
No. of units consumed in last 4 weeks						
intake	319 (468) (60)	244 (376) (58)	358 (525) (48)	241 (340) (47)	395 (534) (60)	325 (428) (58)
change after treatment	−246 (455) (40)	−152 (496) (45)	−231 (482) (35)	−158 (306) (33)	−281 (537) (44)	−199 (468) (46)
Treatment difference:						
mean (95% confidence interval)	−94 (−208 to 12)		−73 (−154 to 80)		−82 (−185 to 80)	
P value	0.42		0.74		0.92	
No. of days since last drink						
intake	35 (47) (64)	32 (41) (59)	31 (35) (59)	26 (36) (54)	32 (35) (64)	27 (35) (58)
change after treatment	+75 (92) (48)	+65 (98) (47)	+74 (92) (43)	+67 (91) (38)	+72 (92) (49)	+70 (89) (48)
Treatment difference:						
mean (95% confidence interval)	10 (−23 to 41)		7 (−30 to 45)		2 (−29 to 26)	
P value	0.55		0.72		0.91	

1 unit of alcohol = 8–9 g ethanol.
*$P \leqslant 0.05$, **$P < 0.01$.

Table 2
Blood test markers: comparison of changes from intake after treatment (means (s.d.))

Marker	Disulfiram (*n*)	Vitamin C (*n*)
MCV: (fl)		
intake	96.6 (5.8) (57)	97.8 (5.8) (52)
change after treatment	−3.0 (5.1) (31)	−2.6 (4.5) (33)
Treatment difference: mean		
(95% confidence interval)	−0.4 (−2.8 to 2.1)	
P value	0.78	
Serum GT: IU/l		
intake	49 (63) (55)	51 (72) (57)
change after treatment	−21 (65) (32)	+13 (83) (38)
Treatment difference: mean		
(95% confidence interval)	−34 (−74 to −7)	
P value	0.02	

($n=63$), mean change with treatment −8.3 (15.8) ($n=35$); vitamin C: 33.1 (13.3) ($n=59$), mean change with treatment −10.8 (16.9) ($n=39$)). Mean (s.d.) problem score reduced more in the disulfiram group (intake: 6.30 (2.59) ($n=56$), mean change with treatment −4.00 (3.21) ($n=43$) than in the vitamin C group (intake: 5.96 (2.25) ($n=54$), mean change with treatment −2.91 (3.02) ($n=45$)), but this difference was not significant ($P=0.06$).

Table 4 shows the opinions of the various participants at the end of the trial regarding the ability of the patients to control their drinking, by which was meant reduction or cessation of their excessive drinking and its problems. Patients, informants and clinicians all thought the disulfiram group to have significantly better control (mostly moderate/full) than the patients on vitamin C, half of whom showed no change. In the opinion of the assessors, however, the patients on vitamin C attained a similar improvement in their control of drinking to those treated with disulfiram.

At the end of the trial two-thirds of the patients on disulfiram wanted to continue treatment, compared with only one-quarter of those on vitamin C ($P<0.001$).

At the end of the study the identity of the test treatment was guessed correctly by the independent assessor for 65% of those followed up. This was not measured at any of the earlier assessments.

Table 3
Number of days since last visit on which alcohol was consumed (assessor's opinion) (means (s.d.))

Week	Disulfiram (*n*)	Vitamin C (*n*)
2	0.76 (2.49) (58)	1.64 (3.34) (53)
4	0.76 (3.07) (55)	2.09 (3.78) (47)*
8	1.63 (4.76) (49)	4.36 (8.44) (45)
12	2.47 (5.71) (45)	2.67 (5.14) (43)
16	3.12 (6.76) (40)	2.82 (6.79) (38)
20	1.76 (5.68) (37)	3.65 (7.27) (34)
Total	7.77 (11.40) (35)	17.91 (31.52) (34)

*$P<0.05$.

Table 4
Final opinions of ability to control drinking

Opinion	Degree of control	Frequency		*P* value
		Disulfiram	Vitamin C	
Patient				
	worse	0	3	
	no change	3	20	
	moderate	15	8	<0.001
	full	25	13	
Informant				
	worse	0	2	
	no change	3	18	
	moderate	16	6	<0.001
	full	21	10	
Clinician				
	worse	0	2	
	no change	4	22	
	moderate	18	9	<0.001
	full	21	11	
Assessor				
	worse	2	4	
	no change	5	5	
	moderate	20	22	0.30
	full	25	19	

Discussion

For the ethical reasons already stated each patient's allocated treatment was known to all but the independent assessor. However, a double-blind design might not necessarily reduce the problems of interpretation, because of the tendency shown in a recent double-blind cross-over study of calcium carbimide (Peachey *et al*, 1989) in which 78% of patients thought they were taking active drug at all times. This compromises the chance of showing the deterrent effect of the drug, depending as it does partly on instruction and belief that an alcohol-reaction could occur. The correct test of the drug is a test of the 'package', which includes emphasising the alcohol-reaction to the active group.

Although by the end of the study assessors were guessing the correct medication better than chance, the two measures for which their ratings significantly differed between the groups were scores summated (by computer) of ratings made over the six months, that is, abstinent days and units consumed. In general there was little discrepancy in the six-month summated scores between the results as perceived by patient, informant and assessor, but despite having guessed accurately in some cases the assessors considered those on vitamin C to have achieved the same control of drinking as the disulfiram group. The explanation for this is not clear, but perhaps it slightly reduces the concern that bias influenced the assessors' ratings.

Estimates of alcohol consumption over the six-month trial generally showed significant differences in favour of disulfiram. There was little difference in the final rating of 'number of days since last drink', however, suggesting that some patients were perhaps using disulfiram to practise occasional limited drinking. By the end of the study there was no statistical difference in the last month's consumption, and this, together with the narrowing of the estimate of days since last drink (Table 3), could indicate a waning of the treatment effect.

Rating of alcohol-related problems (violent episodes, time off work, police involvement, etc.) is less open to bias but it takes longer for changes in the frequency of these relatively rare events to become apparent. The patients on disulfiram none the less showed a strong trend towards a greater reduction in total problem score than the vitamin C group, falling just short of statistical significance. SADQ scores in both groups improved somewhat. The SADQ allocates a score for maximum sessional consumption and some patients on disulfiram did have relapses though perhaps less frequently than those on vitamin C. It also allocates points for 'imagining your symptoms if you had a heavy drinking session', and patients in our study, even though abstinent, would score on these items since they still regarded themselves as 'dependent'. The SADQ is perhaps not a good measure of outcome over six months.

Blood test markers of alcohol consumption, particularly the more rapidly affected serum gamma-GT, are not open to bias and it is important that the disulfiram group showed a significantly greater improvement here. Blood tests for both intake and follow-up were available in only 57% of cases but the patient drop-out rate was similar for both treatment groups.

No previous study has used blood tests as markers of outcome, although supervised disulfiram has been studied, with promising results (Heather, 1989). Our own methods of supervision did not use such a strict 'contract' as some of the successful reports in the American literature (Azrin *et al*, 1982; Keane *et al*, 1984; O'Farrell & Bayog, 1986). We also used a lower dose than in some of the American studies. In the study by Fuller *et al* (1986), unsupervised disulfiram (250 mg daily) plus counselling was associated with a reduction in the number of days on which alcohol was consumed, corroborated by relatives or friends. However, this was demonstrated only in the one-third of patients who provided all seven assessment interviews, and could not be seen in the remainder. It may be that supervision is necessary to the success of disulfiram treatment.

Treatment practices varied in the different centres involved, and some centres appeared to have slightly better results than others. Even so, we suspect that our method was something some general practitioners could profitably arrange, with the spouse or practice nurse supervising treatment.

There were no medically serious disulfiram–alcohol reactions, and at the dose used in the study some patients did not experience a reaction after drinking. Concerns about hepatic toxicity were not borne out. Disulfiram can, though, cause allergic skin reactions and it is still to be recommended that patients taking the drug have medical follow-up.

In conclusion, we found that supervised disulfiram plus counselling enhanced treatment outcome in alcoholics. A few patients developed skin rash, headache or tiredness but there was no disturbance of liver function. Disulfiram is a popular form of treatment among some alcoholic patients and their relatives.

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REVIEW ARTICLE

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Safety Issues Concerning the Use of Disulfiram in Treating Alcohol Dependence

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Contents

Abstract

Disulfiram is known to cause hepatitis, which is sometimes fatal. The best estimate of the frequency of disulfiram-induced fatal hepatitis is 1 case in 30 000 patients treated/year. Its appears to be more common in patients given disulfiram for the treatment of nickel sensitivity. Frequent blood testing for liver function is probably not necessary, but patients taking disulfiram should be in regular contact with a physician.

There are rare reports of psychosis and confusional states in conjunction with disulfiram treatment and peripheral neuropathy and optic neuritis have been reported; these effects are dose-related. Psychiatric complications appear to be more common with the use of disulfiram in India than in Western countries. Of the less serious adverse effects, tiredness, headache and sleepiness are the most common.

Deaths from the disulfiram-alcohol (ethanol) interaction have not been reported in recent years, possibly because the dosages used are lower than those used 40 years ago, and patients with cardiac disease are now excluded from

treatment. There is no evidence to suggest that disulfiram causes cancer. Of note, there are drug interactions with compounds that utilise the cytochrome P450 enzyme system.

Disulfiram can be viewed as a drug with a moderate record of adverse effects. Alcohol dependence, for which it can be a helpful treatment, is associated with a high morbidity and mortality.

Alcohol (ethanol) dependence is a potentially fatal disorder, which often does not respond to medical or psychiatric intervention. Randomised controlled trials of disulfiram have shown that, when patients agree to involve a third party to assist their compliance, this deterrent approach can improve the outcome of treatment.[1] Since disulfiram was first prescribed for alcohol dependence in 1947, there have been concerns about its safety, namely the risks of the disulfiram-alcohol reaction and the risk of toxic effects of the compound on the nervous system and on the liver.

1. Search Procedure

The sources used in the following review were literature searches on Medline (publications from 1966; date of search, early 1998) and the Adis International comprehensive inhouse database; certain specific enquiries to the manufacturer; correspondence with the author of 1 paper; and manual searches from 1966 back to 1950 of Quarterly Journal of Studies on Alcohol, British Medical Journal, and the Journal of the American Medical Association. No exclusion criterion based on study methodology was applied: many papers were individual case reports, although weight was given to reports where re-exposure to disulfiram had replicated the adverse effect. Where a finding has been replicated in successive publications only the study or studies where the finding was most robust have been cited, or a relevant review paper.

2. Hepatotoxicity

The world literature of the last 40 years contains 30 reports of patients with hepatitis related to disulfiram. National Drug Adverse event registers would suggest there are also cases not written up and published. At the recommended dosage level, hepatotoxicity has been noted to occur as rapidly as 13 days after commencing the drug, and after a total dose of as low as 4.5g prescribed at 250 mg/day.[2] Sometimes the hepatitis has resolved on stopping the drug, but at other times a fulminant course has ensued. In some reversible cases, the causal relationship has been demonstrated by a challenge e.g. Morris et al.[3], Bartle et al.[4] Although people with alcoholism clearly have a high prevalence of liver disorders related to other causes, many of the cases of disulfiram-related hepatitis have occurred in patients who had normal liver function tests on commencing the medication. Hepatotoxicity has also been described in patients without alcoholism (disulfiram is sometimes prescribed for nickel sensitivity).[5]

2.1 Frequency

Denmark is probably the country in the world where, per capita, the most disulfiram is prescribed.[6] Reports to the Danish Committee on Adverse Drug Reactions from 1978 to 1987 of all drug-induced hepatic injury revealed that 35 (2.9%) of the 1188 reports were linked to disulfiram, as were 5 (10%) of 52 drug-induced hepatitis fatalities.[7]

However, the most important frequency estimate is of the risk per prescription of disulfiram. There is only 1 such published estimate, also from Denmark. Spontaneous reports of adverse drug reactions to disulfiram treatment were examined for the period 1968 to 1991.[8] There were 11 fatal liver reactions reported in 22 years. Using drug sales figures to estimate the number of patients taking disulfiram to be 15 000 per year, the reported risk of dying of hepatotoxicity caused by disulfiram can

be calculated to be 1 : 30 000 patients per year. Some of these were patients receiving disulfiram as treatment for nickel sensitivity, and it appears from 1 uncontrolled study[9] that the risk of liver disorders linked to disulfiram is vastly greater in these patients than in people with alcoholism, hepatitis occurring in 8% of such patients (nickel in the body is mobilised by disulfiram and can be deposited in the liver).

2.2 Timing

In the Danish data,[8] disulfiram-related hepatitis had commenced between 16 and 120 days after starting treatment, with a peak frequency at 60 days. However, in 1 case, a woman who had commenced taking disulfiram in excess of the prescribed dosage (she took 1.5 to 2 g/day) developed jaundice within 5 days.[10]

2.3 Mechanism

When liver function is monitored during disulfiram treatment, abnormalities in liver enzyme levels may occur but can often be attributed to resumption of drinking. There is 1 report which has shown more liver enzyme level elevations in patients taking disulfiram than in patients in the same programme who did not receive the drug (the Tri-Services Alcoholism Recovery Project study).[11] Allocation to disulfiram or no disulfiram was not random in the study. The clinic offered disulfiram 250 mg/day to all patients, but some were excluded for various reasons including any abnormal liver function test. Compliance was monitored. Patients were inpatients throughout the study period and were screened for use of alcohol at random by breath and urine alcohol tests. At 4 weeks into the study, the level of 1 or more transaminase had become elevated in 30% of patients taking disulfiram and in 11% of control patients. The levels of 2 or more transaminases were elevated in 9% of patients taking disulfiram. Two patients taking disulfiram, compared with none of the control individuals, had an elevation of ALT levels greater than 3 times the upper limit of normal, which is the level at which in other drug hypersensitivities the risk of hepatitis is significant.

Two studies where there was random allocation to disulfiram or a placebo have been published that give follow-up liver function test data. Iber et al.[12] followed 453 male patients for 1 year. In both studies abnormalities in liver function tests did not occur more frequently in the disulfiram patients than in control participants.[12,13] In only 1 of these 2 studies[13] was compliance with medication over 6 months ensured by supervision. In that study, liver enzymes levels showed an on average improvement in the disulfiram group but a deterioration (associated with more frequent alcoholic relapse) in the control participants.

Two reports provide long term data on hepatotoxicity from studies that did not include a control group. Borup et al.[14] reported data from 93 patients who had taken disulfiram for 1 year supervised by the clinic at a dosage of 600 to 800mg twice weekly. No patient developed liver function abnormalities. In a series of 43 patients receiving supervised disulfiram treatment in dosages up to 1 g/day (mean 363 mg/day) for a mean of 7.6 months, Brewer[15] reported that all patients who had abnormal liver function tests at the start of treatment showed improvement. Nine patients were taking 500 mg/day or more and in none of these patients was there even a slight elevation of previously normal liver function tests. In a study of 50 male inpatients randomised to receive either placebo, disulfiram 250 mg/day or disulfiram 500 mg/day no differences in liver function tests emerged.[16]

In a 12-week follow-up study of 57 men with alcoholism, some of whom had elevated transaminase levels and serological evidence of hepatitis C virus infection at commencement of disulfiram therapy, 1 patient showed an elevation of transaminase levels attributable to disulfiram, without clinical complications.[17]

It seems from the Tri-Services Project[11] that under some circumstances disulfiram is associated with an increase in liver transaminase levels, but the weight of evidence is that clinical hepatitis is

rare. There is no evidence that a pre-existing liver disorder increases the risk of disulfiram hepatotoxicity.[18] In most of the reported cases of patients with hepatitis the patients had normal liver function tests at the start of treatment. A fatal outcome was more likely when the drug was continued for some days after jaundice had been noticed.[10] Hepatitis may be due to accumulation of toxic metabolites[10] or in some cases due to the expression of autoantibodies directed against specific cytochrome P450 enzymes.[19]

2.4 Monitoring

There have been several attempts in the literature to specify when liver function in blood tests should be checked. In some treatment centres it became routine practice to assess liver function before and at frequent intervals during treatment with disulfiram (e.g. Wright et al.[11]). A recent single case report, where liver function testing at day 16 produced normal results, but jaundice had developed by day 42, led to another call for 2-weekly testing of all patients receiving disulfiram.[20] However, the onset of the hepatitis is usually very rapid, and so even frequent testing may not detect it. In addition, abnormal enzymes levels are commonly caused by a resumption of alcohol ingestion which might lead to unnecessary withdrawal of the drug. Thus, it can be argued that frequent blood test monitoring is unlikely to be productive, especially given the rarity of severe hepatotoxicity.[21]

In my view, informing the patient, the patient's relatives and the family practitioner, of the 1 in 30 000 risk of fatal hepatotoxicity, emphasising detection of jaundice usually preceded by fever, so that the drug is stopped when adverse effects are noticed, is probably an equally efficient way to prevent fatal hepatitis and still allow many patients to benefit from disulfiram treatment.

Brewer and Hardt[22] recommend that patients should be asked about nickel sensitivity before starting treatment with disulfiram and that liver function tests should be measured near the time of starting therapy (not necessarily in advance) and again after about 1 month.

In summary, hepatitis is very rarely a consequence of disulfiram use. Abnormal liver enzymes levels caused by alcohol use need not be a contraindication to the use of disulfiram. Indeed, when the patient is helped to achieve abstinence by taking disulfiram such abnormalities will probably resolve. However, patients should be informed about even very rare risks associated with drug therapy. Medical supervision of patients taking disulfiram should continue for as long as the patient uses it and should be at least monthly for the first 6 months. There is no compelling evidence to support repeated liver function testing as a way of preventing serious hepatotoxicity.

3. CNS Adverse Effects

3.1 Confusional States/Psychosis

There are occasional reports from Europe and North America of disulfiram-linked psychosis or a confusional state (beginning with fatigue and forgetfulness, rarely proceeding to ataxia or stupor). These reports were commoner in the early days of disulfiram therapy when higher dosages than are commonly used today (500 mg/day or more) were routinely prescribed. This potentially serious adverse effect may be more frequent in some countries than others. While only 4% of adverse drug reactions reported for disulfiram in a Danish database were psychiatric,[8] the WHO database when examined by Enghusen Poulsen et al.[8] showed that 13% of disulfiram adverse effects were psychiatric.

Two papers from India, Krishna Murthy and Praveenlal[23] and Krishna Murthy,[24] have described higher rates of disulfiram-induced psychosis arising *de novo* than other papers, with the effect starting 2 to 3 weeks after commencing treatment with disulfiram. Symptoms included overactivity, overtalkativeness, paranoid delusions, insomnia and auditory hallucinations. Symptoms usually completely resolved after withdrawal of disulfiram and sometimes after a short course of treatment with an antipsychotic drug. In 1 series, 6 cases of disulfiram-induced psychosis occurred in 52 pa-

tients,[23] and in the second series there were 5 cases of disulfiram-induced psychosis among 53 patients.[24] In all patients the dosage of disulfiram was 250mg twice daily. Another paper from India[25] described a series of 38 patients of whom 1 developed a confusional state while receiving disulfiram at a dosage of 250 mg/day. The adverse effect resolved and then recurred on each of 2 re-exposures.

The reason for the apparently high rates in India is unknown. One possibility is that the bioavailability of disulfiram manufactured locally may be different from the compound available in Europe and North America. Two cases of psychosis associated with disulfiram have been reported in Caucasian patients; however, the psychosis seemed to result from an interaction between cannabis and disulfiram.[26,27] The Indian papers do not mention concomitant cannabis, which is widely available in that country; however, Krishna Murthy (personal communication) states that cannabis use was not suspected in the patients in his reports.

In a North American series of 243 patients treated with disulfiram 250 mg/day, 5 patients had 'an organic brain syndrome' (which was not well defined in the paper).[28] In patients with alcoholism, psychiatric disturbances can be caused by drinking alcohol and can occur because of co-existing psychiatric disorders. Therefore, only a controlled study can provide a realistic estimate of the prevalence of unwanted psychiatric effects with disulfiram. In a follow-up study of 612 male North American patients randomised for 1 year to either disulfiram 250 mg/day, disulfiram 1 mg/day or placebo, the incidence of psychiatric complications was 2.4% in the disulfiram-treated groups, and the incidence was not significantly different between the groups.[29] No psychotic illness was diagnosed. This was a treatment outcome study, and previous psychotic illness had been an exclusion criterion. Thus, if disulfiram causes psychosis by precipitating a pre-existing illness, this would explain the absence of any psychotic adverse effects in this and in other placebo-controlled studies (e.g. Chick et al.[13]) where no psychiatric complications have been noted.

There has been 1 report of catatonia attributed to disulfiram therapy and this adverse effect is therefore presumably very rare.[30]

In the data sheet for disulfiram, previous psychosis is an exclusion for the use of this agent. However, alcohol misuse in schizophrenia can be very harmful to the patient and, lacking another effective treatment, clinicians weighing up the risks and benefits of treatment have sometimes recommended disulfiram in this context.[31] A wide-reaching review of all aspects of disulfiram use in patients with alcohol dependence and other psychiatric disorders that also looked at potential drug interactions, concluded that the rate of serious unwanted psychiatric effects was extremely low at recommended disulfiram dosages of 200 to 250 mg/day.[32]

The reason for a possibly higher rate of psychosis in India needs further examination.

3.2 Other Serious CNS Syndromes

A case report was published about a man who took disulfiram 250 mg/day for 30 years, and experienced a gradual decline thereafter in memory and performance IQ tests; this decline partially recovered on stopping the drug.[33] Peripheral neuropathy was also noted to have occurred. A positron emission tomography study,[34] which showed reduced cerebral metabolic rate for glucose in patients with alcoholism taking disulfiram compared with those not taking disulfiram, found no differences between the groups with respect to neuropsychological performance. No adjustments were made for differences in severity or duration of patients' heavy drinking in this study.[34] There are no published randomised controlled studies which have compared cognitive performance changes over the course of disulfiram use.

That very large doses of disulfiram might damage the basal ganglia is illustrated in 3 case reports by Laplane et al.[35] In 1 case report, a patient who took an overdose of 75 disulfiram 500mg tablets, developed parkinsonian symptoms and low den-

sity lesions of the basal ganglia, but made a full recovery. The second case was a young man who took disulfiram 1 g/day for 8 weeks, and his parkinsonian symptoms had not completely resolved at 19 months. The third case was a male patient who had taken disulfiram 500 mg/day for 'several months' and poor cognitive performance and apathy were attributed 12 years later by his family to the period of treatment with the drug. It must be emphasised that such reports are very rare.

4. Neuropathy

The earliest onset of neuropathy in a patient taking disulfiram was 10 days.[36] Most reports place the onset of symptoms as several months after commencing treatment and the peak time in the Danish data[8] was 1 year. The rate of disulfiram-induced neuropathy in that study can be estimated from the sales figures quoted for the reporting period of 22 years as about 1 in 15 000 patient years. Except in 1 patient, who was taking disulfiram 250 mg/day for 30 years,[24] the dosage in patients developing peripheral neuropathy has been 500 mg/day or more. Sometimes patients developing neuropathy have been taking other medications. For example, in 1 report the patient took the sedatives ethchlorvynol and triclofos (trichloroethyl phosphate), which are substituted alcohols.[37] Only 2 patients have developed neuropathy at our Edinburgh clinic after 18 years of treating several hundred patients. These 2 patients were also taking amitryptiline and both patients had on their own initiative been taking disulfiram 500 mg/day or more because at a dosage of 200 mg/day the alcohol-disulfiram reaction was insufficient to be a deterrent.

Systematic investigations of nerve function have found delayed nerve conduction without clinical signs of symptoms in patients taking disulfiram 250 mg/day but not at a dosage of 125 mg/day. Abnormalities develop during the first 3 to 6 months and seem not to have onset thereafter (reviewed by Enghusen Poulsen[8] and Dupuy et al.[38]).

The clinical presentation of disulfiram-induced neuropathy is usually a slow onset; however, acute onset over 24 hours has been described.[39] Recovery may be complete or partial, with residual symptoms such as foot drop or paraesthesia.

4.1 Pathology

Carbon disulphide is a metabolite of disulfiram and industrial exposure to this agent has caused neuropathy with axonal degeneration.[37] The pathology, as well as the clinical presentation of disulfiram-induced neuropathy, also resembles that seen in alcohol-induced neuropathy.

Since 1953, some 11 cases of optic neuropathy, apparently always reversible, have been described.[38]

In summary, 50 years of disulfiram use has established that neuropathy is a risk when higher dosages of disulfiram are administered, but this adverse effect is rare and reversible if detected early. Alerting the patient, even to rare risks, is advisable, and medical monitoring of patients is required.

5. Less Serious Adverse Effects

In controlled studies, the adverse effects which occur more frequently in disulfiram recipients than in control patients are tiredness, headache and sleepiness. Some patients' spouses report an unpleasant odour on the patient's breath. This is sometimes described as a garlic smell. However, in my experience usually the spouses state that they prefer to have a partner who is abstinent and has garlic-smelling breath than one who is drinking and has stale alcohol on the breath.

Skin complaints with disulfiram are rare. However, rashes, pruritus and exfoliative dermatitis have all been described in association with disulfiram. Although these skin complaints have been described as occurring after 1 year of treatment they tend to occur in the first 2 weeks of treatment. Early rashes sometimes clear without the need for treatment or discontinuation of disulfiram; displacement of nickel could perhaps explain the occurrence of skin complaints in some cases (discussed by Enghusen Poulsen et al.[8]).

6. The Disulfiram-Alcohol Interaction

Many patients taking disulfiram 200 to 250 mg/day risk experiencing the disulfiram-alcohol interaction by deliberately ingesting some alcohol. The severity of the reaction at these dosages varies from a slight flush to a distressing state of nausea, headache, dizziness and tightness in the chest. Very rarely, when larger amounts of disulfiram have been taken, the reaction has been fatal. These fatal cases, which only appear in the literature in the first 10 years following disulfiram's introduction, were examined in detail at the time. The patient described in the report by Becker and Sugarman[40] had been given 5g of disulfiram over 4 days and was then given 1oz of whisky (i.e. about 15g of alcohol). He experienced a hypotensive collapse, followed by 4 hours' recovery with some treatment. The patient then died suddenly of acute right heart failure. His coronary arteries showed some atherosclerosis but he had had a prior normal electrocardiogram (ECG) and exercise test. One of the cases investigated by Jacobsen[41] died some hours after the reaction had apparently been at its worst. In the days when patients were given a 'test' reaction, ECG studies showed that most patients developed some ECG changes during the reaction, usually prolongation of the QT interval. Hypotension is clearly a dangerous aspect of the disulfiram-alcohol reaction. However, hypertension has been described in a patient who also developed bronchospasm (he took 300ml of 4.1% lager after 6 days treatment with disulfiram 200 mg/day).[42]

The hypotension associated with the disulfiram-alcohol reaction is greater in older patients,[43] perhaps because the elderly have less cardiovascular tolerance to the toxic reaction. The hypotensive reaction is related to the level of acetaldehyde found in the blood during the reaction. It might be supposed that when liver function is poor, less acetaldehyde might be produced and therefore the disulfiram-alcohol reaction might be less in patients with liver disease. However, in a detailed study in 13 patients, variations in liver function did not help to explain the marked variations found in the severity of the disulfiram-alcohol reaction.[43]

There have been no reports of death due to the disulfiram-alcohol interaction in recent years.[44] This may be due to less reporting, but is perhaps more likely to be due to more cautious dosage and patient selection than in the early years of use.

Because of the potentially fatal outcome of a disulfiram-alcohol reaction in a patient with heart disease or a patient taking hypotensive medication, disulfiram should normally not be offered to such patients. This restriction would apply absolutely in a patient with heart disease who was still in the chaotic stage of alcohol dependence where there is mood disturbance and a risk that the patient might consume alcohol while taking disulfiram.

7. Intentional Overdosage

Patients with alcoholism are at high risk of drug overdose. Disulfiram overdose with or without the ingestion of alcohol has occurred on numerous occasions. Serious results seem to be very rare. A case of acute fulminant polyneuropathy following simultaneous ingestion of alcohol and a high dose of disulfiram has been described in by Rothrock et al.[45] and a case of basal ganglia damage has already been mentioned in section 3.2.[35]

Disulfiram should not be given to a suicidal patient. Despite this caveat, there are patients with alcoholism who take medication overdoses when they are intoxicated and in practice the use of disulfiram can significantly help patients not to drink and thereby reduces or stops this behaviour which is costly to the patient and to health service resources.

8. Drug Interactions

Drugs utilising the cytochrome P450 enzyme system in their oxidative breakdown will show augmented plasma concentrations and longer elimination half-lives if the patient is taking disulfiram. This has been demonstrated for amitryptiline, imipramine, warfarin and phenytoin and will apply to other agents such as, for example, benzodiazepines such as chlordiazepoxide and diazepam, though not lorazepam and oxazepam.[46] A case of delirium with concomitant administration

of phenytoin and disulfiram has been described.[47] An interaction with omeprazole has been reported that resulted in confusion with catatonia, and this was effect was reproduced at a second supervised re-exposure to the two drugs.[48]

Regarding a possible interaction with paracetamol (acetaminophen), a review of 2 studies in rats and 1 in humans suggest that there is no hazardous reaction.[8] Paracetamol overdose is especially poisonous in overdose in patients with alcoholism and theoretically disulfiram might reduce its toxic effect on the liver.

9. Cancer

A long-term, Swedish follow-up study found that 14 out of 24 individuals who had died of neoplasm (mainly lung) had received disulfiram treatment, while among the other 142 deaths only 47 had received disulfiram.[49] This association with lung cancer was almost certainly spurious: the patients with more severe alcoholism in that sample had received disulfiram, and I believe would also have been the heavier smokers. An earlier Canadian mortality study found lung cancer deaths to be lower in those treated with disulfiram.[50] There is therefore no evidence that disulfiram causes cancer.

10. Overall Conclusions

Alcohol dependence is associated with high rates of minor symptoms, numerous serious pathologies and an age-related mortality risk 3 times that of the general population. It is to be expected that a drug used in the treatment of alcoholism might become a suspect cause of some of the adverse consequences of alcoholism, and careful disentangling of causal and noncausal association is needed, as for example in the case of cancer and disulfiram. However, disulfiram can cause fatal hepatitis, albeit very rarely, and can cause neuropsychiatric and skin complications. Taken together, these amount to a frequency of 1 case per 200 to 2000 patients per year.[8] Serious hepatotoxicity and neuropathy probably occur at less than 1 case per 10 000 patients per year. This does not place disulfiram among the high risk category for adverse drug reactions.

There is no unanimity among authors or manufacturers on what monitoring should be in place for early detection of the adverse effects of disulfiram. It has been recommended that greater vigilance is needed in female than male patients[38] and the probable dose relationship for neurological adverse drug reactions should dictate greater vigilance whenever the dosage exceeds 250 mg/day. Clearly, all patients taking disulfiram should seen regularly by a physician at a minimum time interval of every 2 weeks for the first 2 months and monthly thereafter. Patients should be advised that there are some serious rare adverse effects associated with disulfiram treatment and to report any unexplained symptoms immediately. They can also be told that disulfiram can be a very helpful aid in recovery from alcoholism.

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A breath test to assess compliance with disulfiram

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ABSTRACT

Aims To evaluate the ability of a hand-held breath analyser, the Zenalyser® (Zenics Medical), to identify alcohol-dependent patients receiving disulfiram therapy and to assess the sensitivity and specificity of the instrument at different time intervals post-disulfiram dosing. **Design** Breath samples were taken from two groups of alcohol-dependent patients, one group on a daily disulfiram regimen and one group receiving no disulfiram. The breath samples were analysed for the combined concentration of carbon disulphide and acetone produced from the metabolism of disulfiram. From these data, two reference ranges were prepared and used for sensitivity and specificity assessments. **Setting** Breath samples for the reference ranges were obtained from patients at Shelton Hospital, Shrewsbury. Breath samples used to assess the sensitivity and specificity of the instrument were obtained from patients at the Edinburgh Alcohol Problems Clinic. **Participants** Twenty in-patients from Shelton Hospital receiving a daily 200 mg disulfiram regimen and 20 in-patients receiving no disulfiram. At the Edinburgh Clinic, 54 patients taking a thrice-weekly disulfiram regimen and 22 patients not on disulfiram. **Measurements** A total of 489 breath samples from Shelton Hospital and 391 breath samples from the Edinburgh Clinic were analysed for the combined concentrations of carbon disulphide and acetone. **Findings** The breath analyser produced results that distinguished between the disulfiram-treated and untreated groups ($P < 0.001$). At 1 day post-dose, the sensitivity was 100% and the specificity was 100%. At 2 and 3 days post-dose, the sensitivities and specificities were 84.6% and 100% and 88.2% and 100%, respectively. **Conclusion** The breath analyser can improve the assessment of the compliance status of patients receiving a daily dose regimen of disulfiram, but is less useful for this purpose if disulfiram is taken on a thrice-weekly regimen.

Keywords Antabuse, breath test, compliance, disulfiram, Zenalyser®.

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INTRODUCTION

Disulfiram has been used as a treatment for alcohol dependence for more than 50 years [1]. The action of disulfiram is mediated through the production of a metabolite, S-methyl N,N-diethyldithiocarbamate sulphoxide [2,3], which inhibits aldehyde dehydrogenase activity. The rapid increase in blood levels of acetaldehyde produced if alcohol is consumed causes unpleasant systemic reactions, the severity of which are related to the dose of disulfiram [4].

In addition to its role as a deterrent [5], disulfiram is now recognized to have other benefits. There are suggestions in trials that it may be effective as an adjunct to the anti-craving medication acamprosate [6,7]. It is thought to have anti-craving properties of its own [8]. In randomized, open trials in alcohol-dependent men who have family support, it has been found to be superior to both naltrexone and acamprosate in preventing relapse [9,10]. Disulfiram has also emerged as a promising treatment for cocaine addiction [11–13]. These studies found that the benefits of disulfiram combined with cognitive behavioural treatment were most pronounced for patients who were not alcohol-dependent. The conclusion was that disulfiram, together with cognitive behavioural therapy, was an effective treatment for the general population of cocaine-dependent patients, disulfiram apparently exerting its effect directly on cocaine use rather than through reducing concurrent alcohol consumption.

A problem associated with disulfiram therapy in all its applications is the patients' compliance [14,15]. Using riboflavin labelling of tablets and urine testing, a US study found that only 20% of patients treated with disulfiram were fully compliant [16]. A similar picture emerged in a Danish study [17]. However, controlled research has shown that when disulfiram is supervised it is an effective treatment for alcohol-dependent patients [18–21].

There is no reliable method in routine use to assess compliance in patients who are unsupervised. In an attempt to address this a non-invasive breath test has been devised, the accuracy of which is tested in the following study.

MATERIALS AND METHODS

Study 1

Forty patients attending the Drug and Alcohol Unit at Shelton Hospital, Shrewsbury, who had previously been diagnosed as alcohol-dependent and who had given informed consent, were asked to blow into a breath analyser fitted with a disposable mouthpiece. Twenty in-patients were treated with the following supervised disulfiram regimen—loading dose, day 1, 800 mg; day 2, 600 mg; day 3, 400 mg; followed by daily maintenance doses of 200 mg. The time elapse between administration of disulfiram and the taking of breath samples ranged from approximately 1 hour and thereafter at intervals throughout the morning, afternoon and evening up to 16 hours post-dose. Multiple breath samples were obtained from a further 20 alcohol-dependent patients who were not receiving disulfiram treatment. The age, gender, ethnic origin, body mass index and smoker/non-smoker details were recorded for each patient.

A total of 489 breath test results were used in this study. A mean breath result was calculated for each patient. Comparison between groups was made using generalized linear models (GLM) with robust standard errors to allow for clustering.

Breath samples were obtained and analysed by the hand-held breath analyser for the combined concentration of carbon disulphide, a known metabolite of disulfiram [22], and acetone, which is known to increase significantly in patients treated with disulfiram [23].

The method of analysis used to determine the combined carbon disulphide and acetone concentrations in the breath was photoionization detection. The concentrations in breath of carbon disulphide and acetone rise and fall rapidly after each dose. For example, carbon disulphide reaches peak plasma concentrations 5–6 hours after dosing and has a breath elimination half-life of 13.3 hours [24].

The results of the 489 breath tests provided the data from which two reference ranges were established, one for patients known to be on a daily dose of 200 mg of disulfiram and one for patients not on disulfiram treatment. These ranges are suggested as a guide for the expected test results for patients who are compliant with maintenance daily disulfiram treatment. Their sensitivity and specificity were tested in Study 2.

In order to compare the method of photoionization used in the breath analyser with a long-established method, namely gas chromatography mass spectroscopy (GCMS), it was decided to conduct a small study to see if there was a statistically acceptable comparison between the two analytical systems. Twenty samples of breath, taken using the BioVOC™ sampler [25], were obtained from a separate group of 11 supervised alcohol-dependent patients on a daily maintenance dose of 200 mg of disulfiram and from six alcohol-dependent patients not on disulfiram. All patients attended the Shelton Clinic. These breath samples were sent to the Health and Safety Laboratory, a World Health Organization collaborating centre, for independent analysis by GCMS. A generalized linear model (with robust standard errors) was used to assess the difference between those who had had their breath analysed by photoionization (population 1) and those who had had their breath analysed by GCMS (population 2).

Study 2

Seventy-six patients attending the Alcohol Problems Clinic in Edinburgh who had given informed consent were asked to provide breath samples. Fifty-four patients were receiving a supervised disulfiram regimen (meaning that the drug was taken dispersed in 50 ml of water under the view of a nurse) consisting of: Monday, 400 mg; Wednesday, 400 mg; Friday, 600 mg; the remainder, 22, were not receiving disulfiram therapy. Patients were to be in 'steady state', having either received their loading dose or to have been on the supervised regimen and taking disulfiram for at least the previous week.

Breath samples were taken from groups of these patients at post-dose intervals of 72 hours (day 3), 48 hours (day 2) and 24 hours (day 1). The two gases, carbon disulphide and acetone, produced in breath as a result of disulfiram therapy, rise and fall rapidly after each dose. The prolonged time intervals of 3 and 2 days post-dose therefore presented the opportunity to test the breath analyser to the limits of detectable disulfiram breath metabolites.

The investigator conducting the breath-testing procedures in Edinburgh did not know which patients were on disulfiram treatment and which were not. Breath test results were recorded for each coded patient and data were sent to Shelton Hospital where, on the basis of the

breath test results alone, the Edinburgh patients were categorized as either on disulfiram treatment or not on disulfiram treatment. The reports were then returned to the Edinburgh clinic for comparison with the known disulfiram status of each patient to calculate the sensitivity and specificity of the breath analyser for the 3-day, 2-day and 1-day time intervals.

RESULTS

Study 1

Figure 1 shows that in 489 breath tests obtained from alcohol-dependent patients, combined carbon disulphide/acetone breath concentrations were significantly higher in the 20 patients who were on a 200-mg daily maintenance dose of disulfiram than the 20 who were not receiving disulfiram treatment.

The reference range for patients on disulfiram treatment was 374–518 nmol/l, with a mean value of 446 nmol/l. The reference range for patients not on disulfiram treatment was 27–40 nmol/l, with a mean value of 33 nmol/l. Those who were on disulfiram had a breath test result 358 nmol/l higher for every nmol/l for those not on disulfiram [$P < 0.001$, 95% confidence interval (CI) 284–351 nmol/l].

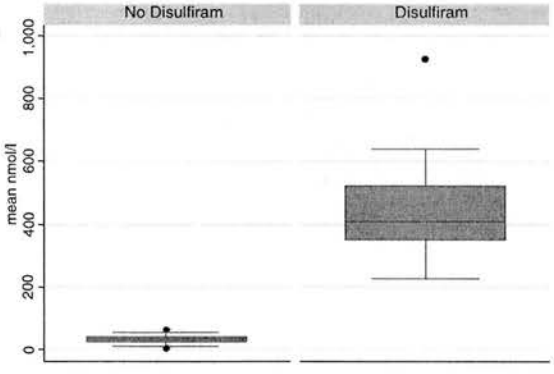

Figure 1 Box-plot showing medians, quartiles and range of breath concentrations (nmol/l), analysed by photoionization, in alcohol-dependent patients receiving no disulfiram ($n = 20$) versus patients receiving a 200-mg daily dose of disulfiram ($n = 20$) at Shelton Hospital

Table 1 Patient groups used to compare data from photoionization and GCMS analyses.

	No disulfiram (n)	*Disulfiram (n)*	*Total (n)*
Photoionization	20	20	40
GCMS	6	11	17
Total	26	31	57

Table 1 summarizes the separate patient groups used to compare data from the two analytical methods, photoionization and GCMS.

Results of the breath samples that were analysed for carbon disulphide and acetone are given in Table 2 and the data compared in box-plots in Fig. 2. There was no significant difference between the methods ($P = 0.47$).

Study 2

Breath sample data taken from patients attending the Alcohol Problems Clinic in Edinburgh are given in Tables 3 and 4.

A total of 13 patients should have been excluded from the study, according to the protocol, for the following reasons: three patients were known to the investigator who was therefore no longer 'blind', three patients had only just completed their loading doses and were not yet on maintenance treatment and seven patients had not complied with their prescribed disulfiram dose regimen during the previous week, so were not at a steady-state. The main analysis has excluded the data for these patients

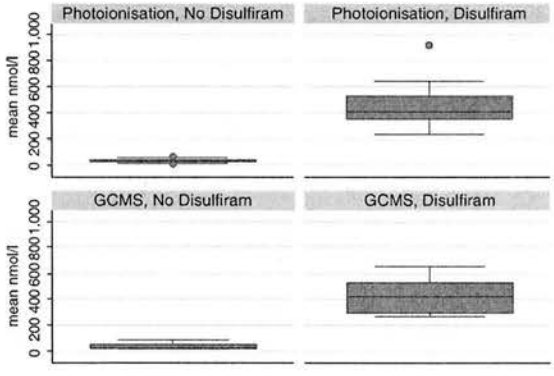

Figure 2 Box-plots comparing photoionization and GCMS data showing medians, quartiles and range of breath concentrations (nmol/l) in alcohol-dependent patients receiving no disulfiram and patients receiving 200 mg daily doses of disulfiram at Shelton Hospital

Table 2 Mean results of breath samples from patients on a 200-mg daily disulfiram regimen comparing photoionization detection ($n = 20$) versus gas chromatography mass spectroscopy ($n = 11$) to measure combined concentrations of carbon disulphide and acetone ($P = 0.47$).

Method of analysis	*Mean nmol/l*	*Lowerlimit (based on 95% CI) nmol/l*	*Upper limit (based on 95% CI) nmol/l*
Photoionization detection	446	374	518
Gas chromatography/ mass spectroscopy	431	344	519

Table 3 Sensitivity and specificity of the breath analyser instrument at different time intervals post-disulfiram dose (all patient analysis). One day post-dose is the intended operating condition of the instrument.

No. of days post-dose	*No. tested*	*Sensitivity (%)*	*Specificity (%)*
3	22d 17c	88.0	100
2	20d 2c	80.0	100
1	12d 3c	100	100

d = patients on disulfiram; c = controls; patients not on disulfiram.

Table 4 Sensitivity and specificity of the breath analyser instrument at different time intervals post-disulfiram dose (per protocol analysis).

No. of days post-dose	*No. tested*	*Sensitivity (%)*	*Specificity (%)*
3	15d 17c	88.2	100
2	11d 2c	84.6	100
1	12d 3c	100	100

d = patients on disulfiram; c = controls; patients not on disulfiram.

('per protocol' analysis). However, all patients were included in the 'all patient' analysis shown in Table 3.

The mean breath test result of the Edinburgh patients on thrice-weekly disulfiram doses were significantly lower, 121 nmol/l, compared to those of the Shelton patients, 446 nmol/l, on daily disulfiram doses. This was a reflection of the different steady-state levels between the two different regimens employed. The known half-life periods of disulfiram and its metabolites [24] would predict this observation. Consequently, Edinburgh patient results that were above the Shelton Clinic 'no disulfiram' reference range of 40 nmol/l (Fig. 1) were scored as positive for disulfiram. This method of assessment produced no false positives (specificity of 100% for 3-day, 2-day and 1-day intervals). However, there were two false negatives at the 3-day and 2-day intervals (sensitivities 88.2% and 84.6%, respectively, for the per protocol sample). Sensitivity at an interval of 1 day was 100%.

DISCUSSION

The results of the first part of this study indicate that the breath analyser is able to distinguish unequivocally between patients who are compliant with a daily regimen of 200 mg of disulfiram from those alcohol-dependent patients who are not on disulfiram therapy. This result was replicated in Study 2 for the 1-day interval. (The exclusion of patients who were found not to meet protocol definitions did not affect the results materially; in particular, the sensitivity and specificity at 1-day intervals remained at 100%; see Table 3.)

The urine riboflavin test, that has been used as a method to assess compliance with disulfiram, has been reported to have a sensitivity and specificity of 86% and 82%, respectively, when the test was performed by medical personnel and 82% and 94%, respectively, when performed by paramedical personnel [26]. A further study using a urinary riboflavin tracer found the inter-rater reliability of the test to range from 73% to 95% (mean = 88%) agreement between two judges [27]. The breath analyser is more sensitive and more specific than the riboflavin test; it produces results more rapidly and is more hygienic than the urinary riboflavin test procedure.

In Study 2 (Table 4), two false negatives were identified after a time interval of 3 days post-disulfiram and two false negatives after 2 days post-disulfiram. It is possible that there were no measurable metabolites present in the patients' breath after the elapse of these time periods, particularly on consideration that the breath elimination half-life of carbon disulphide is only 13.3 hours [24]. Alternatively or additionally the individuals may have been fast metabolizers. The latter possibility is supported by the observation that there is a wide inter-individual variation of plasma levels of disulfiram and its metabolites [28].

There were no false positive results. At 1 day post-dose the sensitivity was 100% and the specificity was 100%. One day post-dose is the intended operating condition of the breath analyser and, because of the rapid decline in detectable breath metabolites, patients on a daily dose regimen who miss one or more daily doses might produce results that indicate non-compliance with a prescribed daily 200-mg dose regimen.

It is important not only to be able to assess the patient who is non-compliant objectively but also, and far more importantly, to have a breath test that identifies the genuinely compliant patient who is at last able to demonstrate and confirm to the clinician that they are indeed adhering to their prescribed therapy. This provides helpful and important information to the clinician and also provides the patient with the opportunity to have their compliance verified.

The breath test is expected to improve compliance because patients on prescribed disulfiram therapy would have no excuse for not recording a positive breath test. Patients who realize that they are to be tested are expected to show a more positive attitude towards adherence to disulfiram therapy.

The breath test can be administered at the discretion of the clinician. The test can be performed at a convenient venue for the patient: for example, at the clinic, the local pharmacy, the work-place or at home. The test interval could be chosen by the clinician with a telephone call or e-mail message to the patient for testing on a chosen date. Once informed of this random monitoring strategy, it would be difficult for the patient to modify the dose regimen.

The breath analyser approach to compliance monitoring has potential applications, particularly in the vital role of objectively assessing alcohol-dependent individuals at risk with their jobs. There are opportunities to monitor expensively trained people who, by the nature of their addiction, could jeopardize the lives of others if they are not abstinent from alcohol.

For example, individuals from backgrounds such as medicine, transport and the armed forces whose non-compliance and subsequent alcohol consumption could prove hazardous to others, notwithstanding the expensive costs incurred during the periods when they are excluded from their professional work because drinking is still suspected. The breath analyser incorporates an electronic data-logging device that enables daily, weekly or monthly sets of data to be recorded and downloaded by the clinician for computer review. Expensively trained individuals who need to be monitored on a daily basis over long-term periods could be provided with the instrument for self-testing over the required time. These data could be monitored daily and as long as compliance levels were maintained, the expensively trained individual could be engaged in full employment.

A further application of objective disulfiram compliance monitoring could be made in keeping offenders convicted of alcohol-related crimes out of prison. Supervised disulfiram has already been recommended as an effective option in this respect [29,30]. Disulfiram treatment, as an alternative to serving a custodial sentence, could potentially reduce the serious problem of overcrowding in prisons and bring about major cost-savings for the prison service. Similarly, courts require high quality information in child-care cases when making decisions about returning a child to the care of a parent with alcohol dependence. The breath analyser provides information that can assist clinicians in monitoring high-risk situations. Because it increases the degree of certainty regarding a patient's compliance with treatment, any serious restrictions (for example, loss of employment or removal of a child from a parent) can be considered with more confidence.

The ability of the instrument to identify rapidly those patients on and those not on disulfiram therapy coupled with an analytical performance comparable to an established GCMS method suggests that this non-invasive monitoring system would provide an important and useful tool in the management of alcohol dependent patients. It has yet to be established whether a patient could test positive (i.e. compliant) on the basis of taking one large dose, on the day of testing or the day before, and deceive the tester. A further study will examine this. The effect of introducing the breath analyser to monitor compliance could be made by comparing standard supervised and daily unsupervised disulfiram, and this will be a useful subject for a further study.

The true potential of objectively monitoring disulfiram treatment with confidence may now bring about opportunities that have not been possible since the introduction of disulfiram more than 50 years ago.

CONCLUSION

The hand-held breath analyser can, within 10 seconds, distinguish between patients who are compliant with a daily maintenance dose of disulfiram and those who, for whatever reason, are not compliant. It may enable the more effective use of disulfiram in those patients so treated.

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Declaration of interest

Sales of Zenalyser® produce royalties shared between the University Hospital of North Staffordshire, Zenics Medical, Richard Martin Faulder and George Charles Faulder.

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A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF NALTREXONE IN THE TREATMENT OF ALCOHOL DEPENDENCE OR ABUSE

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Abstract — The opioid antagonist, naltrexone, is reported, in single centre studies, to improve the clinical outcome of individuals with alcohol dependence participating in outpatient psychosocial programmes. This is the first multicentre controlled study to evaluate the efficacy and safety of naltrexone as adjunctive treatment for alcohol dependence or abuse. Patients who met criteria for alcohol dependence ($n = 169$) or alcohol abuse ($n = 6$) were randomly assigned to receive double-blind oral naltrexone 50 mg daily ($n = 90$) or placebo ($n = 85$) for 12 weeks as an adjunct to psychosocial treatment. The primary efficacy variable was time to first episode of heavy drinking; secondary efficacy assessments included time to first drink, alcohol consumption, craving, and changes in the serum biological markers gamma-glutamyl transferase (GGT), and aspartate and alanine aminotransferases. Compliance was assessed by tablet counts and, in the naltrexone-treated group, by measurement of urinary concentrations of 6-β-naltrexol. Forty-nine (58%) patients randomized to placebo and 53 (59%) randomized to naltrexone did not complete the study. In intention-to-treat analyses, there was no difference between groups on measures of drinking. The median reduction from baseline of serum GGT ($P < 0.05$) and the reductions in alcohol craving (Obsessive and Compulsive Drinking Scale: OCDS) were greater in the naltrexone group ($P < 0.05$), from approximately half-way through the study. Of 70 patients (35 placebo; 35 naltrexone) who met an *a priori* definition of compliance (80% tablet consumption, attendance at all follow-up appointments), those allocated to naltrexone reported consuming half the amount of alcohol ($P < 0.05$), had greater median reduction in serum GGT activity ($P < 0.05$), and greater reduction in alcohol craving (OCDS total score: $P < 0.05$; Obsessive subscale score: $P < 0.05$), compared to patients in the placebo group. Use of naltrexone raised no safety concerns. Naltrexone is effective in treating alcohol dependence/abuse in conjunction with psychosocial therapy, in patients who comply with treatment.

INTRODUCTION

Psychosocial treatment programmes for alcoholism have only limited success and pharmacotherapy may help to prevent early relapse. Preclinical and clinical findings support the hypothesis that alcohol stimulates endorphin activity and reduces deficiencies in endogenous opioid transmission [reviewed by Froehlich and Li (1993) and Volpicelli *et al.* (1995*a*)].

The orally administered opioid antagonist, naltrexone, was shown in randomized, double-blind, placebo-controlled clinical trials to reduce the relapse rate of individuals with alcohol dependence participating in outpatient psychosocial programmes (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992) with moderate effect sizes of 0.42 and 0.60 respectively (Volpicelli *et al.*, 1995*c*). Further studies have replicated this (Volpicelli *et al.*, 1997; Anton *et al.*, 1999). Another opioid antagonist, nalmefene, appears to have a similar action in the treatment of alcohol dependence (Mason *et al.*, 1994, 1999).

This paper reports the first multicentre study, and the largest study to date, of naltrexone's efficacy and safety in alcohol dependence and abuse and differs from previous studies in offering generally less intensive psychosocial support, which varied between centres, thus perhaps better reflecting routine clinical practice.

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PATIENTS AND METHODS

The study was conducted over a 13-month period at six sites in the UK, which were five alcohol treatment units and one academic department of hepatology with a special interest in alcohol-related illness.

Patient selection

Men and women, aged 18–65 years, who met DSM-III-R (American Psychiatric Association, 1987) criteria for alcohol dependence or alcohol abuse were eligible for the study. Patients had to be abstinent from alcohol for 5–30 days before entry into the study and enrolled in, or about to enter, an outpatient alcohol rehabilitation treatment programme or routine out-patient follow-up. Patients were excluded if they had psychiatric conditions requiring medication, polysubstance abuse, serum aspartate (AST) or alanine aminotransferase (ALT) activities greater than three times the upper reference range, a total serum bilirubin concentration greater than twice the upper reference range, or significant physical illnesses such as, for example, ischaemic heart disease, chronic obstructive airways disease or insulin-dependent diabetes mellitus. Patients using opioids in any form, other opioid antagonists, disulfiram, acamprosate, lithium salts, antidepressants, antipsychotics or benzodiazepines except as a bedtime hypnotic, were also excluded. All patients provided written informed consent. The study was conducted in accordance with world-wide standards for Good Clinical Practice (GCPs) and conformed to acceptable ethical standards as outlined by local requirements and the Declaration of Helsinki.

Randomization and treatment

Patients with alcohol dependence or abuse were randomized to receive either naltrexone 50 mg or a placebo preparation, identical in appearance, once daily for up to 12 weeks in addition to psychosocial treatment. Randomization was stratified according to diagnosis based on DSM-III-R criteria (alcohol dependence or alcohol abuse) with equal assignment of placebo and naltrexone in each stratum. Each study centre entered the trial patients into its usual psychosocial treatment programme; the type and amount of treatment provided was not subject to protocol constraints. Patients were free to attend alternative facilities, such as Alcoholics Anonymous or other support groups. At the point of giving consent, patients were informed that naltrexone had been shown in previous studies in alcoholism treatment centres to reduce craving for alcohol and alcohol consumption. After screening and enrolment visits, patients returned for study visits every 2 weeks during the 12-week treatment period.

Assessments

The primary goal of each patient's treatment was to support abstinence from alcohol and to reduce the likelihood of relapse to heavy drinking. The primary efficacy variable was the time to first episode of heavy drinking, as assessed by the Time-Line Follow-Back (TLFB) method (Sobell and Sobell, 1992). An episode of heavy drinking was defined as five drinks on a single occasion for men and four drinks for women. (One 'drink' is defined as that amount of beverage containing 13 g ethanol, corresponding to the USA tradition, which was used in this study to permit comparison with the previous naltrexone trials, rather than the UK unit system where 1 'unit' is that amount containing 8 g ethanol.) This was chosen as the primary efficacy variable, first, because it has clinical meaning, in that it is heavy drinking which causes problems, and, second, because it was the outcome variable used in the two previous studies (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992). Secondary effectiveness measures included time to first drink, overall alcohol consumption, number of abstinent days, craving as measured by the Obsessive–Compulsive Drinking Scale (OCDS; Anton *et al.*, 1995, 1996), a physician rating of global severity ('need for treatment') from an abbreviated version of the Addiction Severity Index (aASI; McLellan *et al.*, 1991), and changes in serum gamma-glutamyl transferase (GGT), ALT and AST (Rosalki and Rau, 1972; Chick *et al.*, 1981; Salaspuro, 1986). Urine was collected at each visit. Safety was assessed by observed or volunteered adverse clinical events (ACE) and laboratory test results. All clinical laboratory determinations were performed by a central laboratory. (The markers carbohydrate-deficient transferrin and mean red corpuscular volume were not used.) The above measurements were made at baseline and repeated at 2, 4, 6, 8, 10 and 12 weeks.

Compliance with medication was assessed by counting returned tablets. For the naltrexone group, compliance was also assessed by identification of the presence in urine of 6-β-naltrexol, a metabolite of naltrexone with a half-life of 14–18 h (Cone *et al.*, 1974). Urinary 6-β-naltrexol concentration of 1 μg/ml was set as the limit for detecting those who actually took their dose during the preceding 24 h (Pieniaszek *et al.*, 1996). No comparable biological marker of placebo compliance was used.

Statistical analysis

Based on the assumption that 50% of patients treated with placebo relapse to heavy drinking, compared to 25% of patients treated with naltrexone during a 12-week period, 75 patients per treatment arm were needed to obtain 80% power when testing at the 5% significance level. All statistical analyses were performed using the Statistical Analysis System package, version 6.08 (SAS Institute, Cary, NC, USA). A result was deemed statistically significant when the statistical test yielded a two-tailed probability (*P*-value) of ≤ 0.05. Baseline was defined as the last observation obtained prior to initiation of study medication. Endpoint was defined as the last observation available during the 12-week treatment period for each patient.

Survival analysis methods (Kaplan–Meier estimates and log-rank test) were used to analyse the time-to-event variables. For continuous variables, differences in means between groups were tested using an analysis of variance model (ANOVA). Changes from baseline were tested within each treatment group using a paired *t*-test. Biochemical test results were not normally distributed, so median changes from baseline were compared between treatment groups using the Kruskal–Wallis test. Discrete variables were compared between treatments using χ^2-test or Fisher's exact test. Adverse clinical events were classified and summarized according to World Health Organization Adverse Reaction Terms (WHOART; WHO, 1992)

Initial analyses were carried out on an intention-to-treat basis, including all patients who received at least one dose of study medication. Drop-outs were assigned to the heavy-drinking category. The analysis plans detailed in the study protocol identified *a priori* that compliance with study medication would be used to identify subgroups of patients for further analyses. For these analyses, a patient was considered compliant if at least 80% of the scheduled medication was consumed, as documented on the basis of tablet counts, and all appointments had been attended.

RESULTS

Of the 175 patients entering the trial, 85 were randomized to receive placebo and 90 to receive naltrexone (Fig. 1). No significant differences between the naltrexone and placebo groups were observed for any baseline variable (Table 1). Overall, patients tended to lack social support: only 40% were married or in a permanent relationship, 26% lived alone and only 27% were in full-time employment. During the week prior to study entry, the mean attendance at an intervention session or a 12-step meeting was 3.1 (±5.5) times for the naltrexone group and 2.4 (±3.2) times for the placebo group.

Forty-nine (58%) patients randomized to placebo (P) and 53 (59%) randomized to naltrexone (ntx) discontinued the study before the end of the 12-week treatment period because of: adverse clinical events (P 11, ntx 13), protocol violations including starting other medicines (P 12, ntx 18), withdrawal of consent (P 9, ntx 3), poor compliance (P 1, ntx 2) and loss to follow-up (P 16, ntx 17).

Of the 73 patients (P 36, ntx 37) who completed the study, 70 (P 35, ntx 35) attended all follow-up appointments and showed 80% compliance based on tablet counts. In this completed and compliant subgroup, patients randomized

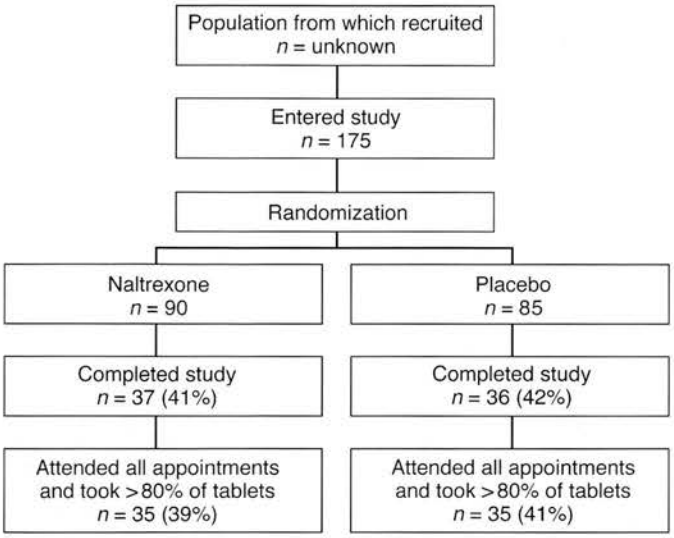

Fig. 1. Recruitment, randomization and retention in study.

to naltrexone or placebo were still matched with respect to demographic and baseline characteristics (Table 1).

Analysis of urinary concentrations of 6-β-naltrexol revealed that naltrexone patients who discontinued the trial during the first 6 weeks of the study had substantially higher rates of non-compliance with study medication than those who remained in treatment for more than 6 weeks. Thus, for example, at the 2-week visits, 78 urine specimens were tested and 40% of those who completed 6 or more weeks in the study were compliant with their naltrexone medication, compared to only 5% of those who subsequently dropped out before the 6th week.

Efficacy results: intention-to-treat analyses

Alcohol consumption. Alcohol consumption data for patients who received at least one dose of randomized study medication were available for 164 patients (79 placebo and 85 naltrexone) for some or all of the 12-week study period. Overall, no significant differences between treatments were observed in the time to first heavy drinking episode or the time to first drink (Fig. 2). Complete abstinence for the entire study period was achieved by 19% of placebo patients and 18% of naltrexone patients. The number of drinks consumed during the last 4 weeks of the study was lower in the naltrexone group (mean ± SEM: 49 ± 12.0) than in the placebo group (mean ± SEM: 86 ± 15.4) but this difference was not significant.

Biochemical markers. In the 76 patients for whom more than baseline biochemical test results were available, significant decreases in serum GGT activities were observed in both treatment groups at all time points. In these patients, there had been no difference at baseline in median serum GGT, AST or ALT activities between the treatment groups. The median reduction in serum GGT activity for the naltrexone group was significantly greater than in the placebo group at week 8 ($P < 0.05$). Reductions in serum AST and ALT activities did not discriminate between the groups (data not shown).

Craving. Significant mean decreases from baseline in total OCDS score were observed at all time points in the naltrexone group, compared to a significant decrease from baseline only at week 6 for the placebo group. The reduction in total OCDS score in the naltrexone group was significantly greater ($P < 0.05$) than in the placebo group at weeks 10 and 12.

Physician's global assessment. The alcohol component of the aASI assesses the patient's 'need for treatment for alcoholism' as a global measure of severity. A significantly greater percentage of patients in the naltrexone group than in the placebo group (64% versus 45%; $P < 0.05$) were characterized as 'needing less treatment' at week 12, than at baseline.

Table 1. Demographic and alcohol history

	All patients		Completed and compliant	
Variable	Placebo ($n = 85$)	Naltrexone ($n = 90$)	Placebo ($n = 35$)	Naltrexone ($n = 35$)
Age (years; mean ± SD)	43.9 ± 9.7	43.1 ± 8.3	43.9 ± 11.0	43.9 ± 8.0
Gender: male (%)	66 (78)	65 (72)	27 (77)	27 (77)
Length of drinking (years; mean ± SD)	25.9 ± 10.6	22.9 ± 8.7	25.4 ± 10.8	22.2 ± 8.8
Average intake (drinks/day)[a] (mean ± SD)	10.3 ± 7.5	10.1 ± 9.1	9.2 ± 5.0	11.4 ± 12.3
Abstinence before study initiation (days; median, range)[b]	11 (0–30)	10 (0–30)	11 (0–30)	11 (3–29)
DSM-III-R criterion: alcohol dependence (%)	82 (97)	87 (97)	35 (100)	34 (97)
Alcohol abuse (%)	3 (4)	3 (3)	0	1 (3)
Serum GGT (U/l; median) (reference range 7–64)	36	45	54	52
Serum ALT (U/l; median) (reference range 8–48)	24	26	26	28
Serum AST (U/l; median) (reference range 6–37)	22	22	34	27
Not married/cohabiting (%)	52 (59)	53 (59)	18 (52)	16 (49)
Living alone (%)	26 (31)	20 (22)	8 (23)	6 (17)
Employed full time (%)	18 (21)	29 (32)	9 (26)	13 (37)

[a]During the 90 days preceding the first day of the study, based on the Time-Line Follow-Back method.
[b]The actual range differs from that specified in the protocol (5 to 30) because of protocol violations.
ALT, alanine aminotransferase; AST, serum aspartate; GGT, gamma-glutamyl transferase.

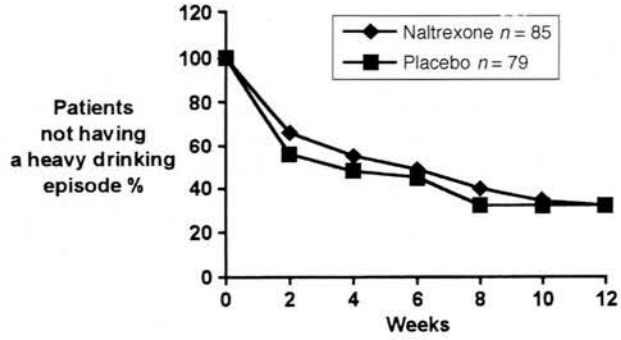

Fig. 2. Time to first episode of heavy drinking: intention-to-treat analysis.

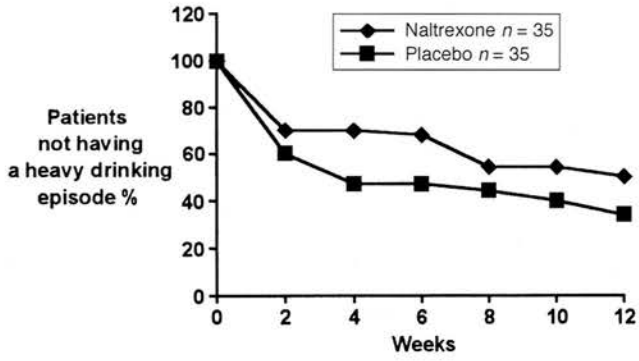

Fig. 3. Time to first episode of heavy drinking: completed and compliant patients.

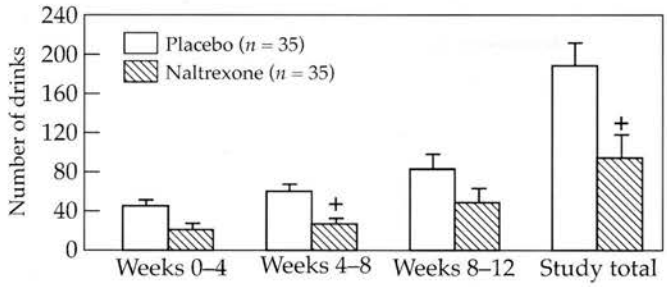

Fig. 4. Mean alcohol consumption during periods between assessments: completed and compliant patients.
Bars show means + SE. $+P \leq 0.05$.

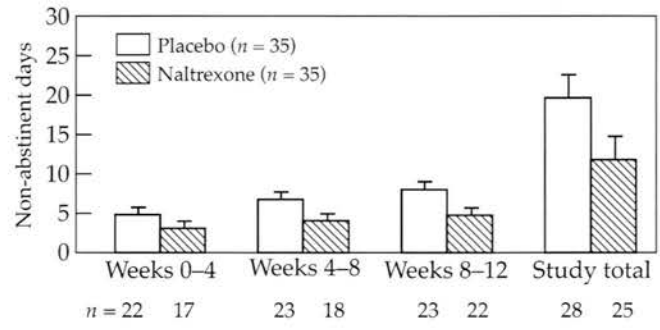

Fig. 5. Mean number of non-abstinent days during periods between assessments: completed and compliant patients.
Bars show mean + SE. The differences are not significant.

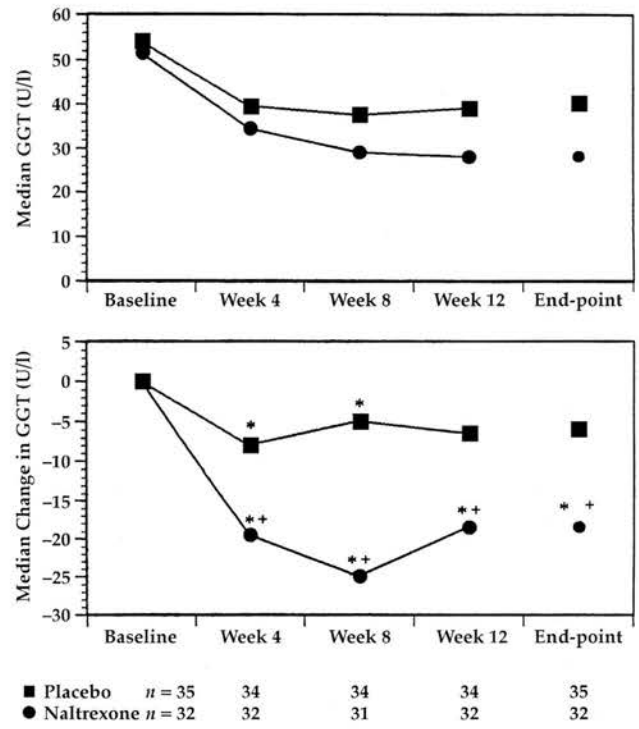

Fig. 6. Median, and median change from baseline, in serum gamma-glutamyl transferase (GGT) activities (U/l): completed and compliant patients.
*Statistically significant change from baseline $P \leq 0.05$; +statistically significant difference between groups $P \leq 0.05$.'Endpoint' is the last result available for each patient.

Efficacy results: completed and compliant patients

Alcohol consumption. In the completed and compliant subgroup, there was no significant advantage of naltrexone over placebo in time to first episode of heavy drinking or time to first drink (Fig. 3). The naltrexone patients consumed, on average, half the total amount of alcohol consumed by placebo patients, during weeks 4–8 ($P < 0.05$) and cumulatively over the whole study ($P < 0.05$) (Fig. 4). The number of non-abstinent days accruing in each of the 4-week periods is shown in Fig. 5. There was a trend suggesting that naltrexone patients had fewer non-abstinent days (i.e. more days of abstinence) than placebo patients but this did not reach significance.

Biochemical markers. The median decrease in serum GGT activity in the naltrexone group was greater than that in the placebo group at all time points ($P < 0.05$) (Fig. 6). Median reductions in serum GGT activity ranging from 19 to 25 U/l were observed for the naltrexone group throughout the study period, compared to median reductions ranging from 5 to 8 U/l in the placebo group. Significant decreases from baseline in serum GGT activity were observed at all time points for the naltrexone group and at weeks 4 and 8 for the placebo group. A similar trend which reached significance at 12 weeks, of a greater median reduction in the naltrexone patients than

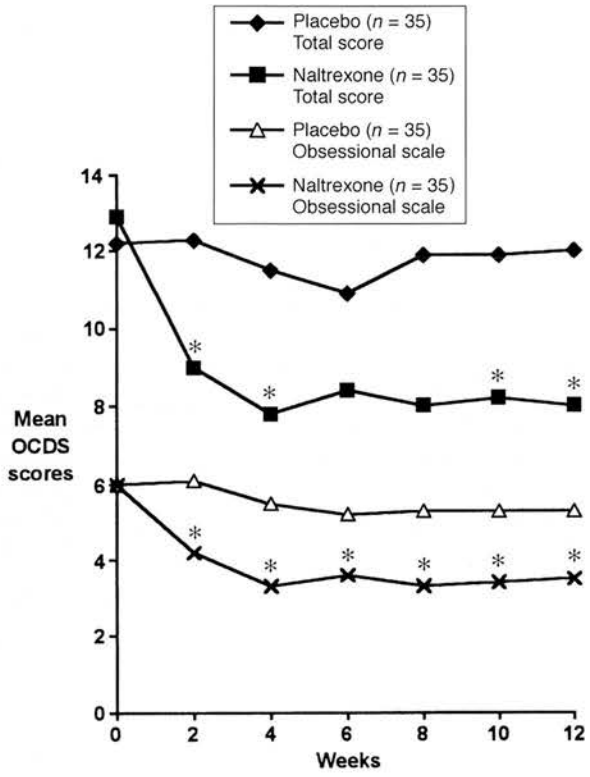

Fig. 7. Mean Obsessive–Compulsive Drinking Scale (OCDS) total score and obsessive subscale score: completed and compliant patients. *$P \leq 0.01$.

placebo patients, was seen for serum AST, but not for serum ALT, activities (data not shown).

Craving. There were significant mean decreases from baseline in total OCDS scores in the naltrexone group at all visits. No significant mean changes from baseline in total OCDS scores were observed in the placebo group. Significant between-group differences in total score favouring naltrexone were observed at all time points, except week 6 and over the whole 12-week study period ($P < 0.01$) (Fig. 7). Because there is a component of the total score which measures alcohol consumption itself, a separate analysis of the scale without the consumption items, the obsessive subscale, was conducted. There was a significantly greater reduction in the obsessive subscale in the naltrexone patients than the placebo patients over the 12-week period ($P < 0.01$) (Fig. 7).

Physician's global assessment. Global benefit of naltrexone was observed in the alcohol component of the aASI: a significantly greater percentage of patients in the naltrexone group than in the placebo group (69% versus 43%; $P \leq 0.05$) were characterized as 'needing less treatment' at week 12 than at baseline.

Safety

Safety results were based on data for all patients who received at least one dose of study medication (P n = 83; ntx n = 90). The most frequently reported adverse clinical event was headache (P 51%, ntx 44%) (Table 2). Significant differences between treatments were observed for the incidences of nausea, pain, dyspepsia and anorexia. Dyspepsia occurred more frequently in the placebo group than in the naltrexone group. Nausea, pain and anorexia occurred more frequently in the naltrexone group. Although events classified by the non-specific WHOART term 'pain' occurred more often in the naltrexone group, incidences of other 'pains' such as

Table 2. New-onset adverse clinical events with an incidence of ≥10%: all patients

	Placebo		Naltrexone	
Adverse clinical event	n	(%)	n	(%)
Total no. of patients evaluated[a]	78		85	
Total no. of patients with an ACE	71	(91)	81	(95)
Headache	40	(51)	37	(44)
Upper respiratory tract infection	17	(22)	29	(34)
Nausea	13	(17)	27[b]	(32)
Insomnia	15	(19)	14	(16)
Vomiting	11	(14)	15	(18)
Depression	13	(17)	13	(15)
Somnolence	7	(9)	15	(18)
Dizziness	11	(14)	10	(12)
Diarrhoea	9	(12)	11	(13)
Anorexia	1	(1)	8[b]	(9)
Abdominal pain	9	(12)	11	(13)
Arthralgia	12	(15)	8	(9)
Anxiety	7	(9)	12	(14)
Fatigue	9	(12)	10	(12)
Back pain	10	(13)	9	(11)
Pain	3	(4)	13[b]	(15)
Coughing	3	(4)	9	(11)
Dyspepsia	9	(12)	2[b]	(2)

[a]Excludes patients who withdrew before adverse clinical events could be reported.
[b]Significant difference between treatment groups, $P \leq 0.05$. In addition to the events in this table, the incidence of anorexia was significantly higher in the naltrexone group than the placebo group (9% vs 1%).
ACE, adverse clinical events.

headache, back pain, abdominal pain, and arthralgia were comparable in the two groups.

Eleven (14%) placebo patients and 13 (15%) naltrexone patients discontinued the study because of adverse clinical events, the most common being nausea. One placebo patient discontinued the study because of deteriorating liver function presumed to be alcohol-related. There were no deaths during the study. No scale of depressive symptoms was used in this study. Depression did not emerge as commoner in patients taking naltrexone.

DISCUSSION

An attrition rate in excess of 50% within the first month of treatment for alcohol is common (Stark, 1992). The discontinuation rate in the present study was higher than in the previously published naltrexone trials. High discontinuation rates have been a feature of multicentre alcoholism treatment studies in the UK (e.g. Chick *et al.*, 1992, 2000).

As in many currently published controlled trials, no attempt was made to assess whether the blindness of patients or staff to the treatment allocated had been maintained (Moncrieff and Drummond, 1998). In the present study, the comparability of the incidence of side-effects makes it unlikely that side-effects would have significantly disturbed the blindness.

The analyses of the completed and compliant subpopulation in this study were performed to elucidate more clearly the treatment effects of naltrexone in patients motivated to stay in treatment and to comply with study medication, the rationale being that naltrexone will only benefit patients who take it. In the subgroup defined by full attendance and tablet count, greater reduction in total alcohol consumption reported by the naltrexone patients was corroborated by improvements in serum GGT activities, improvements in physicians' global rating of alcoholism severity, and by greater reduction in craving.

However, a statistically significant advantage in the primary efficacy variable, time to first heavy drinking episode, was not seen, although there was a trend in favour of naltrexone. Thus, the study has not replicated the results of the previous clinical trials. One possible explanation could be that the psychosocial treatment offered at these six UK sites was in general much less intensive and was not specified, compared to that offered in previous studies. (This was not intended in the design, but resulted from the real-life National Health Service environment of the research.) In samples of patients where few are likely to sustain complete abstinence, structured coping skills training possibly interacts with the use of naltrexone to help prevent major relapse. This is suggested in the studies of O'Malley *et al.* (1992) and Anton *et al.* (1999) and the preliminary report of a Swedish study (Balldin *et al.*, 1997), and the nalmefene study of Mason *et al.* (1999). It could, however, also be argued from this UK study that, at least in compliant patients, some benefits from naltrexone can be seen with varied and non-intensive psychosocial treatment.

Our findings with respect to compliance are similar to those seen previously in studies in the USA. O'Brien *et al.* (1996) found that the size of the naltrexone treatment effect among compliant patients was substantially greater than that in the less compliant. In a different outpatient population, Volpicelli *et al.* (1997) found large naltrexone treatment effects for highly compliant subjects, but no naltrexone effect for the less compliant.

Mechanism of action

Our result, that in compliant patients naltrexone helped reduce alcohol intake, without an unequivocal reduction in number of drinking days, would be consistent with the hypothesis that naltrexone reduces the loss of control which some dependent drinkers experience when they start to drink (Volpicelli *et al.*, 1995*b*) or that naltrexone reduces the amount consumed by reducing the euphoric effect or inducing an aversive effect of drinking alcohol (e.g. Swift *et al.*, 1994; Davidson *et al.*, 1999). Although all patients recruited to the study had been advised to abstain, less than 20% did so. Many of the therapists at the centres where the studies were carried out would have been prepared to continue working towards a modified goal of 'safer drinking' with some patients who gave up aiming for total abstinence, and perhaps naltrexone helped here.

Craving appeared to be reduced by naltrexone, and yet abstinence was not enhanced. At first, this appears to be a discrepancy. However, craving may result from heavy drinking as well as being a stimulus to start drinking. Patients taking naltrexone drank less heavily and this could be a partial explanation of why they reported less craving.

In summary, efficacy, as defined in the protocol's primary measures, was not demonstrated in the whole study population. In those patients who complied with medication and attended appointments, naltrexone over a period of 3 months helped patients reduce their alcohol consumption, reduced their perceptions of craving and improved their global recovery as assessed by their physician, and was accompanied by a reduction in serum markers of alcohol consumption.

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UNITED KINGDOM MULTICENTRE ACAMPROSATE STUDY (UKMAS): A 6-MONTH PROSPECTIVE STUDY OF ACAMPROSATE VERSUS PLACEBO IN PREVENTING RELAPSE AFTER WITHDRAWAL FROM ALCOHOL

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Abstract — A 6-month randomized controlled study of acamprosate versus placebo in preventing relapse following withdrawal from alcohol was undertaken in 20 centres throughout the UK. Patients diagnosed as alcohol dependent and detoxified within the preceding 5 weeks were randomly assigned to treatment with either acamprosate (A) 666 mg three times/day or identical placebo (P). A total of 664 patients were screened; 581 were entered into the treatment phase. One-third were episodic drinkers, 84% were male, 44% were unmarried and 48% were unemployed. Medication was first taken on average 24 days after the start of detoxification; 32% of patients had already relapsed by this time. The 6-month study period was completed by 35% of patients; adverse events led to withdrawal of a further 14% (A) and 9% (P) respectively. Compliance was poor in that, by the end of the second week, only 57% of patients were judged to be taking at least 90% of their tablets. The mean total of abstinent days achieved was 77 (A) and 81 (P). Complete abstinence for 6 months was achieved by 12% (A) and 11% (P); drinking remained within controlled limits in a further 3% (A) and 6% (P). An effect of acamprosate on consumption was not seen when subgroups, including those defined by the Lesch typology, were analysed separately. However, the mean percentage reduction in craving for alcohol measured on a visual analogue scale was greater in the acamprosate, than placebo, patients at week 2 and week 4 ($P < 0.001$) and the mean decrease in the Hamilton Anxiety score at the 4th week was greater in the acamprosate than placebo patients ($P = 0.017$). In comparison with other published trials of acamprosate, patients started study medication after a longer time following detoxification, had more often recommenced drinking before medication was started and had a higher drop-out rate, and this might have contributed to the lack of a treatment effect in this study.

INTRODUCTION

The rapidity of relapse in alcohol-dependent patients who have sought assistance to withdraw from alcohol is a cause for concern. Admissions of patients diagnosed as alcohol-dependent is placing an increasing burden on acute medical services (Chick, 1997). Advances in understanding the neuropharmacology of alcohol dependence and the rapid reinstatement of the syndrome after abstinence have supported hopes that pharmacotherapy may aid recovery (Chick and Erickson, 1996).

There is evidence that acamprosate, calcium acetyl homotaurinate, can lengthen time to relapse, reduce drinking days, and increase the percentage attaining complete abstinence among alcohol-dependent patients who have accepted treatment for their condition (see e.g. Sass *et al.*, 1996; Whitworth *et al.*, 1996; Geerlings *et al.*, 1997; Pelc *et al.*, 1997; Poldrugo, 1997). Homotaurinate is a naturally occurring structural analogue of γ-aminobutyric acid (GABA); acamprosate is a synthetic derivative. This compound crosses the blood–brain barrier, modulates GABA transmission (Daoust *et al.*, 1992), decreases postsynaptic potentials in the neocortex, perhaps by affecting excitatory amino acid (*N*-methyl-D-aspartate: NMDA) receptors (Zeise *et al.*, 1993), and diminishes voluntary alcohol intake in alcohol-preferring rats (Boismare *et al.*, 1984; Le Magnen *et al.*, 1987*a*; Gewiss *et al.*, 1991). Evidence by Lamblin *et al.* (1993), Rassnick *et al.* (1992) and other studies reviewed by Tsai *et al.* (1995) implicates glutamate neurotransmission, and NMDA modulation thereof, in the GABA system in alcohol-seeking behaviour. Tsai *et al.* (1998) assessed glutamatergic neurotransmission and oxidative status in alcohol-dependent patients after acute alcohol withdrawal and 4 weeks later and found persistent abnormalities in cerebrospinal fluid. Littleton (1995) has proposed that one of acamprosate's actions, mediated by its effects on calcium channels as well as on the NMDA receptors in the glutamate system, is to suppress conditioned alcohol withdrawal craving.

Acamprosate administration to animals does not give rise to a dependence syndrome (Grant and Woolverton, 1989), nor does it exacerbate either acute or chronic ethanol toxicity in rats (Le Magnen, 1987*b*). When alcohol-dependent patients who have been abstinent while taking acamprosate cease taking the drug they do not experience a rebound of craving or alcohol misuse (Whitworth *et al.*, 1996). The drug thus has no abuse potential.

This paper reports the results of the first study into the safety and efficacy of acamprosate in a sample of patients attending specialized treatment centres in the UK. Its design differed in some respects from previously reported trials, including its use of a diary card on which patients were to record on a daily basis any alcohol consumed instead of relying on memory at assessment visits. Some preliminary data from this study were previously published in Conference Proceedings (Soyka, 1996).

PATIENTS AND METHODS

Design

This work was undertaken in 20 UK clinics during 1991–1993 as a 6-month randomized controlled study of acamprosate versus an identically presented placebo. The clinics were connected with psychiatric services and a general hospital, including both teaching hospitals and district general hospitals. It was intended that the medication would be used

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as an adjunct, not an alternative, to the clinic's usual psychosocial out-patient treatment programme. No check on blindness of patients or assessors was made; in other ways this study design followed criteria recommended by Moncrieff and Drummond (1998) and the Plinius Maior Society (1994).

A recruitment examination and assessment was conducted within 5 weeks of the end of detoxification (defined as at least 5 days of abstinence). Detoxification may have been carried out on an in-patient or an out-patient basis. The length of this 'pre-baseline period', up to 5 weeks, was chosen, because some patients to be recruited would be undergoing in-patient treatment of about 4 weeks duration. There was then a 'wash-out' period of 1 week, during which patients had to be free of benzodiazepines and were instructed not to drink alcohol. Patients were then reassessed and, using randomization in blocks of eight, allocated to treatment with either active medication, acamprosate 1998 mg (two tablets of 333 mg each three times per day), or identically presented placebo (also two tablets three times per day). Assessments were made after 1 week on medication, then at 2-weekly intervals, and later at 4-weekly intervals for a total of 24 weeks. Medication was stopped and patients then reassessed 4 weeks later to monitor the effects of the abrupt withdrawal of the study medication. In all, 11 assessments were planned (see Fig. 1).

During the study, the protocol was amended to allow reduction of the dosage to four tablets per day if gastrointestinal side-effects were distressing. The study was approved by the local Ethics of Research Committee at each UKMAS centre.

Treatment for detoxification when on medication during the study, even if hospital admission were required, was not a reason for withdrawal from the study, nor was the prescription of benzodiazepines for periods up to 7 days. Admission to hospital for reasons other than alcohol withdrawal was regarded as a serious adverse event and led to withdrawal from the study. Benzodiazepines were not permitted for other purposes, but the urine checks made did not systematically include a check for these or other drugs.

Inclusion and exclusion criteria

Patients were included if they were 18–65 years of age, weighed >60 kg (later modified to 50 kg), fulfilled criteria for alcohol dependence (DSM-III; American Psychiatric Association, 1980), had at least a 12-month history of alcohol dependence, had undertaken withdrawal from alcohol during the preceding 5 weeks, had been abstinent for at least 5 days before enrolment to the study and gave written informed consent.

Patients were excluded if they were receiving disulfiram or calcium carbimide, drugs known to induce hepatic enzymes with the exception of oral contraceptives, or tranquillizers on a regular basis. Patients were also excluded if they had abused drugs in the previous 12 months, had serious medical or psychiatric disorders, or were pregnant or at risk of becoming pregnant. During the study any patient given drugs known to induce hepatic enzymes or psychotropic medication, apart from hypnotics, were withdrawn from the study.

Baseline measures

At baseline, a drinking history was obtained, and the following scales completed: the SADQ (Stockwell *et al.*, 1983) in which a score of 30 suggests severe dependence (range 0–60), the MAST (Selzer, 1971) in which a score of 5 indicates 'alcoholic' (range 0–52) and the CAGE (Ewing, 1984) in which a score of 2 indicates a probable alcohol problem (range 0–4).

Safety monitoring

Tolerance of the drug, concomitant diseases, concurrent medications, and vital signs were recorded at every visit; physical examination including ECG was conducted before and after the study, and blood samples for measurement of haematological and biochemical variables (analysed at a centralized laboratory) were taken at entry and after 1 month, 3 months and at the end of the medication period. At the visit immediately prior to starting medication, and at 1, 3 and 6 months, the clinician rated the Hamilton Anxiety and the

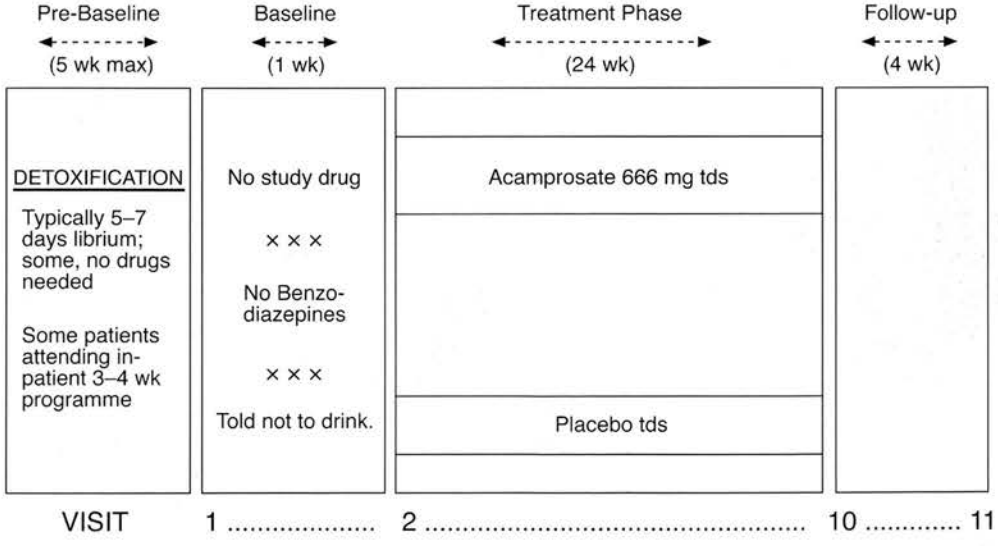

Fig. 1. UK Multicentre Acamprosate Study plan.

Hamilton Depression scales (Hamilton, 1959, 1967 respectively).

Outcome variables

Indicators of alcohol consumption. At each assessment, breath alcohol was checked using an alcolmeter (Lion Laboratories, Ty Verlon, Cardiff, UK); the patients rated their degree of craving on a visual analogue scale 100 mm long [no desire for alcohol (0 mm) to uncontrollable desire for alcohol (100 mm)]; a record card (Fig. 2) was issued on which patients were asked to note on a daily basis whether or not they drank and how much, and the previous period's card was collected. At 1 month, 3 months and 6 months, mean red blood corpuscular volume (MCV) and serum γ-glutamyl transferase (GGT) activity (Chick *et al.*, 1981), and also serum aspartate aminotransferase (AST) activity and urinary ethanol concentration were all assessed. At the end of the study, the Alcohol-Related Problems Questionnaire (Patience *et al.*, 1997) was administered; this contains eleven questions about problems in relationships with friends or family, or the areas of health, work or the law. Attempts were made to contact patients who did not attend by telephone and letter, in order to obtain missing data.

At completion of the study, each patient was asked to rate how effective his or her 'control' in abstaining from alcohol had been during the study. Each investigator was asked to rate in a similar way their patients' success in 'control'.

Compliance. Returned tablets were counted. Failure to attend or to return the tablet bottle even at a subsequent visit, was recorded as 'no data'. Some patients were permitted to reduce their daily dosage if they suffered unwanted side-effects. This was taken into account when assessing compliance.

Typology categorization. A retrospective categorization of the patients enrolled in the Edinburgh and London centres was undertaken using the Lesch typology algorithm, which has been used to predict response to acamprosate (Lesch and Walter, 1996). Patients were traced through contact addresses, hospital and primary care National Health Service Records, and the Register of Deaths. The data necessary to classify a patient were obtained at interview by a psychologist from the Lesch clinical group, supplemented if necessary from clinical records, and the research database. Classification was based on a computer-held algorithm. Analysis was made of outcome in relation to typology.

Analysis

Power. For the primary efficacy variable of abstinence for 6 months, based on previous reports of an expected placebo response of 25% and an expected response to acamprosate of 40% (Lhuintre *et al.*, 1985), a sample of 512 would have a 95% power of detecting a difference between treated and untreated patients using a 5% significance level and a two-tailed test.

Efficacy. Following the intention to treat (ITT) principle, any randomized patient who took at least one dose of study medication was entered into the analysis. It was assumed that all patients who terminated treatment before the end of the study, including those experiencing adverse events, were treatment failures. Primary efficacy variables were pre-defined as: duration of continuous abstinence; duration of continuous abstinence or controlled drinking. Abstinence was defined as: diary card available *and* no reported drinking *and* negative breath and/or urine alcohol levels. Controlled drinking was defined as mean daily self-reported consumption of 5 units or

DATE															
Have you had any alcoholic drink today ? (Yes or No)															
How was your sleep last night ? (see scale below)															
How many units of alcohol have you had today in total ? (see scale below)															
How was your appetite today ? (see scale below)															
How was your mood today ? (see scale below)															
MEDICATION How many study tablets have you taken today (No. of tablets)															

Please complete this card every evening until your next visit to the hospital. **Notes/Comments:**
Please use a black pen.

Units of Alcohol

half pint beer	=	1 unit
half pint cider	=	1 unit
1 glass of wine	=	1 unit
1 measure of spirits	=	1 unit
1 bottle of spirits	=	30 units

Sleep/Appetite/Mood Scores

0 poor
1 moderate
2 good
3 excellent

Please put the appropriate number in the box to record your score.

Fig. 2. Monthly daily record card.

below (men) or 3 units or below (women) and no single day exceeding 8 units (men) or 6 units (women). A unit was that amount of beverage containing 8 g of ethanol. Secondary outcome variables were cumulative abstinence duration, and craving for alcohol.

Compliant subgroup. A subgroup of more compliant patients was identified *post hoc* as those who (1) met inclusion criteria; (2) did not take any prohibited medication during the first 14 days on study medication; (3) attended at least one of the scheduled visits in the first 2 weeks after starting medication; (4) took at least 50% of study medication according to tablet counts during the first 14 days. Excluded from this subgroup were 24 patients who had not met the initial inclusion criteria, but which had not been identified at the outset.

To examine predictors of outcome, subgroups were created according to ratings on certain baseline characteristics (e.g. gender) and the proportions of good responders in the two treatment groups were compared either using χ^2 or two-tailed Fisher's exact probability tests, as appropriate. Multiple regression analysis was used to examine the significance of these relationships.

RESULTS

Recruitment to the study

An unspecified number of patients was considered or approached without formal evaluation of eligibility. Staff were asked later about their reasons for pre-recruitment exclusion; the commonest were medical or psychiatric unfitness, patient's refusal, or patient requesting disulfiram. A total of 664 patients were formally examined for eligibility to enter the study. Of these, 83 did not go forward to randomization. These 83 comprised: 24 lost to follow-up between assessment and randomization, 40 failed to meet inclusion criteria, three showed worsening of their condition, 10 changed their minds about taking medication or otherwise withdrew co-operation, and in the remaining six no reason for exclusion was specified.

Thus 581 patients were randomized and included in the ITT sample.

Baseline data

At the point of randomization, the acamprosate (A) and placebo (P) groups were well matched on the following variables: age (A 42.8, P 43.8 years), gender (A 87% male, P 80% male), marital status (unmarried: A 43%, P 45%), and employment status (unemployed: A 51%, P 46%); pattern of drinking ('episodic': one-third of each group); mean SADQ score (A 34, P 33), CAGE [a score of 4 in 76% (A) and 74% (P)] and MAST [mean score 38(A), 37(P)], including being matched for those items in MAST with an antisocial component (involved in fights, been arrested, trouble with police, drunk driving), blood MCV (A 98.3, P 98.2 fl), serum GGT (A 122 U/l, P 108 U/l, n.s.); mean craving at baseline (A 24 mm, P 22 mm, not significant).

The groups were not matched on: prior weekly alcohol consumption (A 188 units/week, P 168 units/week, $P = 0.022$); place of detoxification (home not hospital: A 55%, P 45%, $P = 0.020$).

The mean interval between the beginning of detoxification and start of study medication was 24 days (A), 25 days (P). However, in 158 patients (27%) (A 74, P 84) this was between 29 and 42 days and in 34 patients (6%) (A 18, P 16) between 43 and 56 days. Patients for whom there was more than 5 weeks between the beginning of detoxification and randomization should not have been included according to the protocol; however, some were randomized and therefore are included in the analysis except when stated. Some patients (168) drank alcohol in the 7-day 'wash-out' period between the assessment intake interview and the start of study medication. This was controlled drinking in 13% (A) and 16% (P), and uncontrolled drinking in 15% (A), 14% (P), with no data available in 3% of patients in each group.

Attendance

There were no statistically significant differences in attendance between the treatment groups at any time point in the study. At the mid-point of the study (84 days) 51% of the acamprosate group and 54% of the placebo group attended; this fell to 35% (A) and 37% (P) by the 24th week. Only 203 patients completed the study [A: 100 (35%), P: 103 (35%)]. The commonest reasons for early withdrawal were: lost to follow-up (A 23%, P 25%), adverse events (A 14%, P 9%), condition worsened (A 7%, P 9%), refused medication (A 11%, P 8%), and 'non-compliance' (i.e. missing many appointments) (A 6%, P 9%). A major effort to contact all patients was made 1 month after the end of the medication phase; 486 were interviewed. A summary of patient retention in the study is shown Fig. 3.

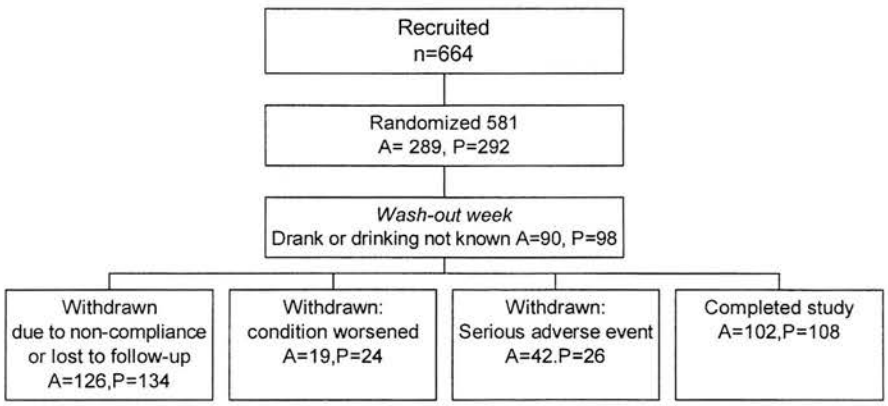

Fig. 3. Retention in the study.

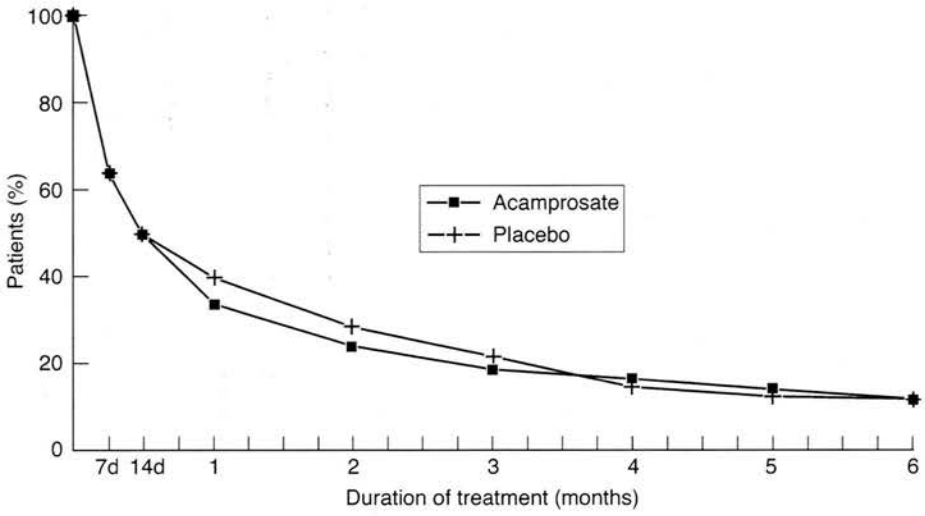

Fig. 4. Survival curve for complete abstinence (n = 581). d, days.

Efficacy

Continuous abstinence: survival analysis. The survival curve for complete abstinence is shown in Fig. 4. At randomization to study medication, 32% of patients had already relapsed. No significant differences emerged at any visit in the proportion of patients abstinent, nor in the proportion drinking in a controlled way, between study groups. Continuous abstinence for the 24 weeks was achieved by 12% (A) and 11% (P). A further 3% (A) and 6% (P) drank some alcohol but without meeting criteria for our definition of 'uncontrolled'.

Cumulative abstinence duration (CAD). CAD is the totalled number of abstinent days recorded on all diary cards for the period between first study medication and end of medication. CAD did not differ between treatment groups: 77 days (A) and 81 days (P) (P = 0.492).

'Control' and craving. Of the 203 patients still in contact at the end of the study, who answered the question 'how effective they perceived their 'control' in abstaining from alcohol during the study', 70% (A) and 73% (P) stated 'good' or 'excellent'. In this group of compliant patients, investigators were also positive about the patient's response to treatment, rating 84% (A) and 82% (P) as 'success'.

The mean decrease in craving was significantly greater in the acamprosate group after 2 weeks of treatment ($P < 0.001$) and after 4 weeks ($P < 0.001$) and there was a trend at 1 week (P = 0.079) and 12 weeks (P = 0.069). One month after the end of the medication phase, the mean decrease in craving was greater in the acamprosate-treated patients than in those receiving placebo (P = 0.022, n = 486) (Fig. 5).

The scores on the Alcohol-Related Problems Questionnaire medication phase improved during the medication phase between intake and 6 months by the same amount, a mean of 3.8 points, in both groups.

Blood tests

Laboratory test results improved throughout the study in both treatment groups; no significant differences were observed between treatment groups in either mean values at any of the time points or in the percentage change in values from baseline. The proportion of patients attending at each visit with an elevated serum GGT (>50 U/l) did not differ between treatment groups. At visit 1, 50% of patients had elevated serum GGT activities and at the end of the medication phase 29% had raised activities. The proportions of patients having an increased blood MCV (>97 fl) at baseline were 56% (A) and 49% (P). There was no difference between the groups at any visit. At visit 10, increased blood MCV was detected in 35% (A) and 36% (P). For patients completing the study in whom complete data on blood tests were available, the mean GGT corroborated self-reported drinking as recorded in the diary cards (Fig. 6).

Secondary effects

Hamilton Anxiety and Depression scores. At baseline, the means and SD for the Hamilton Anxiety scores were: mean 9.8 ± 8.1 (A) and 9.6 ± 7.9 (P). The mean decrease after 4 weeks was greater in the acamprosate group (2.6 ± 7.7) than in the placebo group (1.0 ± 5.4) (P = 0.017). A trend in the same direction was still visible at 3 months (P = 0.076), but was no longer apparent at the end of treatment. A significant

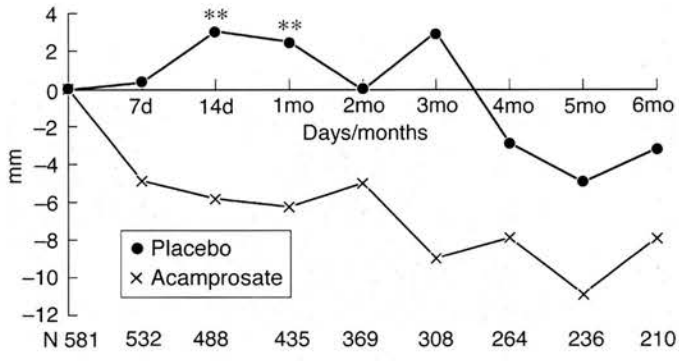

Fig. 5. Alcohol craving: mean difference from baseline on visual analogue scale (mm); **$P < 0.01$. d, days; mo, months.

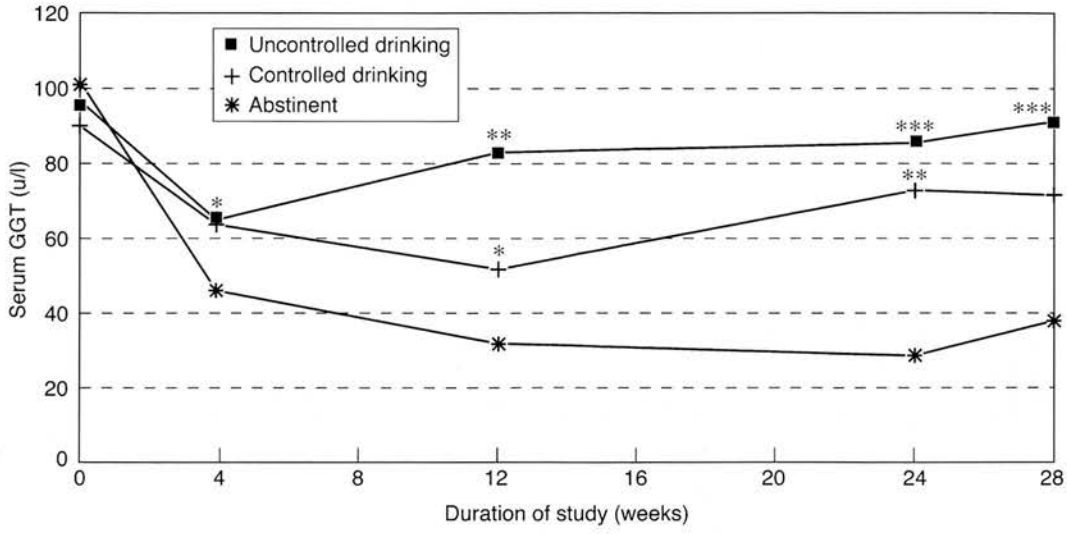

Fig. 6. γ-Glutamyl transferase (GGT) changes by drinking classification at 24 weeks: patients completing the study with all blood samples available ($n = 210$ for each point); $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

difference was, however, again noted at 1 month post treatment ($P = 0.014$). Improvements in the Hamilton Depression ratings were noted overall, without differences between the treatment groups.

Safety and tolerability

The most frequently reported adverse events were headache, diarrhoea, nausea and vomiting. The protocol permitted a reduction in the total daily dose from 6 to 4 tablets/day if gastrointestinal symptoms were distressing and this was done in 11.4% of the acamprosate group and 9.2% of the placebo group. Serious adverse events were reported in 83 patients (29%) in the placebo group and 93 (28%) in the acamprosate group. Hospital admission occurred for detoxification in 14 patients (2%): for an alcohol related disorder in six patients (1%) and a non-alcohol related disorder in nine (1.5%). Two patients ingested large quantities of the active drug in a deliberate overdose, the larger overdose being approximately 128 of the 333 mg tablets, but did not suffer harmful effects.

No changes which could be attributed to the drug occurred in body weight, electrocardiography, haematology or biochemistry test results.

Compliance

By the end of the first 2 weeks of receiving medication, 57% of patients in each group were taking at least 90% of their tablets. This gradually reduced until the end of the 6-month medication phase, when 27% (A) and 28% (P) met this criterion. A separate analysis of those patients attending and compliant with medication was not conducted. It would have been a small subset and a separate analysis could not be justified.

SUB-GROUP ANALYSES

Sub-groups according to certain baseline characteristics

The groups were not matched at baseline with respect to where they were detoxified (Table 1). However, this did not have an influence on outcome: of the 290 patients detoxified in hospital, 16.9% achieved 6 months of abstinence or controlled drinking, compared to 14.8% of the 291 patients detoxified at home. There was no significant difference in outcome in relation to gender: 21.8% of the 96 women attained 6 months of complete abstinence or controlled drinking, compared to 14.6% of the 485 men. Being abstinent in the 'wash-out' week before starting study medication, not unexpectedly, predicted, indeed was a necessary condition for, abstinence during the whole treatment period. No patient who drank in the wash-out week attained complete abstinence. However, three patients (one A, two P) who drank in the wash-out week succeeded in not losing control of drinking during the 6-month treatment period. There was a non-significant trend for those who had had a longer abstinent period between detoxification and starting the study to remain abstinent throughout the study. This is to be expected: patients able to abstain for a month tend to stay abstinent for longer. Baseline craving predicted outcome, with only five of the 106 patients (4.7%) with high craving (>50 cm on the visual analogue scale) achieving controlled drinking or abstinence for 6 months.

When outcome by treatment group was examined in subgroups defined according to the predictor variables in Table 1 (namely: gender; place where detoxified; drinking pattern in baseline week; severity of baseline craving; interval till start of medication) no interaction with acamprosate emerged. Multiple regression analyses including these five variables did not identify an acamprosate effect. This was the finding when either continuous abstinence, or continuous abstinence/controlled drinking, were used as outcome criteria. Although baseline previous weekly consumption had been higher in the acamprosate group, when added to this multiple regression analysis, an acamprosate treatment effect did not emerge. (The slightly higher baseline consumption in the acamprosate group may have reflected the slightly greater proportion of males.)

Compliant subgroup

A sub-group was defined excluding early non-compliance with medication in the first two weeks and those patients

Table 1. Baseline characteristics of patients. Abstinence at every visit: rates for various subgroups

Characteristic	Acamprosate			Placebo			Significance (*P*)
	Abstinent	*n*	%	Abstinent	*n*	%	
Sex							
Male	24	252	9.5	25	233	10.7	0.660
Female	6	37	16.2	7	59	11.7	0.544
Place where the patient was detoxified							
Home	12	158	7.6	13	132	9.8	0.496
Hospital	18	130	13.8	19	160	11.9	0.617
Days between detoxification and commencing study medication							
0–14	4	61	6.6	1	67	1.5	0.191
15–28	15	135	11.1	16	124	12.9	0.657
29–42	8	74	10.8	15	84	17.9	0.210
43–56	3	18	16.7	0	16	0.0	0.230
Drinking pattern in week between recruitment and commencing study medication							
Abstinent	29	199	14.6	30	194	15.5	0.805
Controlled	0	32	0.0	0	41	0.0	1.000
Uncontrolled	0	41	0.0	1	41	2.4	1.000
Missing data	1	17	5.9	1	16	6.3	1.000
Alcohol craving visual analogue scales at recruitment (mm)							
0–50	29	231	12.6	30	244	12.3	0.932
51–100	1	58	1.7	2	48	4.2	0.589

Total population, $n = 581$.

randomized but who had been ineligible on inclusion criteria. This group consisted of 378 patients (A 194, P 184). In terms of their baseline characteristics, these groups were slightly unbalanced in that the patients receiving placebo were more likely to be female (P 22.3%, A 13.4%, $P = 0.024$). They were, however, balanced for place of detoxification as well as on all other baseline characteristics. Within this subgroup, there were no differences between those receiving acamprosate and those receiving placebo on any of the outcome criteria, except for craving at weeks 2 and 4 which was lower in the acamprosate group ($P = 0.045$ and 0.050 respectively).

There were no significant interactions between treatment group and any of the baseline factors singled out as likely predictors of outcome (gender, previous weekly consumption, place where detoxified, interval to starting medication, drinking between enrolment and commencing medication, and baseline craving). In the 78 patients who started study medication within 14 days of the start of detoxification, four (5%) sustained abstinence, and all were in the acamprosate group ($P = 0.052$).

Post-medication assessment

At a minimum of 1 month after stopping medication, 385 patients were assessed. Of these, 203 had completed the study (A 100; P 103) and they tended to be seen at or near to the 1-month point post-treatment; others had withdrawn early for various reasons and hence tended to be seen at a relatively later point than the completers. The proportion of patients abstinent 1 month after medication ended was slightly higher than at the last visit on medication. This was because some patients who had relapsed and terminated before the end of the study were now abstinent. There was no evidence of sudden relapse in drinking when the medication was discontinued.

Centre differences and psychosocial treatments offered

Analysis of outcomes by centre did not suggest that acamprosate was more effective in some centres than others, but the numbers analysed were small, and the data by centre are not presented here.

Data were available on the psychosocial treatments offered at the 16 centres which contributed most patients to the study. Nine were specialized alcohol problem clinics, five were addiction centres, one was a general psychiatric setting and one a general medical setting which contributed 72 patients. Day-patient facilities were available in 11 centres. All but two centres reported that a typical in-patient stay, if indicated, would be less than 4 weeks, with two centres specifying less than 2 weeks. Cognitive–behavioural group therapy was offered at 13 centres, and out-patient support groups at nine centres. Eight offered 'educational groups'. Only five offered marital therapy, and five social skills training. Only two centres had on-site meetings of Alcoholics Anonymous (AA), but 14 centres used AA as a resource. The amount of other treatment taken up by patients in the study period was not documented at the time. However, later estimates revealed that, at seven centres, less than 20% of the patients attended appointments outside the research visits, whereas at five centres more than 75% did so. When asked to compare their clinical impression of patients they had recruited to the study, nine centres said that patients recruited had been 'typical', but six said they had been 'less severe' than typical patients.

Typology

An attempt was made to trace all 149 patients randomized into the study at the two main centres. Two patients were too cognitively disabled to give an interview, 10 refused, 29 were untraceable and 32 had died. An interview was obtained and a classification made in 76. The two Lesch types tending to be responsive to acamprosate in the Austrian study of Lesch and

Walter (1996), Types I and II, accounted for 25% and 18% of the sample interviewed respectively. Types III and IV, which in the Austrian study tended to be non-responsive to acamprosate, accounted for 15% and 42%. 'Types' were equally distributed between the two treatment groups; 17 Type I and II patients received the placebo while 16 received acamprosate. There was no trend suggesting that these Type I and II patients had a better outcome in one treatment group rather than another.

DISCUSSION

In terms of abstinence for the duration of study, the success of this patient population was low, at ~11%. Analysing data on the whole population, no evidence of an effect of acamprosate on drinking in the 6 months following detoxification was found. This is not explained by effects of those baseline characteristics which were imbalanced between the groups, namely gender, place of detoxification and mean previous weekly alcohol consumption.

The craving rating at weeks 2, 4 and at the month after medication ceased was lower in patients treated with the active drug.

The findings of this study differ from those of previously published randomized controlled trials (Table 2), all of which have shown that acamprosate improves self-reported abstinence rates in recently abstinent alcoholics, over periods varying from 3 to 12 months of medication, with two exceptions: Roussaux *et al.* (1996), and Lhuintre *et al.* (1990) who did not report consumption data. Not all studies reported corroborative advantages in objective markers of alcohol consumption, such as serum GGT activity. There are a number of possible explanations for these contrasting findings.

Patient characteristics

Severity of condition or resistance to treatment may have been greater in the UK patient population, than in some other samples. Thus, in the study of Paille *et al.* (1995), half of the patients treated were receiving treatment for their alcohol problem for the first time. While previous treatment experience was not recorded in the UKMAS sample, it is believed that more than 50% had a history of treatment failure. Where details have been published, it appears that patients' social supports in the positive studies were greater than in UKMAS. Thus, in the study of Sass *et al.* (1996), 26% were unemployed, and in the study of Paille *et al.* (1995), 21% were unemployed, compared to 48% in UKMAS. [In the other negative study (Roussaux *et al.*, 1996) 60% were unemployed and only 20% married, resembling the low social support of the UKMAS sample.]

Response to the MAST questionnaire is sometimes used as an index of severity of alcoholism. However, great caution must be used when comparing MAST scores between cultures, and between samples with differing proportions of men and women, because some items depend on the interaction between the drinker and society. For example, 5 MAST points can be scored for attending AA, but the availability of AA varies between countries; similarly, several points can be scored for legal infringements, but the rate of police activity towards drinkers also varies between societies and in relation to gender. However, the UKMAS sample scored a mean of 37, similar to the Ladewig *et al.* (1993) sample (mean 38), but higher than those of Whitworth *et al.* (1996) (mean 32) and Poldrugo (1997) (mean 27). The other studies did not use MAST.

Within our population, therefore, we proceeded to examine whether groups of different severity, defined on baseline MAST or consumption, had a greater or lesser response to acamprosate. However, no such interaction was found. The UKMAS sample may have contained a higher proportion of patients with personality disorder than the other studies. No specific measure was used in any study, but there are certain MAST items relating to social disorder, police trouble and violence, which, to illustrate this point, we have calculated as a separate index. The mean score on these 'sociopathic' items in the UKMAS patients was 6.5 (SD 2.7, max. score 11), but these data are not available for other studies.

As regards typology, the Austrian study (Whitworth *et al.*, 1996) contained 39% of non-responding patient types, Types III and IV (Lesch and Walter 1996). If the two UKMAS centres are representative of patients from other centres, then the UKMAS sample contained a higher proportion (57%) of Type III and IV than at least one of the studies from continental Europe. However, there was no trend in the limited data obtained to suggest that Type I and II patients had relapsed less if receiving acamprosate than if receiving placebo.

Pattern of drinking

One-third of our patients drank episodically rather than continuously. Few data on patterns of drinking are given in the other trials of acamprosate. However, in the study of Whitworth *et al.* (1996), 18% were episodic drinkers and Poldrugo (1997) reported that, in his Italian study, 86% of patients drank on 7 days per week. At this juncture, there are insufficient data to state whether an acamprosate response is more likely in continuous than episodic drinkers.

Diary card

Using such a card, which the patient had to return in person, may introduce stricter criteria for monitoring alcohol consumption than employed in some of the previously reported studies. Perversely, it could encourage less accurate overall recording of consumption if the assessors did not also use careful questioning and their clinical sense. We have no way of assessing either of these possibilities, though we can state that the objective marker, serum GGT activity, correlated well with our diary card measures and did not reveal any advantage to the acamprosate group.

Timing of the medication

The mean interval between the last drink and the start of medication was 25 days and, in some patients who were randomized and given medication, was over the 5 weeks specified in the protocol. The range of intervals in the other studies was shorter (Table 2). The effect of acamprosate in the German and Austrian studies was most prominent in the first 30 days. In the UKMAS study, only 78 (13%) of the patients began study medication within 14 days of the start of detoxification, and of the four patients who achieved complete abstinence all were in the acamprosate group, a difference which, however, failed to reach significance ($P = 0.052$). Altogether, 35% of patients had relapsed before starting medication. In some of the

Table 2. Published randomized controlled studies of acamprosate (A) versus placebo (P) in the treatment of alcohol dependence

First author, date, country	Patients entered (*n*)	Last drink to 1st drug	Duration of treatment (months)	Daily dose	Outcome measures: Continuous abstinence (%)	Outcome measures: CAD (days)	Outcome measures: Serum GGT activity	Outcome measures: Study completed %
Lhuintre *et al.* (1985)[a,b] France	85	~6 days	3	25 mg/kg max. 2250 mg	48% A; 28% P $P < 0.02$	n/r	'abstinent = normal' GGT	85%
Lhuintre *et al.* (1990)[a,b] France	569	5–30 days	3	1332 mg	n/r	n/r	A:1.38 × normal; P:2.02 × normal $P < 0.02$	63%
Pelc *et al.* (1992) Belgium	102	n/r	6	1998 mg	27% A; 4% P $P < 0.05$	A > P $P < 0.01$	n/r	63%
Tempesta (2000) Italy	330	>5 days	6	1998 mg	47% A; 31% P $P < 0.01$	110 A; 89 P $P < 0.05$	n/r	75%
Ladewig *et al.* (1993)[b] Switzerland	62	>4 days	6	1998 mg[c]	38% A; 17% P n.s.	122 A; 78 P $P = 0.039$	n/r	66%
Paille *et al.* (1995)[b,d] France	548	7–28 days	12	1332 mg (low) and 1998 mg (high)	35% A high 28% A low 19% P ($P < 0.01$ for A high vs P)	223 A high 198 A low 173 P $P = 0.0005$	<uln: 35% A 21% P ($P < 0.05$)	52% A high 45% A low 35% P
Roussaux *et al.* (1996) Belgium	127	n/r	3	1332 mg and 1998 mg	29% A 33% P n.s.	n/r	No differences in means	70%
Whitworth *et al.* (1996)[a,b] Austria	448	>4 days	12	1998 mg[c]	18% A; 7% P $P = 0.0007$	139 A; 104 P $P = 0.012$	n/r	40%
Sass *et al.* (1996) Germany	272	14–28 days	12	1998 mg[c]	45% A; 25% P $P = 0.005$	224 A; 162 P $P < 0.001$	trend in favour of A	49%
Pelc *et al.* (1997) Belgium	188	14 days	3	1332 mg and 1998 mg	51% A; 15% P $P < 0.001$	57 A high 52 A low 34 P; $P < 0.05$	'significantly lower in A than P' (data n/r)	31% P 48% A
Geerlings *et al.* (1997) The Netherlands	262	5–28 days	6	1998 mg[c]	20% A; 10% P $P < 0.02$	61 A; 43 P $P = 0.026$	n/r. CDT improved A > P ($P = 0.016$)	41% A 31% P
Poldrugo *et al.* (1997) Italy	246	>4 days	6	1998 mg[c]	48% A; 32% P $P < 0.05$	99 A; 70 P $P = 0.007$	<1.3uln: 48% A; 21% P $P = 0.0017$	41%
Besson *et al.* (1998)[a,e] Switzerland	110	>4 days	12	1998 mg[c]	25% A; 9% P n.s.	137 A; 75 P $P = 0.013$	P > A till 270 days $P \leq 0.02$	35%
UKMAS	581	0–56 days	6	1998 mg[c]	12% A; 11% P	77 A; 81 P	Reduced in both	35%
UK (this report)		mean 25			n.s.	n.s.	(n.s)	

[a]Other psychotropic drugs permitted for various periods.
[b]Inclusion specified GGT > ×2 upper limit of reference range (uln) and/or MCV >98 fl (Poldrugo: and/or >95 fl).
[c]Less than 60 kg body weight, 1332 mg.
[d]Detoxification as out-patient in 20%; half were receiving treatment for the first time.
[e]Some patients also received disulfiram.
CAD, cumulative abstinence days; GGT, γ-glutamyl transferase; MCV, mean red corpuscular volume; CDT, carbohydrate deficient transferrin; n/r, not reported; n.s., not significant.

published studies (e.g. Besson *et al.*, 1998), patients were withdrawn from the study before medication was started if they were drinking on the day of commencement.

If the calcium channel abnormalities or NMDA receptor changes in the recovering alcohol-dependent patient are most marked in the immediate weeks after the last drink, then it may be that, if acamprosate is to be effective, it should be started as soon after detoxification as possible, or even during detoxification.

There was a very early relapse in our UKMAS sample: 155 (27%) drank in the first 7 days after detoxification, that is, the week between evaluation and randomization during which they were on no medication, and no data are available for a further 33 patients, suggesting that these individuals had already been lost to follow-up and were probably drinking. If acamprosate could prevent this early relapse in, say, half of these patients, then the difference in overall total abstinence rates could have been 16%. In retrospect, if patients had been given a placebo preparation during that period they might have been less likely to drink.

Location of withdrawal treatment

Approximately 50% of patients entering the UKMAS study were detoxified as outpatients. This contrasts with other studies, in which home detoxification was uncommon. Even in the study of Paille *et al.* (1995), only 20% had not been hospitalized for detoxification. It is difficult to see why this should influence the efficacy of acamprosate; it may however indicate that UKMAS patients had slightly lower motivation/were not willing to come into hospital; or it may reflect the relatively low intensity of the UKMAS clinic approaches compared to approaches in the centres taking part in some of the other studies; or that, compared to those in the other studies, UKMAS patients tended to be less severely dependent, which was also mentioned by six UKMAS centres.

Type of psychosocial treatments offered

Descriptions of the psychosocial treatments offered in the other studies are sparse. However, it should be noted that, in UK centres, relatively few were offering those psychosocial therapies which are perhaps of most proven value, such as 12-step facilitation leading to regular attendance at AA meetings, marital therapy, social skills training (Miller *et al.*, 1995; Project Match, 1997). Attendance at AA was more common in the German study, in that, during the first month, 25% of patients went to at least one meeting and by the end of the 12 months, 14% were still attending. The figures for the present UK study are not exact, but it is believed that there was much less AA attendance.

Drop-outs

In all the other studies, even those of 12-month duration, completion rates were better than in UKMAS. This may reflect higher rates of patients with personality disorder or lack of social resources, or reflect that with some exceptions the UK centres tended to offer a less intensive approach.

Loss to follow-up is a major problem when interpreting results of treatment outcome in alcohol-dependent samples when studies extend over many months. All the studies described here, including UKMAS, reported results analysed using 'the intention to treat' principle, which classifies patients who drop out as treatment failures, and does not risk sub-group analyses where original matching between the groups may be lost. It takes no account of whether or not those patients remaining in the study actually complied with treatment. Many consider the 'intention to treat' analysis to be the only correct approach in analysing treatment outcome. Nevertheless, one other analysis was carried out here, of the sample defined as those who had not violated the protocol in any way and who complied for the first 2 weeks, taking at least 50% of their medication according to tablet count. However, no evidence of a trend towards an effect of acamprosate on outcome was revealed.

Was the sample too small to show a treatment difference?

The effect size in the other studies has been at least the 15% allowed for when the power calculations for the UKMAS study were made: at first sight, the UK result seems unlikely to be due to a lack of statistical power. However, the power calculation had assumed that all patients would be abstinent at the start of the treatment period. The fact that 155 patients were no longer abstinent at the start of treatment would have reduced the statistical power of the study.

By chance, a negative study has occurred

As the number of controlled studies of apparently successful treatments increases, the proportion of studies which fail to show an effect may also increase. This may be due to variations in the application of the treatment, characteristics of the sample or treatment setting, or perhaps chance. For example, Morris and Beck (1974) reviewed all the randomized controlled studies of tricyclic antidepressant drugs which had been published up to 1 January 1973. Out of 93 studies, tricyclic antidepressants were more effective than placebo in 61 studies, no difference was found in 32 studies, and there were no studies where placebo was more effective than tricyclic drug. Despite the many negative studies, tricyclic antidepressants became accepted as a valuable therapy for depression. It remains to be seen what will be the eventual proportion of positive to negative studies for acamprosate.

GENERAL CONCLUSIONS AND COMMENTS

The weight of results of the other studies reported to date lead to the conclusion that acamprosate is a helpful adjunct to conventional outpatient treatment after detoxification, approximately doubling the number of patients achieving continuous abstinence, and increasing by some 30–40% the cumulative total of days abstinent. This UK study does not support these findings. Contributing to an explanation of this negative result may be loss of statistical power due to a higher drop-out rate and relapse into drinking before starting the drug, but also a background of less intensive treatment in general, although the amount and type of preceding and collateral psychosocial and/or pharmacological treatment which best facilitates response to acamprosate has yet to be specified.

From the other studies it is, of course, clear that not all patients respond. The characteristics of responders have yet to be defined. Perhaps the delta (continuous) rather than the gamma (episodic) alcoholic might respond better (Jellinek, 1960), and our UK sample probably had a much higher proportion (33%) of episodic drinkers than other centres,

particularly the wine-drinking centres of Italy, Austria, France and Southern Germany. Lesch and Walter (1996) showed that a more classical, primary type of alcoholic, rather than the alcoholic with other psychiatric or organic disorder or many social problems, is more likely to benefit from acamprosate. Specification of the optimal patient characteristics and optimal accompanying psychosocial treatments is required so that acamprosate can be used to its best advantage.

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Does acamprosate improve reduction of drinking as well as aiding abstinence?

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The study aimed to discover whether acamprosate reduces the severity of relapse for those patients undergoing abstinence–orientated treatment who are unable to abstain completely. Data on patients' alcohol consumption from 15 placebo-controlled treatment studies (n = 3309) were examined to test whether, at a given time point, patients who have taken one or more drinks since the last assessment ('relapsers', n = 1010) take alcohol on fewer days, report lower average number of drinks per day, and consume less alcohol in total with acamprosate compared to placebo. These studies had varying duration (90 days, 180 days and 360 days). There were four dates that were common to some studies (days 30, 90, 180 and 360). Among relapsers, acamprosate was significantly associated with less quantity (Q) and frequency (F) of drinking compared to placebo in each of the four follow-up periods ($p < 0.001$). The differences were most marked for the product $Q \times F$ (overall weekly consumption). For each period, there were fewer who were drinking an average of five or more drinks per day in the acamprosate compared to the placebo groups. Acamprosate helps reduce the severity of relapse in patients undergoing abstinence-orientated treatment.

Key words: acamprosate, alcohol consumption, binge drinking, controlled drinking, lapse, outcome, relapse, treatment

Introduction

Acamprosate has been shown in many individual trials, systematic reviews (Garbutt *et al.*, 1999; Mason and Ownby, 2000) and meta-analyses (Kranzler and Van Kirk, 2001; Slattery *et al.*, 2003), to help sustain continuous abstinence in detoxified alcohol dependent patients during the whole duration of the trial. These studies have also shown that acamprosate is associated with more total days of abstinence than placebo.

Tempesta *et al.* (2000) reported a placebo-controlled trial of acamprosate in 246 detoxified alcohol dependent patients, which showed that, at a given time point, those who had taken one or more drinks since the last assessment drank less frequently and a lesser amount of alcohol if they were in the acamprosate-treated group rather than the placebo-treated group. Although the mechanism may be different, the phenomenon has been shown for naltrexone. Thus, newly detoxified patients, who resumed drinking, consumed less alcohol if treated with naltrexone than if treated with placebo (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1995; Anton *et al.*, 1999; Chick *et al.*, 2000a). Volpicelli *et al.* (1995) hypothesized that naltrexone reduces the loss of control that some dependent drinkers experience when they start to drink. This has received some support in laboratory studies, which suggest that a possible mechanism might be that naltrexone reduces the euphoric effect or induces an aversive effect of drinking alcohol (Swift *et al.*, 1994; Davidson *et al.*, 1999).

This study examined the hypothesis that acamprosate helps to prevent a lapse becoming a relapse. The specific predictions to be tested were that, at any given time point, patients who have taken one or more drinks since the last assessment will (i) have taken alcohol on fewer days; (ii) report lower average drinks per day; (iii) consume less alcohol in total; and (iv) will be less likely to have consumed five or more drinks/day ('uncontrolled drinkers') in the acamprosate group compared to placebo.

Materials and methods

Of the double-blind controlled studies of the efficacy of acamprosate in enhancing abstinence for detoxified patients, 15 were found from which usable data on alcohol consumption were available. These studies had varying duration. Two studies had a duration of 90 days (Roussaux *et al.*, 1996; Pelc *et al.*, 1997). Eight studies lasted 180 days (Pelc *et al.*, 1992; Ladewig *et al.*, 1993; Geerling *et al.*, 1997; Poldrugo, 1997; Chick *et al.*, 2000b; Tempesta *et al.*, 2000; Gual and Lehert, 2001; Borg, 2003). Five studies lasted 360 days (Paille *et al.*, 1995; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Barrias *et al.*, 1997; Besson *et al.*, 1998) (Table 1).

Follow-up assessments were not planned at the same time from baseline in each study although, depending on the overall length of the study, there were four common dates (days 30, 90, 180 and 360).

Table 1 Description of the trials

Study	Country	Plac (*n*)	Acamp (*n*)	Total (*n*)	Treatment duration (months)
Pelc *et al.* (1997)[a]	Belgium/France	62	126	188	3
Poldrugo (1997)[a]	Italy	124	122	246	6
Chick *et al.* (2000b)	U.K.	292	289	581	6
Tempesta *et al.* (2000)[a]	Italy	166	164	330	6
Gual and Lehert (2001)[a]	Spain	147	141	288	6
Whitworth *et al.* (1996)[a]	Austria	224	224	448	12
Barrias *et al.* (1997)[a]	Portugal	152	150	302	12
Sass *et al.* (1996)	Germany	136	136	272	12
Geerlings *et al.* (1997)[a]	Benelux	134	128	262	6
Paille *et al.* (1995)	France	177	361	538	12
Ladewig *et al.* (1993)[a]	Switzerland	32	29	61	6
Besson *et al.* (1998)[a]	Switzerland	55	55	110	12
Pelc *et al.* (1992)[a]	Belgium	47	55	102	6
Borg (2003)[a]	Sweden	5	5	10	6
Rousseaux *et al.* (1996)[a]	Belgium	64	63	127	6

n, Number of patients; Plac, placebo-treated patients; Acamp, acamprosate-treated patients. Study medication was dose adjusted according to following regimen: patients below 60 kg body weight receiving 1332 mg and those above 60 kg received 1998 mg acamprosate or matching placebo. [a]Categories were used to collect consumption data.

The method of collecting consumption data at the assessment points varied from study to study. In some studies, patients were asked to complete a daily card that was used as a basis for arriving at the most accurate figures for that period. In other studies, mean consumption for the last period was derived solely from the patient's interview with the investigator, sometimes with information from relatives.

Drinking since last assessment was recorded at each examination in terms of abstinence, average quantity per drinking day and frequency of drinking. For each period, the patient was classified as abstainer, relapser, or 'missing' (not attending the examination).

Depending on the study, the average daily consumption of alcohol was documented either as the estimated mean number of drinks/week, or by categories (never, less than five drinks, between five and 10 drinks, and more than 10 drinks). A 'drink' contained 10–12 g ethanol except in the UK study (Chick *et al.*, 2000b) where a unit was 8–9 g, a small difference that was ignored for the present purposes because of the lack of significant Study–treatment interactions. Weekly frequency of drinking was documented as number of days on which drinking occurred, or using four categories from none to 'daily'.

The population of interest in this paper comprised relapsers (i.e. patients who took at least one drink in at least one period). Non-attenders, for whom detailed consumption data are missing, were not included in the analysis.

Statistical analysis

Because some of the studies used categories to collect consumption data, we used medians (and interquartiles) instead of arithmetic means (and SDs) to estimate daily quantities and frequencies of consumption. Three measurements of alcohol consumption could thus be calculated and comparisons made between the two treatment groups: median drinks per drinking day (Quantity), median number of drinking days per week (Frequency), and the weekly Total Consumption defined as the product $Q \times F$. In addition, for each study period, we determined the percentage of relapsers with a consumption of an average of five drinks or more per day ('uncontrolled drinkers').

As more than one study is involved, a meta-analytic estimation was necessary. This was calculated on an Individual Patient Data (IPD) basis (i.e. data on individuals, not on treatment groups, were entered). Because the categorical aspect of data collection may lead to departures from usual normality and homoscedasticity assumptions, the assessment of the difference between the two groups was carried out with a non-orthogonal analysis of variance (ANOVA) on ranks considering the Treatment (fixed factor), the Study (random factor), and the interaction between Treatment and Study. For each period, we compared the percentage of uncontrolled drinkers (≥ 5 drinks/day) between treatment groups using the simple random model of DerSimonian and Laird (1986).

Statistical analysis was performed using the SAS statistical software package (version 6.02 for Windows) (SAS Institute, Cary, NC, USA).

Results

The numbers of relapsers, abstainers, and missing patients for each study and for each period are shown in Table 2.

Quantity, frequency and total consumption for relapsers

The three measurements of alcohol consumption, estimated across studies by their observed medians, remain similar over the four examined periods, within each treatment group (Table 3). On averaging the relative difference (acamprosate – placebo)/placebo over the four periods, we found a relative decrease of 29.40% (Quantities), 27.8% (Frequencies) and 50.23% in the Total Consumption estimate.

The *p*-values associated with the analysis of variance cannot be considered as confirmatory, given the repetition of the tests. Also, these *p*-values cannot be compared between periods because different sample sizes are involved. The Treatment effect is overwhelmingly significant for all measurements in all periods, consumption under acamprosate appearing to be reduced compared with the placebo. A linear correlation of $r = 0.74$ was observed between Quantity and Frequency, for all the periods together.

ble 2 Percentages of patients missing, relapsed and abstinent within each treatment group for the four periods

	Day 30		Day 90		Day 180		Day 360	
	Plac	Acamp	Plac	Acamp	Plac	Acamp	Plac	Acamp
c *et al.* (1997)	0.022		0.008					
lissing	16	9	45	26	–	–	–	–
elapse	37	24	29	26	–	–	–	–
bstinent	47	67	26	48	–	–	–	–
drugo (1997)	0.019		0.051		0.035			
lissing	29	19	52	39	61	47	–	–
elapse	12	6	8	7	6	5	–	–
bstinent	59	75	40	55	32	48	–	–
ick *et al.* (2000b)	0.304		0.692		0.875			
lissing	26	28	46	49	63	65	–	–
elapse	34	38	26	24	19	18	–	–
bstinent	41	35	29	27	18	17	–	–
mpesta *et al.* (2000)	0.049		0.108		0.033			
lissing	5	2	18	16	27	24	–	–
elapse	39	29	34	25	28	18	–	–
bstinent	56	68	48	59	45	58	–	–
al and Lehert (2001)	0.342		0.351		0.331			
lissing	7	6	26	19	35	27	–	–
elapse	24	17	20	19	16	16	–	–
bstinent	69	77	54	62	50	57	–	–
itworth *et al.* (1996)	0.319		0.035		0.041		0.043	
lissing	17	13	38	31	51	48	63	59
elapse	20	17	24	19	22	16	16	11
bstinent	63	70	38	50	26	36	21	30
rias *et al.* (1997)	0.028		0.004		0.125		0.029	
lissing	2	2	11	11	24	27	43	39
elapse	30	17	42	25	39	28	31	22
bstinent	68	81	47	65	37	45	26	39
s *et al.* (1996)	0.140		0.010		0.003		0.002	
lissing	15	12	38	24	52	35	60	43
elapse	22	15	18	15	19	17	18	15
bstinent	63	74	44	62	29	49	22	42
erlings *et al.* (1997)	0.490		0.127		0.057			
lissing	15	15	50	43	69	59	–	–
elapse	40	33	28	23	18	16	–	–
bstinent	46	52	22	34	13	25	–	–
lle *et al.* (1995)	0.069		0.155		0.007		0.002	
issing	8	7	23	19	46	33	64	49
elapse	36	26	37	33	24	26	17	20
bstinent	56	66	40	48	30	42	19	31
lewig *et al.* (1993)	0.031	0.396	0.184					
issing	13	10	19	14	31	31	–	–
elapse	47	17	56	45	47	28	–	–
bstinent	41	72	25	41	22	41	–	–
sson *et al.* (1998)	0.019		0.081		0.010		0.141	
issing	9	7	33	27	44	49	65	65
elapse	44	20	35	20	40	16	20	9
bstinent	47	73	33	53	16	35	15	25
c *et al.* (1992)	0.068		0.202		0.012			
issing	28	13	55	38	79	56	–	–
elapse	30	24	17	20	13	11	–	–
bstinent	43	64	28	42	9	33	–	–
g (2003)	1.000		1.000		0.497			
issing	0	0	0	0	0	0	–	–
elapse	20	20	20	20	20	40	–	–
bstinent	80	80	80	80	80	60	–	–
ussaux *et al.* (1996)	0.916		0.874					
issing	22	19	28	30	–	–	–	–
elapse	27	29	39	41	–	–	–	–
bstinent	52	52	33	29	–	–	–	–
studies	0.000		0.000		0.000		0.000	
issing	15	12	34	28	49	42	59	50
elapse	30	24	28	24	22	19	20	17
bstinent	55	64	38	48	29	39	21	33

each cell, p (chi-square test) is provided at the top of the cell.

Table 3 Median estimates of consumption and assessment of Treatment, and Treatment by Study, effect significances

	Quantities (Q)			Frequencies (F)			$Q \times F$		
Period	Placebo	Acamp	p	Placebo	Acamp	p	Placebo	Acamp	p
D30	5.76	4.22	0.006	3.52	2.93	0.101	20.27	12.36	< 0.001
	2.51, 27.58	1.94, 9.10	(0.015)	2.25, 5.35	2.06, 5.26	(0.201)	15.1, 26.5	7.4, 18.5	(0.062)
D90	4.83	3.76	0.005	3.75	2.75	0.027	18.11	11.14	< 0. 001
	2.28, 9.47	1.55, 8.44	(0.099)	1.73, 5.34	1.35, 4.92	(0.084)	12.4, 24.4	5.3, 17.5	(0.091)
D180	5.19	3.52	0.004	3.22	2.64	0.005	16.03	10.05	< 0.001
	2.63, 9.87	1.43, 6.94	(0.435)	1.83, 5.61	1.27, 4.71	(0.522)	10.3, 22.7	5.2, 12.4	(0.17)
D360	5.12	3.25	0.074	4.17	2.5	0.245	21.35	8.12	< 0.001
	2.36, 8.92	0.93, 6.73	(0.922)	1.89, 6.06	0.94, 4.83	(0.880)	16.2, 26.2	5.1, 12.3	(0.15)

For each period and treatment Group, Median (first row) and Interquartiles (second row) are shown. p-values of main Treatment effect are in the first row. p-values of the corresponding interaction Treatment-with-Study are beneath (in parentheses).

Concerning the interaction Study–Treatment (i.e. whether or not acamprosate has a greater effect on these measurements in relapsers in some studies than in others), no difference was found in 11 out of 12 tests performed. However, the Study effect (not shown) was always highly significant, indicating that some studies showed better overall outcome than others.

The observed median consumptions were similar across studies for each treatment group. Thus a pooled estimate based on the four periods is reasonable. In averaging the relative differences for each period, the pooled relative difference between consumption Frequency under acamprosate (C_a) and placebo (C_p), $(C_a - C_p)/C_p$, is –26.7%, whereas the analogous relative difference for Quantity is –25.8%.

Finally, the observed proportions of uncontrolled drinkers for each period were found to be similar (Table 4). The difference between treatment groups, adjusted for Study, was from –11% until –14%, with a mean estimated difference of –12.5%. As the studied sample decreases in time, the precision of the estimation (measured by 95% confidence interval) decreases. The treatment effect remained significant and, except for day 30, the heterogeneity of the difference between studies was not suspected. Moreover, the observed power for the three first periods range from 0.89–0.956. Thus, in light of the observed differences, this test was reasonably powered with respect to clinically significant differences.

Discussion

The principal finding of this analysis is that those patients who relapsed and who were taking acamprosate drank less than those relapsers taking placebo. In relapsers, a significant effect of acamprosate in reducing either quantity (Q), or frequency (F) or both was seen for each of the four follow-up periods ($p < 0.001$). The differences were most marked for the product $Q \times F$ (Total Consumption). The difference in consumption was of the order of 10 additional drinks per week in the placebo-treated relapsers. If relapse is defined as drinking five or more drinks per day on average ('uncontrolled drinkers'), the result also favours acamprosate.

Limitations

A first possible limitation, in common with any alcoholism treatment outcome study using self-reported consumption, is the reliability of the consumption data. However, in research studies, self-reported data are shown to be consistent with blood investigations (Fine *et al.*, 1978; Babor *et al.*, 2000) and independent informants (Hesselbrock *et al.*, 1983; Chermack *et al.*, 1998; Babor *et al.*, 2000).

Another possible limitation of our analysis is the lack of precision of the consumption estimates in those studies which used categories for the mean reported number of drinks per drinking day and mean number of drinking days per week. Using categories instead of values, on the one hand, increases residual variance, but is not expected to bias consumption estimates under general conditions of a unimodal, not markedly skewed, distribution (Elderton and Johnson, 1969; Sahai and Misra, 1992). Thus, these estimates, although less efficient, are not biased. In addition, we estimated the central tendency of consumption by using medians on the one hand, and percentage of patients drinking five or more drinks, on the other.

Another criticism might be that a mean estimated consumption cannot differentiate a uniformly distributed consumption in time from a discontinuous, erratic, or occasional consumption, which could indeed be of interest. Aiming for this greater accuracy researchers have sometimes used more complex procedures: diary cards completed daily by the patient, supposedly prospectively

Table 4 'Uncontrolled drinking': meta-analytic estimate of difference of proportion of patients drinking on average five or more drinks per day (random model)

Period	Placebo, %	Acamp, %	Adj Diff	Treat	Homog	Power	Sample size
D30	53%	41%	–13 (–19, –8)	< 0.001	< 0.001	0.956	983
D90	48%	36%	–11 (–19, –8)	0.002	0.224	0.936	927
D180	51%	32%	–14 (–22, –6)	0.001	0.475	0.890	651
D360	51%	33%	–11 (–23, 0)	0.056	0.475	0.469	244

Columns 2 and 3 (Placebo, % and Acamp, %) are the unadjusted percentages of patients drinking on average five or more drinks per day. Fourth column (Adj Diff) is the meta-analytic estimate of the difference in proportions with 95% confidence interval. Treat and Homog are the tests of significance for Treatment effect and Heterogeneity. Power is the observed power, and last column is the sample size.

and Time Line Follow Back where patient and investigator attempt to reconstruct, in detail, drinking day by day. Although these procedures might increase accuracy, they might be criticized as departing widely from normal clinical practice, and therefore artificially having an additional effect on the outcome, possibly even introducing a bias on the measured difference between the two groups.

Finally, these results were obtained from patients who attend assessments. This has several implications. First, our estimate is not generalizable to all the relapsers but only to those in touch with the clinic. Second, because it was necessary to examine the results for each period, several analyses were carried out, and the sample sizes are different because the number of missing patients increases at each period. Thus, conclusions are essentially based on the estimated effect size, and test significances are only indicated as safeguards and do not constitute the most important information. We cannot guarantee excluding a global experiment-wise type 1 error, nor a comparability between the p-values at every period, because the sample sizes are not identical.

The treatment effect

The effect of the acamprosate is modest, with an estimated 29.4% reduction in quantity and 27.8% in frequency. However, the difference is larger when considering the effect on total consumption (estimated reduction of 50.20%). When looking at the proportion of uncontrolled drinkers, an estimated difference of 13% was found. As the Study–Treatment interaction effects were essentially non-significant, we conclude that there is only a small difference, if any, between the treatment effect in different studies. Thus, to the extent that the reliability of the data is accepted, we conclude that a prescription of acamprosate was associated with a reduction in the quantity and frequency of consumption which followed a lapse. Furthermore, because we did not find a significant interaction between Study and Treatment, this finding can be generalized to different sites and different practice conditions.

An analogous effect has been shown in rodents made 'dependent' on ethanol. When re-exposed to ethanol after a period of abstinence, reinstatement of drinking is attenuated by pre-dosing with acamprosate (Spanagel *et al.*, 1996). There is no ready neuropharmacological explanation for this, nor for our result obtained from patients. Acamprosate was believed to act by facilitating inhibitory neurotransmission (mediated by taurine or, more likely by γ-aminobutyric acid) (Dahchour and De Witte, 2000) and by modulating the activity of voltage-dependent calcium channels (Al-Qatari and Littleton, 1998). Recent consensus is that the mechanism of action of acamprosate for its effect on alcohol consumption is attenuation of excitatory glutamatergic neurotransmission in the brain, leading to changes in the reinforcing efficacy of alcohol (Littleton, 1995; Koob *et al.*, 2002).

With any subgroup analysis, because the original matching following randomization may be lost, there is the chance that a confounding factor may become implicated. However, it is hard to conceive why some characteristic of the subgroup, Relapsers, should predispose them to benefit from acamprosate, other than their tendency to relapse, which was the object of our study.

Implications for clinical practice

As for most treatments, especially for a condition of such heterogeneous aetiology as alcohol dependence, all patients do not necessarily respond. Thus for acamprosate, when patients continue to repeat the relapse cycle with unremitting severity, acamprosate prescription should cease and another treatment approach be attempted. However, until that point, a relapse should not be taken, on its own and without re-evaluation, as a reason for stopping acamprosate.

We do not know whether the patients who relapsed in these studies continued to take study medication after starting to drink. However, protocols did not instruct them to stop medication. Thus, we do not know whether the benefit of being in the acamprosate group was because they had taken acamprosate before relapse, or because they continued taking it during the relapse. However, on the basis of this analysis and current knowledge, and because there is no known adverse interaction between ingested alcohol and ingested acamprosate, the advice to patients should be that, if they relapse, they should continue taking the medication. Definitive answers will only be provided by a study in which patients who relapse are randomly allocated to continue acamprosate or switched to placebo.

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Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology

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Abstract

Patients with a diagnosis of alcohol dependence, detoxified and abstinent for 10–30 days, were randomly allocated to placebo or the serotonin reuptake inhibitor, fluvoxamine (up to 300 mg per day), plus counselling and support.

In the intention to treat sample of 493, there was a trend for the fluvoxamine group to do worse than the placebo group on the primary outcome criteria: abstinence; and relapse defined as drinking ≥5 units on an occasion and ≥4 such occasions in a week, or ≥12 units on an occasion (1 unit = 9 g ethanol).

When typology of alcoholism was assigned by scores on the Tridimensional Personality Questionnaire, Types I and II had similar rates of survival without relapse on placebo (PLC I: 19.3%, $n = 135$; PLC II: 18.2%, $n = 110$), but on fluvoxamine Type II did worse than Type I (FLU I: 13.7%, $n = 131$; FLU II: 6.14%, $n = 114$) ($P < 0.01$). When typology was assigned on the basis of age of onset of alcohol problems (≤ or > age 25), early-onset patients in the fluvoxamine group relapsed more frequently than late-onset patients in that group (no longer significant after adjustment for gender), as did those who commenced regular drinking before age 25 (both with and without adjustment for gender). One explanation for our finding could be that impulsivity in early-onset or Type II patients may be accentuated by serotonin enhancement.

Keywords: Alcohol dependence; Outcome; Treatment; Fluvoxamine; SSRI; Typology; Age of onset

1. Introduction

Serotonin neurotransmission may mediate alcohol-seeking behaviour in animals (Lê et al., 1996; Gerald and Higley, 2002). Low levels of serotonin metabolites in the cerebrospinal fluid were noted in detoxified alcohol dependent patients and in alcohol dependent patients who commit suicide (Roy et al., 1987). Evidence suggesting a more general serotonergic abnormality in alcoholics came from studies showing significantly reduced serotonin uptake into platelets from these subjects (Kent et al., 1985), a finding which has been associated especially with those in whom alcohol problems develop early (reviews: Hill et al., 1999; Johnson, 2000).

General practitioners often prescribe serotonergic drugs to patients whose main diagnosis is alcohol dependence. One-fifth of new patients referred to a Scottish alcohol problems clinic in 1999 were already taking an antidepressant prescribed by their general practitioner, usually a specific serotonin re-uptake inhibitor (SSRI) (unpublished report, University of Edinburgh). However, the efficacy of SSRIs in preventing relapse in alcohol-dependent patients is equivocal (see reviews by Lejoyeux, 1996; Pettinati, 1996; Garbutt et al., 1999 and Pettinati et al., 2000a); and two

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sertraline studies published subsequently, namely, Co-kunol et al. (2002) reported a small, transient effect in 59 non-depressed patients, and Gual et al. (2003) reported no effect in 83 depressed patients. The possibility has been raised by Pettinati et al. (2000b), in a study in which sertraline was compared to placebo, that 'Type B' patients (early onset of alcohol dependence, with prominent social problems) (Babor et al., 1992) are a group that do not benefit from SSRIs, and Kranzler et al. (1996) published data suggesting that the SSRI fluoxetine might actually reduce the treatment gains of cognitive behavioural therapy and increase the risk of relapse compared to placebo in Type B patients. Johnson (2000) explored one explanation for this.

Fluvoxamine is a monocyclic SSRI registered worldwide for the treatment of depression and obsessive-compulsive disorder; the therapeutic dose range is 100–300 mg per day. The study reported here, on the efficacy of fluvoxamine in preventing relapse in alcohol dependence, was conceived and executed from 1990 to 1994. Its negative result, though available in 1994, has not been published. However, concerned about the bias which can develop in the medical literature if negative results are not published (Garattini and Liberati, 2000), and questioning whether SSRIs may even be harmful to some alcohol dependent patients (Kranzler et al., 1996), we have returned to our data.

This study had three primary aims: to test fluvoxamine's efficacy in reducing relapse in newly detoxified alcohol dependent patients; to examine fluvoxamine's efficacy, relative to placebo, in alleviating symptoms of depression and anxiety associated with abstinence in alcohol dependence; and to investigate fluvoxamine's safety in the long-term treatment of alcohol dependence. A secondary aim, formulated a priori, was to examine the interaction between pharmacotherapy, outcome, and type of patient defined either according to age of onset regular drinking or of problem drinking, or to the typology of Cloninger (1987a,c). (Limitations to the clinical validity of the original Cloninger typology have since been published (Marcus, 1997; Cloninger, 1999) with classifications which include dimensions of alcohol use and frequency of negative consequences appearing more useful (e.g. Carpenter and Hasin, 2001).)

Reports on characteristics of our study sample and their prognosis have appeared (Meszaros et al., 1996, 1999). Relapse in this sample was predicted by high trait anxiety, and the traits of high novelty seeking and low harm avoidance implying exploratory excitability, impulsiveness, extravagance, disorderliness and uninhibited optimism (Willinger et al., 2002).

2. Materials and methods

The design was a one-year, prospective, randomised, placebo-controlled, multicentre study in parallel groups. Ten sites in the United Kingdom, Eire, Austria and Switzerland participated. The site principal investigators were senior psychiatrists experienced in the treatment of alcoholic patients. Local Committees granted ethical approval.

Patients (of either gender, aged 21 and over) were to have a DSM-III-R diagnosis of alcohol dependence (American Psychiatric Association, 1987) at randomisation, and to have been detoxified and abstinent for 10–30 days.

The *sample size* was calculated on the basis of "the proportions of patients assessed as relapsed to uncontrolled drinking". For these calculations, two analyses were proposed: an analysis of those patients completing the study either by receiving treatment for 1 year, or by dropping-out as a result of relapsing to uncontrolled drinking (the group of "completers"); and an analysis of "the group of all patients" defined as those patients receiving double-blind treatment and providing drug efficacy data—in which all drop-outs were to be regarded as treatment failures. For both analyses the following assumptions were made: that the range of non-completers would be between 10 and 50%; that the relapse rate on placebo would be between 30 and 70%; and that a clinically relevant benefit would be a 50% reduction in relapse rates.

On the basis of these assumptions the numbers of patients per group to be enrolled for an 80% power, 2-tailed, was calculated to be between 43 and 748 depending upon relapse rates, completer rates and choice of group to analyse. However, it was noted that 250 patients per group would suffice if drop-out rates (not due to relapse) did not exceed 50%, the relapse rate on placebo was at least 50%, and the group of all patients was analysed. These assumptions were thought not unreasonable (Pickens et al., 1985; Welte et al., 1983).

The following criteria led to *exclusion* from participation: failure to give signed consent; pregnancy; breast feeding; not wishing to aim for total abstinence; suicidal thoughts; previous schizophrenia; mania; seizure disorder; amnesic disorder; dementia; dependence on psychoactive drugs other than alcohol; clinically important medical illness; use of disulfiram in the 10 days preceding allocation to double-blind treatment; receiving monoamine-oxidase inhibitor or lithium with 10 days of allocation to double blind treatment; previous drug allergies; currently in remission from alcohol dependence.

Randomisation after meeting inclusion and exclusion criteria was within centres, in blocks of eight, four patients per block to each treatment. At randomisation, patients were given the next sequential number at that centre, and received the trial supplies for that patient number. The randomisation code was provided by the department of statistics and data management at Solvay–Duphar B.V. It was maintained in a locked file, and access by monitors or other staff was not possible until after the study database had been locked. Per patient emergency disclosure envelopes were provided to the investigators and to the pharmacies responsible for the storage and dispensing of trials supplies. If an envelope was opened, the investigator had to note the date and reason in the case report form. Such an action automatically terminated the study for that patient.

2.1. Dose selection

The literature available at the point of design of this study suggested that the effect of SSRIs on drinking was seen at relatively high doses, at or above the antidepressant dose. For example, fluoxetine is an effective antidepressant at 20 mg per day while the anti-alcohol effect was seen at 60 mg per day but not at 40 mg (Naranjo et al., 1988).

The choice was made for this study of a fluvoxamine dose of 100–300 mg per day, with the intention to give doses at the higher end of this range if well tolerated. The Company literature had shown that fluvoxamine was effective as an antidepressant at around 100 mg per day in most people.

Fluvoxamine (50 mg) and placebo were supplied in indistinguishable yellow enteric-coated tablets, in numbered containers for dispensing, according to a randomisation schedule held centrally and by the clinic pharmacist. Neither the investigator, their staff, nor the patients were aware of the treatment allocation. No attempt was made to assess how accurately the patient or investigator could guess to which group the patient had been allocated.

2.2. Efficacy measures

The following measures were listed in the protocol as primary efficacy variables:

- the proportion of patients abstinent since the last assessment (with missing values in LOCF analysis (last observation carried forward) replaced by 'not abstinent');
- the proportion of patients not relapsing to uncontrolled drinking since baseline (assessed only at Weeks 12 and 52), defined as 5 or more units on an occasion and 4 or more such occasions in a week, or 12 or more units on an occasion (a unit contained 9 g ethanol i.e. as either: a half-pint of beer, or one glass of wine (11% by volume), or one measure of spirits (40% by volume)); missing values in LOCF analysis were replaced by 'relapsed';
- alcohol dependence severity index (based on the sum of the symptoms listed in DSM-III-R criteria) (missing values in LOCF analysis replaced by baseline value);
- the proportion of days not drinking since last assessment (missing values in LOCF analysis replaced by baseline value for proportion of typical heavy drinking week prior to detoxification).

2.3. Supportive efficacy variables were

- serum gamma glutamyl transferase (GGT);
- clinical global index (CGI) severity of illness score (National Institute of Mental Health, 1976) (missing values in LOCF analysis replaced by last known on-drug score);
- Hamilton depression scale (HAMD) (Hamilton, 1960): total score and depressed mood score;
- STAI-Y state anxiety score (Spielberger, 1983).

The following *informative* measurements were made at intake:

SADQ scale of severity of alcohol dependence (Stockwell et al., 1983) (the dependence severity described above was preferred as an outcome measure to SADQ), the TPQ personality scale (Cloninger, 1987b); answers to the questions 'age at which patient started drinking regularly?' and 'age when drinking became a problem?' (the interview being conducted, and the age entered, by experienced clinicians, mostly psychiatrists); and at intake and at follow-up: mean red cell volume (MCV), breath alcohol, average amount of alcohol consumed per week, visual analogue scale of alcohol craving, ARPQ (the Alcohol-Related Problems Questionnaire on health, family, work, legal adverse consequences: Patience et al., 1997) and proportion of patients not satisfying DSM-III-R criteria for alcohol dependence.

To improve the accuracy of data collected, monitors visited each study site regularly, and checked investigators' case report forms against raw data including patients' hospital case records where appropriate, all subjects having given prior consent to this. The computer database was constructed using a procedure which called for double entry of case report form data, and which had inbuilt checks for erroneous data entry.

2.4. Statistical testing

The data from the contributing centres were to be combined. An all-patient sample was to be used for safety and tolerance analysis and an intention to treat (ITT) sample for efficacy analysis (defined in Fig. 1). Tests were to be two-sided and conducted at the 5% level of significance. No formal adjustments were to be made for multiple testing, though this was to be taken into account before interpreting results should a number of comparisons reached statistical significance.

The TPQ score was to be used according to the Type I/II dichotomy defined by Cloninger (1987a,b,c) in which TPQ score = (Harm avoidance score + Reward-dependence score − Novelty-seeking score) and Type I are patients who exhibit high TPQ sores, while Type II have scores in the opposite direction. The median TPQ score in this study was to be used to differentiate the sample into two types, with those scoring above the median being classed as Type I and those below the median as Type II.

Concordance between the typologies was assessed using Goodman and Kruksal's gamma (http://www2.chass.ncsu.edu/garson/pa765/assocordinal.htm#gamma).

It was specified in the protocol that for each primary efficacy variable an analysis of covariance would be conducted for the Week 52 (LOCF) data, with the covariates being binary indicators: gender, TPQ type and age at onset of regular drinking and of problem drinking—before age 25 versus at/after age 25.

Continuous data were analysed by *t*-tests and parametric analysis of variance. Binary data were analysed by

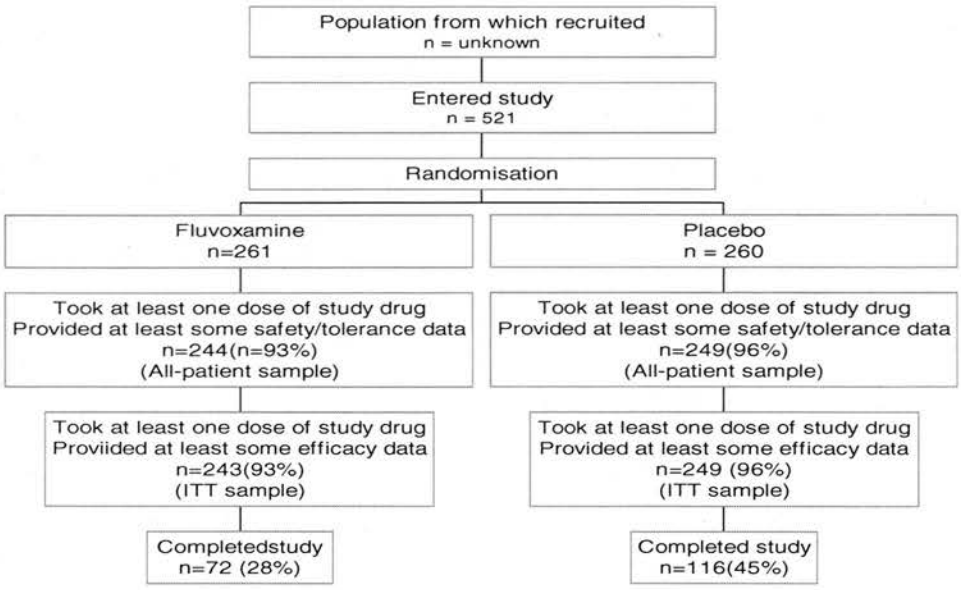

Fig. 1. Recruitment, randomisation and retention.

chi-square tests and binary logistic regression when covariates were included. Ordinal data were analysed by ordinal logistic regression. Assumptions underlying these procedures were checked appropriately and alternative methods considered when assumptions were violated. In particular, the Wilcoxon rank sum test was used when the *t*-test proved invalid in a particular situation. Multiple logistic regression analysis was employed to examine interactions between outcome, treatment group, typology and gender.

2.5. *Concurrent treatments*

2.5.1. *Psychosocial therapy*

The outpatient psychosocial treatment usually offered at each clinic was available to all patients in the study. This varied between centres, but tended to be individual or group therapy according to the precepts of cognitive-behavioural therapy. Patients would often have been advised to attend meetings of Alcoholics Anonymous. The amount of psychosocial treatment received by each subject was not recorded.

2.5.2. *Medication*

Disulfiram was not permitted. All additional psychoactive medications were forbidden, with the exception of night sedation and medication, if required at some point in the study, for alcohol detoxification. Night sedation, prescribed for as short a period and as infrequently as possible was permitted as follows: either chloral hydrate up to 2 g or temazepam up to 20 mg taken 30 min before retiring. Electro-convulsive therapy was forbidden.

If a patient relapsed to dependent drinking and required detoxification, double-blind treatment was suspended and the centre's own typical detoxification regimen was used. Double-blind therapy could be restarted after completion of detoxification and resumption of abstinence.

2.6. *Assessments*

Patients were assessed, usually by the same rater at each occasion, after detoxification on the day of randomisation, and after 2, 4, 6, 8, 12, 16, 24, 32, 40 and 52 weeks of treatment. The scheduled end of the study was Week 52. To allow for flexibility in scheduling appointments, individual patients could receive their final evaluation up to two weeks early or late. They would still be considered to have completed the study, provided that they had also received double-blind medication until this final assessment.

2.7. *Withdrawals*

Should a patient permanently discontinue medication, or be instructed to discontinue study medication before the end of Week 52, he or she was to be considered a premature withdrawal.

Within the first eight weeks, any patient who missed 14 consecutive or 21 cumulative days of double-blind drug was to be withdrawn from the study for non-compliance. The underlying reason for non-compliance was considered when deciding upon the 'reason for termination'. Likewise, the reason for permanently stopping study medication was noted on the withdrawal form, according to predefined categories.

Some patients continuing into the later weeks of the study missed doses of medication for longer periods of time and continued in the study. Such patients could continue, provided that:

- study medication had not been missed for four or more consecutive weeks, medication was retitrated, according to the time off drug,
- the dates of and reason for the drug holiday were documented,
- and every effort was made to perform assessments on schedule.

Should a patient's condition worsen or should a major depressive episode emerge, the investigator had to decide a course of treatment in the patient's best interest. Options included: (1) increase study medication, (2) add concurrent therapy or (3) discontinue study medication and consider alternative therapy. Premature termination could be due to 'relapse to uncontrolled drinking after an adequate trial of study medication (six tablets daily for at least 4 weeks)'; or to 'uncontrolled drinking requiring a medical intervention prohibited by the protocol'.

2.8. Initiation of medication

Patients were instructed to take one tablet during the first 3 days, then two tablets up to Day 7 and three tablets during the second week all at bedtime. After Week 2, the dose could be adjusted, if the patient was not suffering dose-limiting symptoms, according to response. The maximum permitted dose was six tablets per day. For dosages in excess of three tablets, the dose was divided to twice daily. Records of dispensed and returned medication were maintained.

3. Results

3.1. Recruitment and retention

Fig. 1 shows that out of 521 patients who entered the trial 493 took at least one dose of trial drug and contributed at least some efficacy data (ITT sample). From the UK, 331 patients were entered, from Austria 120, from Eire 48 and from Switzerland 22. In age, gender and severity of dependence (Table 1) they are typical of patients treated at specialised alcoholism treatment centres. At entry, there were no differences that reached statistical significance in the characteristics measured of patients allocated to the two treatment groups.

Fewer patients on fluvoxamine (flu) (28%) than on placebo (pla) (45%) completed the study. Table 2 shows the reasons for the higher numbers of drop-outs on fluvoxamine: ineffectiveness, intercurrent illness and adverse experiences (clinical details in Table 4). The mean duration of double-blind treatment was 173 days (S.D. 143, range 2–388, median 131) on fluvoxamine and 231 days (S.D. 144, range 1–399, median 280) on placebo.

Doses were to be titrated to the highest dose allowed by the protocol (six tablets per day). After the sixth week, of patients still taking medication, about twice the number on placebo than on fluvoxamine were receiving the full six tablets.

Table 1
Demographic and baseline clinical data, all-patient sample

	Fluvoxamine	Placebo
Age		
Males	$N = 183$	$N = 183$
Mean (S.D.)	41.6 (10.0)	42.4 (10.0)
Range	21–67	19–72
Females	$N = 61$	$N = 66$
Mean (S.D.)	42.4 (10.4)	41.7 (7.8)
Range	21–68	25–61
Age at start of regular drinking		
Mean (S.D.)	21.5 (8.3)	21.8 (7.6)
Range (median)	12–65 (18)	12–50 (18)
Age at start of problem drinking		
Mean (S.D.)	31.3 (10.9)	31.5 (9.8)
Range (median)	14–66 (30)	15–65 (30)
Current pattern		
Heavy drinking most days	65%	69%
Episodes interspersed with abstinence	5%	6%
Mixed	30%	24%
Number of units in typical week's recent heavy drinking: mean (S.D.)	182 (117)	174 (118)
Number of days drank in typical week: mean (S.D.)	6.3 (1.4)	6.1 (1.5)
DSM-III-R (severity of dependence)		
Mild	5%	5%
Moderate	30%	31%
Severe	66%	64%
SADQ: mean (S.D.)	32.0 (14.4)	32.2 (12.8)
GGT u/l: mean (S.D.) (median)	77 (98) (45)	81 (165) (40)

Efficacy by Week 2, 76% (flu) and 72% (pla) were still abstinent but by Week 12 (LOCF) these proportions had fallen to 42% (flu) and 46% (pla), and by Week 52 (LOCF) to 29% (flu) and 29% (pla). Clearly, there are no differences between the treatment groups on outcome measured as complete abstinence (Table 3).

Fig. 2 shows a trend towards less relapse to uncontrolled drinking in the placebo group than the fluvoxamine group at Week 12 in the LOCF analysis, but the difference is not statistically significant ($P = 0.18$; Table 3).

Table 2
Reasons for withdrawal (numbers of cases) (total sample $n = 492$)

	Fluvoxamine	Placebo
Adverse experiences	34	11
Ineffectiveness	39	23
Intercurrent illness	13	7
Lost to follow-up	53	51
Non-drug related	24	27
Protocol violation	5	4
Death other than suicide	1	1
Attempted suicide	3	8

Table 3
Primary efficacy variables: ITT sample

		Completely abstinent since last assessment	Not relapsed since baseline	Mean dependence severity (1–6)	Days not drinking since last assessment
(a) LOCF					
Week 12	Fluvoxamine ($N = 243$)	42%	54%	2.9	69%
	Placebo ($N = 249$)	46%	60%	2.5	77%
	P-value	0.40	0.18	**0.029**	**0.009**
Week 52	Fluvoxamine ($N = 243$)	29%	36%	3.6	56%
	Placebo ($N = 249$)	29%	36%	3.5	62%
	P-value	0.94	0.47	0.42	0.13
(b) Observed cases					
Week 12	Fluvoxamine ($N = 151$)	50%	64%	2.5	83%
	Placebo ($N = 192$)	54%	69%	2.0	87%
	P-value	0.46	0.38	0.087	0.081
Week 52	Fluvoxamine ($N = 75$)	55%	55%	2.4	88%
	Placebo ($N = 117$)	63%	63%	2.3	88%
	P-value	0.24	0.24	0.75	0.99

In the LOCF analysis, at Week 12 the percentage of days not drinking since the last assessment and the mean dependence severity was significantly more favourable for the placebo group. In the observed cases analysis (i.e. including only those on whom an assessment was made), there were non-significant trends ($P < 0.10$) at Week 12 for these two measures in favour of placebo. There were no statistically significant differences between the two treatment groups at the Week 52 endpoint for any of the four primary efficacy variables.

3.2. Supportive efficacy variables

CGI: observed case analyses showed no difference between treatment groups on the score change from Day 1 for CGI at any assessment point. However, there were hints that the outcome may be slightly less favourable on fluvoxamine than on placebo in the CGI severity score change ($P < 0.10$) at Weeks 12 and 52 on LOCF analyses. This was not found at Week 24 LOCF.

HAMD total score: scores were low at baseline (mean 10, range 0–41) and fell in both groups during treatment, with no statistically significant treatment-related effects.

HAMD depressed mood item. No significant differences between treatment groups were found.

STAI-YI: in general, no treatment related effects were present. At one time point (Week 24) on one analysis (number of patients with a 12-point fall from baseline), separation ($P = 0.035$) was shown in favour of fluvoxamine.

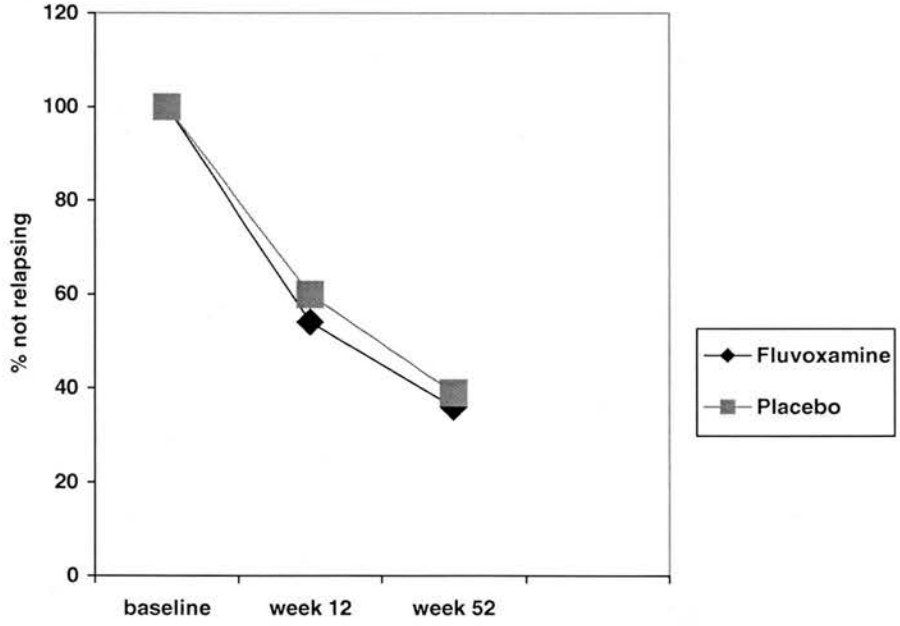

Fig. 2. Proportion of patients not relapsing to uncontrolled drinking since baseline: ITT sample, analysis based on last observation carried forward (LOCF) ($n = 492$).

3.3. Informative variables

Breath alcohol: at two time-points, fluvoxamine-treated patients were found to have higher mean breath alcohol levels than placebo treated patients; Week 12, $P = 0.012$ and Week 32, $P = 0.023$. The converse never occurred.

ARPQ: at three out of eight time-points on which total alcohol-related problems were scored, fluvoxamine-treated patients were rated as having more problems than patients on placebo (Week 4, $P = 0.064$; Week 16, $P = 0.006$; Week 40, $P = 0.042$).

GGT: no treatment-related effects were found.

Craving: no treatment-related effects were found.

3.4. Covariates affecting efficacy results

No sub-group analysis was made of patients who had the higher depression scores at intake. The finding that the fluvoxamine group did not benefit in terms of HAMD scores more than placebo suggests that such a post hoc analysis would not have been fruitful.

3.5. Typology by TPQ score

Table 5 shows data on relapse by typology and by treatment group, with all missing values deemed 'relapse'. Types I and II, categorised according to TPQ scores (Cloninger), had similar rates of survival over 52 weeks without relapse on placebo (PLC I: 19.3%, $n = 135$; PLC II: 18.2%, $n = 110$), but on fluvoxamine Type II did worse than Type I (FLU I: 13.7%, $n = 131$; FLU II: 6.1%, $n = 114$) (log rank test, $P = 0.0006$). (This effect was visible already at Week 12 (log rank test, $P = 0.0007$); data not shown.) The corollary of this is that Type II patients did worse on fluvoxamine than on placebo. This was not the case for Type I patients, whose outcome was about the same on either drug. The data for Week 52 are shown in Table 4.

3.6. Typologies by ages of onset

There were 243 subjects who reported starting regular drinking below age 25, and of these 130 also had their first problems before that age, concordance between these parameters being low (gamma = 0.067; where there is complete concordance, gamma = 0.5). There was also little concordance between TPQ score (high/low) and start of regular drinking (below/at or after 25 years) (gamma = 0.094) and age of onset of problems (below/at or after 25 years) (gamma = 0.057).

Table 4
Percentages of patients at Week 52 who had not relapsed (all patient sample) alcoholism typology according to TPQ

Fluvoxamine ($N = 260$)		Placebo ($N = 260$)	
Type I	Type II	Type I	Type II
$N = 131$	$N = 114$	$N = 135$	$N = 110$
13.7%	6.14%	19.3%	18.2%

Chi-square test: $P = 0.0172$. Log rank test: $P = 0.000602$.

Age of start of regular drinking was a slightly stronger predictor of relapse by 52 weeks ($P = 0.0224$) than age of onset of problems ($P = 0.0537$). The predictive effect was greatest for relapse in first 16 weeks: for age of start of regular drinking, $P = 0.0048$, and for age of onset of problems, $P = 0.0438$. If adjustment is made for gender as an additional explanatory variable, age of regular drinking below 25 still predicts both relapse by 52 weeks ($P = 0.0299$) and relapse by 16 weeks ($P = 0.0056$).

Males tended more often than females to report an onset of regular drinking and of problems before age 25. Gender affected subjects' response to treatment, males responding better to placebo than fluvoxamine which was an interaction that was not seen for females (log rank test, $P = 0.0052$; Week-52 data). Therefore, the interaction between age of onset typology and treatment was examined adjusted for gender. Adjusted for gender, onset of problems before age 25 did not predict poor response to fluvoxamine (log rank test, $P = 0.143$) though numbers in some cells being small may have affected accuracy. Unadjusted for gender, interaction with treatment was significant (log rank test, $P = 0.002$), with onset of problems before age 25 indicating poorer response to fluvoxamine.

For age of start of regular drinking, adjusting for gender does not significantly reduce the interaction: fluvoxamine patients are still more likely to have relapsed at 52 weeks than placebo patients ($P = 0.0117$) (Table 5). When males only are examined, the interaction between age of start of regular drinking, and treatment group, is still significant ($P = 0.0124$).

Table 5
Multiple logistic regression: relation between treatment group, age of start of regular drinking and gender (all patient sample)

	Estimate	Standard error	Z-value	Pr (>[Z])
Intercept	2.018	0.131	6.746	9.4×10^{-11} [a]
Treatment group	−0.666	0.264	−2.520	0.0117[b]
Age of start of regular drinking <25 years	−0.345	0.570	−0.605	0.5450
Gender	−0.005	0.309	−0.017	0.9862
Interaction: gender × start of regular drinking <25 years	1.498	0.710	2.111	0.0348[b]

[a] Highly significant.
[b] Significant.

Table 6
Adverse events reported by at least two patients in the fluvoxamine-treated group and reported at least twice as often as patients on placebo

Adverse experience	Number of reports: fluvoxamine	Number of reports: placebo
Asthenia	5	1
Abdominal pain	3	0
Anorexia	3	0
Diarrhoea	9	1
Nausea	10	3
Agitation	5	1
Anxiety	3	0
Depression	8	4
Hallucinations	2	0
Insomnia	4	0
Manic reaction	3	0
Paranoid reaction	3	0
Tremor	2	0
Rash	2	0
Sweat	2	0

Adverse events Table 6 shows the adverse experiences that occurred more often in the fluvoxamine than the placebo group. Asthenia, abdominal pain, diarrhoea, nausea, agitation and tremor are typical of a selective serotonin reuptake inhibitor. The frequencies of these events are typical of studies with fluvoxamine at this dosage in other indications. It is notable that suicide attempts occurred in eight of the placebo patients but only in three of the fluvoxamine group.

Two deaths occurred during the study. A 63-year-old male placebo-treated patient died suddenly, after only 7 days in the study. One fluvoxamine-treated patient (a 54-year-old male) died following a massive haematemesis from oesophageal varices after 31 days of treatment. Oesophageal varices are a long-term consequence of alcoholic liver cirrhosis. The investigator on site did not attribute this death to the study drug.

4. Discussion

This study shows no evidence that fluvoxamine helps prevent relapse in detoxified, abstinent, alcoholics. On the contrary, fluvoxamine was associated with worse outcome than placebo for early-onset drinkers, or Type II on the basis of their TPQ scores. If the outcome overall was no different for fluvoxamine than for placebo, and a worse outcome was seen with fluvoxamine than for Type II, why did the data not show a 'balancing' advantage for fluvoxamine in Type I? The reason, we suggest, is that although the overall result showed that outcome for fluvoxamine was not significantly different from the outcome for placebo, there was nevertheless a trend towards a worse overall outcome for fluvoxamine—attributable to the harmful effect (which reached significance) in Type II patients.

There was a high drop-out, especially in fluvoxamine-treated patients, and thus for analysis a procedure that permits missing values to be entered was necessary. LOCF analysis is such a method. On LOCF analysis, at Week 12, fluvoxamine-treated patients appear to be drinking on more days, and appear to have a worse dependence severity score. Observed cases analyses only showed a trend towards that effect which suggests that perhaps the apparent differences between the two treatment groups can be accounted for by the adoption of the "worst-case" LOCF analyses. Three explanations will be considered for the three-way association between being in the fluvoxamine group, dropping-out of the study and drinking more with more problems.

First, in the LOCF analyses, drop-outs were allocated baseline DSM-III-R alcoholism dependence severity derived index scores, and were assumed to be drinking. There were more drop-outs on fluvoxamine, so fluvoxamine seems to have a negative effect as an artefact of entering LOCF values. Frequent drop-out on fluvoxamine was noted by Kranzler et al. (1993), who aborted a placebo-controlled study of fluvoxamine in alcoholism because 6 out of 10 subjects given fluvoxamine withdrew due to side effects (nausea, headache and sedation) and 2 out of 10 due to return to heavy drinking, compared to one placebo-treated patient who withdrew due to return to heavy drinking and none due to side effects.

A second explanation is that perhaps subjects on fluvoxamine drank more as a result of dropping-out, albeit due to their intolerance of the drug, because they did not continue to benefit from other aspects of the treatment offered at the clinic.

Third, perhaps SSRIs by themselves increase the risk of drinking in some patients. This could be due to adverse-effects. Many of the symptoms reported in excess on fluvoxamine resemble alcohol withdrawal symptoms (diarrhoea, nausea, anxiety, agitation, insomnia, tremor). Patients are used to self-medicating themselves to reduce withdrawal symptoms. Or it could be due to an action of an SSRI which increases, in some patients, the likelihood of relapse. For example, anecdotally, patients being treated for depressive or anxiety disorders sometimes report feeling more carefree and optimistic, even more ready to take risks. Indeed, this may be one explanation for the success of the SSRIs in obsessional patients crippled by over-cautiousness. The patient who is newly abstinent from alcohol may do best if he is very cautious and does not take risks especially with alcohol. Poor prognosis in our sample was predicted by risk-taking, and impulsive traits (Willinger et al., 2002) and conceivably this could be exacerbated by an SSRI.

4.1. Typology analysis

Our result replicates that of Kranzler et al. (1996) who found that random allocation to fluoxetine rather than placebo impaired drinking outcome of 'Type B' alcoholics (who are in part defined as early onset). The result also recalls that of Pettinati et al. (2000a), who found that

sertraline, while benefiting Type A alcoholics, had no effect in Type B patients. There was variation between sites in our study in the psychosocial intervention received by the subjects, which could theoretically have been a confounder, but the fact that the above two studies which used manualised therapies found a similar typology relationship supports the typology construct we report here.

One explanation for our finding is that impulsivity in Type B patients, instead of being reduced by serotonin enhancement as previous authors suggested, may be worsened. Another could be that early onset regular drinkers or Type II subjects (cf. Type 'B') patients are more prone to drink to reduce the side effects of these drugs such as agitation or insomnia.

In the only other published completed randomised controlled study of fluvoxamine in preventing relapse in alcohol dependent patients (Angelone et al., 1998), fluvoxamine (150 mg per day) was associated with nearly twice the abstinence rate over 16 weeks as the no-tablets control group. That was a single-blind study. Note that in this study the fluvoxamine group had a relatively high proportion of women (40%) and tended to be 'late onset patients' (mean age 44.8 years, mean duration of alcohol dependence 107 months).

A possibly relevant finding with the SSRI citalopram has been reported by Berggren et al. (2001). They found that alcohol-dependent patients who had low or no prolactin response to fenfluramine (a measure of central serotonergic function), tended to have a worse drinking outcome than patients with a more normal prolactin response. Deficient serotonergic responsivity is one feature of early onset alcoholism (Roy et al., 1987; Fils-Aime et al., 1996). It is possible that a serotonin antagonist is a more appropriate medication, if one is to be offered, for a Type II or early-onset patient (Johnson, 2000).

5. Conclusion

Systematic reviews find that serotonergic medications probably only benefit alcoholics who have a definite depressive illness or anxiety disorder (Garbutt et al., 1999). Our fluvoxamine study adds to other data suggesting that, unless there is an over-riding clinical reason such as specific psychiatric co-morbidity, caution should be exercised in the use of SSRIs in patients whose regular drinking commenced before age 25 or who report problems from their drinking before age 25.

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Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study

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Abstract

Objective To compare the risk of non-fatal self harm and suicide in patients taking selective serotonin reuptake inhibitors (SSRIs) with that of patients taking tricyclic antidepressants, as well as between different SSRIs and different tricyclic antidepressants.

Design Nested case-control study.

Setting Primary care in the United Kingdom.

Participants 146 095 individuals with a first prescription of an antidepressant for depression.

Main outcome measures Suicide and non-fatal self harm.

Results 1968 cases of non-fatal self harm and 69 suicides occurred. The overall adjusted odds ratio of non-fatal self harm was 0.99 (95% confidence interval 0.86 to 1.14) and that of suicide 0.57 (0.26 to 1.25) in people prescribed SSRIs compared with those prescribed tricyclic antidepressants. We found little evidence that associations differed over time since starting or stopping treatment. We found some evidence that risks of non-fatal self harm in people prescribed SSRIs compared with those prescribed tricyclic antidepressants differed by age group (interaction $P = 0.02$). The adjusted odds ratio of non-fatal self harm for people prescribed SSRIs compared with users of tricyclic antidepressants for those aged 18 or younger was 1.59 (1.01 to 2.50), but no association was apparent in other age groups. No suicides occurred in those aged 18 or younger currently or recently prescribed tricyclic antidepressants or SSRIs.

Conclusion We found no evidence that the risk of suicide or non-fatal self harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants. We found some weak evidence of an increased risk of non-fatal self harm for current SSRI use among those aged 18 or younger. However, preferential prescribing of SSRIs to patients at higher risk of suicidal behaviour cannot be ruled out.

Introduction

Data in adults have not consistently shown any influence on suicide or self harm from use of selective serotonin reuptake inhibitor (SSRI) antidepressants.[1] Randomised controlled trials in young people, however, indicate that they may increase the risk of suicidal thoughts and self harm in those aged under 19.[2 3]

The most comprehensive studies of suicidal behaviour are based on data from the General Practice Research Database.[4 5] The first found some evidence of an increased risk of suicide among people prescribed fluoxetine,[4] but the drug's safety in overdose may have led to selective prescription to people at risk of self harm. The other study found no notable differences between a range of antidepressants and risk of fatal or non-fatal suicidal behaviour.[5] However, the study was not restricted to patients treated for depression and examined only four antidepressants.

We report a nested case-control study, based on the General Practice Research Database, of patients with a new diagnosis of depression who were prescribed antidepressants for the first time between 1995 and 2001. We compared the risk of non-fatal self harm and suicide in association with the use of SSRIs and tricyclic antidepressants.

Methods

Materials

Our cohort comprised patients aged 10 to 90 years with a first recorded prescription for antidepressants between 1 January 1995 and 31 December 2001. Members of the cohort were required to have contributed a minimum of 365 days to the database before their first recorded prescription for antidepressants and to have received a diagnosis of depression in the 180 days before or 90 days after entry to the cohort. The date of the first prescription of antidepressants defined entry to the cohort. Follow up ended with the earliest of either an episode of suicidal behaviour, the end of the first treatment episode, the end date of the study, or when the patient left the practice.

We identified depression by a set of Read and Oxford Medical Information System (OXMIS) medical terms indicative of depression, bipolar disorder, or dysthymic disorder. We classed severity of depression as mild, moderate, or severe (see bmj.com). We categorised antidepressants into three classes: tricyclic and related antidepressants, SSRIs, and other antidepressants (see bmj.com).

We studied two outcomes, non-fatal self harm and suicide, using the relevant medical terms, review of the patient's free text notes, and death certificates when available (around 60% of cases).

We selected a random sample of up to 20 controls for each case from the cohort, matching for sex, year of birth within one year, and duration of cohort membership. We derived the duration of prescriptions from the quantity of drug prescribed and the daily dose plus an additional seven day washout period (see bmj.com).

Data analysis

We classified the cases and controls as currently or previously exposed to an SSRI, tricyclic antidepressant, or

P+ *A classification system for the severity of depression, the method used to measure exposure to antidepressants, and supplemental tables are on bmj.com*

ELPS *This is the abridged version; the full version is on bmj.com*

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Table 1 Characteristics of study cohort according to first antidepressant class prescribed. Values are numbers (percentages) unless otherwise indicated

Characteristic	SSRIs (n=90 403)	Tricyclic antidepressants (n=50 829)	Other antidepressants (n=4863)	Total (n=146 095)
Age in years:				
10-18	3830 (4)	1316 (3)	141 (3)	5287 (4)
19-30	23 561 (26)	10 145 (20)	1086 (22)	34 792 (24)
31-45	31 541 (35)	15 431 (30)	1548 (32)	48 520 (33)
46-60	18 310 (20)	11 506 (23)	989 (20)	30 805 (21)
61-75	7949 (9)	7538 (15)	605 (12)	16 092 (11)
76-89	5212 (6)	4893 (10)	494 (10)	10 599 (7)
Women	58 444 (65)	33 399 (66)	2924 (60)	94 767 (65)
Men	31 959 (35)	17 430 (34)	1939 (40)	51 328 (35)
Median (interquartile range) duration of observation (years)	0.67 (0.57-1.03)	0.65 (0.57-1.02)	0.65 (0.57-1.02)	0.66 (0.57-1.03)
Severity of depression:				
Mild	60 537 (67)	36 893 (72)	3306 (68)	100 736 (69)
Moderate	26 710 (30)	12 116 (24)	1329 (27)	40 155 (27)
Severe	3156 (3)	1820 (4)	228 (5)	5204 (4)
Referral to psychiatrist or psychologist*	721 (1)	211 (0)	75 (2)	1007 (1)
History of self harm†	479 (1)	201 (0)	33 (1)	713 (<1)
Concomitant conditions:				
Diagnosis of, or therapy for, anxiety and panic disorders	21 501 (24)	11 209 (22)	1476 (30)	34 186 (23)
Schizophrenia	101 (0)	97 (0)	10 (0)	208 (0)
Antipsychotic therapy	2947 (3)	1916 (4)	252 (5)	5115 (4)
Drug misuse	61 (0)	45 (0)	3 (0)	109 (0)
Alcohol misuse	2408 (3)	1269 (2)	184 (4)	3861 (3)

*In year previous to index day.
†Includes drug overdose, poisoning, self laceration, and other non-fatal suicidal attempts before entry to cohort.

other antidepressant, or co-exposed to more than one antidepressant, according to the exposure status on the index day (day of self harm or suicide or equivalent control day). We standardised the incidence rates to the UK population in 2001.

We assessed risks associated with "current exposure" by using multivariable conditional logistic regression controlling for a range of possible confounding factors (see bmj.com). We investigated whether risk varied in relation to duration of current use of antidepressants, time since stopping treatment, and age at entry to the cohort (10-18, 19-30, and >30). We stratified by the duration of exposure (days) to antidepressants and time since discontinuation. In all comparisons, we compared SSRI monotherapy with tricylic antidepressant monotherapy for the same duration of exposure.

Results

Our cohort included 146 095 patients with a first prescription for an antidepressant for depression, contributing 62 224 person years of follow (see bmj.com). Almost twice as many women as men received antidepressants. SSRIs were the most commonly prescribed antidepressants. People prescribed SSRIs tended to be younger, with a more frequent history of self harm and referral to psychiatrists than those prescribed tricyclic antidepressants (table 1).

The strongest predictors of non-fatal self harm were a history of self harm, referral to a psychiatrist, alcohol misuse, and drug misuse. The strongest predictors for suicide were a history of non-fatal self harm, antipsychotic therapy, number of antidepressants prescribed in the previous year, alcohol misuse, and referral to a psychiatrist.

Over the study period, 1968 people had a record episode of non-fatal self harm: 1344 were exposed antidepressant medication at the time, and 624 h stopped treatment before the episode. Drug overdo accounted for most episodes of non-fatal self ha (81%). The incidence rate of non-fatal self harm, star ardised by age and sex, per 100 000 person years follow up among people prescribed antidepressa was 2894 (95% confidence interval 2618 to 3170). T rate per 100 000 person years for men was 2834 (25 to 3089) and for women was 2952 (2471 to 3432).

Overall, 69 suicides took place (56 men, women); 36 of those people were taking antidepr sants at the time of death. The overall standardis incidence rate for suicide was 62 (40 to 85) per 100 0 person years; in men this was 117 (72 to 163) and women 9 (1 to 18).

The adjusted odds ratio for non-fatal self ha among SSRI users compared with users of tricy antidepressants was 0.99 (0.86 to 1.14). We found evidence that the risk of non-fatal self harm var among the different individual SSRIs or tricy antidepressants (P=0.35 and P=0.69, respectiv and no evidence of an increased risk of suicide asso ated with use of SSRIs compared with tricyclic anti pressants (odds ratio 0.57, 0.26 to 1.25; table 2).

We found borderline evidence that the risk of n fatal self harm (P for interaction = 0.05), but not suic (P for interaction = 0.73), differed between the differ antidepressant categories in relation to time si starting therapy. This association showed no cl pattern.

We found evidence of a difference in risk non-fatal self harm for current SSRI users compa with current users of tricyclic antidepressants

Table 2 Risk of non-fatal self harm and completed suicide in people prescribed SSRIs, other antidepressants, or exposed to more than one antidepressant compared with people prescribed tricylic antidepressants and among specific SSRIs compared with paroxetine and specific tricyclic antidepressants compared with dothiepin (all ages)

	Non-fatal self harm				Completed suicides			
Exposure	Cases (n=1344)	Controls (n=19 953)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	Cases (n=36)	Controls (n=664)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any current use of tricylic antidepressant	319	4901	1	1	15	201	1	1
Any current use of SSRIs	854	13 636	0.97 (0.85 to 1.12)	0.99 (0.86 to 1.14)	17	406	0.59 (0.28 to 1.27)	0.57 (0.26 to 1.25)
Other antidepressants	86	894	1.30 (1.01 to 1.68)	0.99 (0.76 to 1.29)	3	28	1.51 (0.39 to 5.85)	0.80 (0.16 to 4.06)
Co-exposure†	85	522	2.55 (1.96 to 3.31)	1.53 (1.15 to 2.04)	1	29	-	-
Specific SSRIs:								
Paroxetine	289	4209	1	1	8	135	1	1
Citalopram	128	1915	1.03 (0.83 to 1.29)	1.01 (0.80 to 1.26)	2	5	-	-
Fluoxetine	304	5239	0.88 (0.74 to 1.04)	0.94 (0.79 to 1.11)	6	159	0.60 (0.20 to 1.81)	0.42 (0.13 to 1.39)
Fluvoxamine	42	810	0.74 (0.52 to 1.03)	0.73 (0.52 to 1.04)	0	29	-	-
Sertraline	91	1463	0.92 (0.72 to 1.17)	0.86 (0.67 to 1.10)	1	33	-	-
Specific tricyclic antidepressants:								
Dothiepin	136	2334	1	1	7	102	1	1
Amitriptyline	66	926	1.21 (0.89 to 1.65)	1.18 (0.86 to 1.61)	2	31	-	-
Lofepramine	68	1096	1.11 (0.82 to 1.50)	1.08 (0.79 to 1.47)	4	47	1.12 (0.30 to 4.20)	0.94 (0.24 to 3.61)
Other tricylic antidepressant	49	545	1.43 (1.01 to 2.02)	1.19 (0.83 to 1.69)	2	21	-	-

*Adjusted for severity of depression; time depression was diagnosed in relation to start of therapy; referral to psychiatrist or psychologist before index day; history of self harm; diagnosis of, or treatment for, anxiety or panic disorder; schizophrenia; antipsychotic drugs; drug misuse; and alcohol misuse.
†Any exposure to more than one antidepressant of same class or different classes.

relation to age (P for interaction = 0.02), with an increased risk associated with SSRI use among those aged 18 or younger, but not in 19 to 30 year olds or those older than 30 (table 3).

In people aged 18 or younger, we found no evidence of any difference in risk of non-fatal self harm between individual tricyclic antidepressants, but among SSRIs (figure), the greatest risk was in relation to paroxetine use.

The risk of non-fatal self harm or suicide did not seem to differ between or within antidepressant classes according to the time since stopping treatment (see bmj.com).

Discussion

In patients with newly diagnosed depression treated with antidepressants for the first time, we have found no evidence that the risk of suicide or non-fatal self harm in people currently prescribed SSRIs is higher than in those prescribed tricyclic antidepressants.

We found no strong evidence of variability in the risk of non-fatal self harm between substances or between drug classes associated with time since starting or stopping antidepressant therapy. However, in patients aged 18 or younger, we found the risk of non-fatal self harm was higher in people prescribed SSRIs than with tricyclic antidepressants. In this age group, we found a weak indication that the risk of non-fatal self harm among users of the SSRIs studied is highest in those who used paroxetine. These findings are in keeping with those of Jick et al.[5]

Limitations

SSRIs are relatively non-toxic in overdose; it is possible that they were selectively given to individuals at higher risk of overdose and that SSRI overdose did not result in presentation to hospital or general practice.

Table 3 Risk of non-fatal self harm in people prescribed SSRIs compared with tricyclic antidepressants in relation to age

	Non-fatal self harm			
Exposure	Cases (n=1344)	Controls (n=19 953)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
10-18 years†:				
Any current use of tricyclic antidepressants	24	493	1	1
Any current use of SSRIs	168	2148	1.73 (1.10 to 2.72)	1.59 (1.01 to 2.50)
19-30 years:				
Any current use of tricyclic antidepressants	106	1687	1	1
Any current use of SSRIs	312	5013	1.00 (0.79 to 1.27)	1.04 (0.82 to 1.32)
>30 years:				
Any current use of tricyclic antidepressants	189	2721	1	1
Any current use of SSRIs	374	6475	0.83 (0.69 to 1.01)	0.86 (0.71 to 1.04)

Participants exposed to more than one antidepressant or prescribed non-SSRI, non-tricyclic antidepressants (see table 2) were included in models but, for presentational purposes, data are not given in table.
*Adjusted for severity of depression; time depression was diagnosed in relation to start of therapy; referral to psychiatrist or psychologist before index day; history of self harm; diagnosis of, or treatment for, anxiety or panic disorder; schizophrenia; antipsychotic drugs; drug misuse, and alcohol misuse.
†Includes nine cases of non-fatal self harm and 86 controls exposed to SSRIs, and no cases and 18 controls exposed to tricyclic antidepressants among patients aged 10 to 14 years.

Previous self harm is an important predictor of further self harm and suicide. The prevalence of recorded past self harm among study members who harmed themselves (<5%) is considerably lower than reported among case series of people who harmed themselves (50%)[6] and completed suicides (30% to 47%),[7] which indicates the possibility of residual confounding if non-fatal self harm is recorded differentially for SSRIs compared with tricyclic antidepressants. Three other limitations are worth noting. Firstly, we assumed prescribing to be a marker for exposure, but not all prescriptions are dispensed, and some of those dispensed are not taken. Secondly, it is possible that some associations may be chance findings. Thirdly, we did not deal with the question of whether people treated with SSRIs are at greater risk of self harm than those with equivalent morbidity who do not receive treatment. We have assessed risk only relative to people receiving tricyclic antidepressants.

Representativeness of the study

The suicide rate in our study (62 per 100 000 patient years) was higher than in the general population (9 per 100 000 people). The incidence of non-fatal self harm was seven times higher than that of around 400/100 000 in 1995 reported in Oxford.[8] The ratio of cases of non-fatal to fatal self harm (approximately 30:1) in our study approximates to the ratio of the estimated number of hospital presenting episodes of self harm (n=142 000)[8] and suicides in the general population of England and Wales (n=5000).[9]

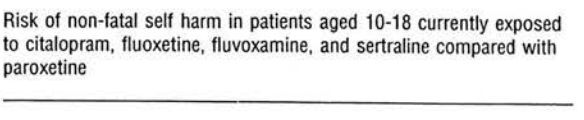
Potential biases

Our findings for people younger than 19 are consistent with the results from randomised controlled trials,[2 3] but they may have resulted from confounding by indication. For example, patients with personality disorders and adjustment disorders may be given a diagnosis of depression in primary care and be prescribed SSRIs.

Strengths of the study

The main strengths are the large sample size, detailed exposure data, and confounder information. Our study covered 1995 to 2001 and patients with a first prescription of antidepressants in this period. Furthermore, our approach to the ascertainment of cases of non-fatal self harm and suicides gives us considerab more power than previous studies.

We have endeavoured to control as closely as poss ble for factors that may be associated both with the ri of suicidal behaviour and the choice of antidepressar



Risk of non-fatal self harm in patients aged 10-18 currently exposed to citalopram, fluoxetine, fluvoxamine, and sertraline compared with paroxetine

What is already known on this topic

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressant.

Evidence from recent clinical trials shows that SSRIs may increase the risk of self harm and suicidal thoughts in children and adolescents

Previous studies of the risk of suicide in adults have been restricted to the four most frequently prescribed antidepressants and have lacked statistical power to identify whether risks differ in children compared to adults

What this study adds

Risks of self harm and suicide were no different in adults prescribed SSRIs compared with those prescribed tricyclic antidepressants.

Children and adolescents prescribed SSRIs seemed possibly to be at increased risk of self harm compared with those prescribed tricyclic antidepressants

No children taking antidepressants in this study committed suicide

The absence of excess risk of self harm in adult users of SSRIs may be interpreted as reassuring evidence of their safety or that any adverse or protective effects of SSRIs are no different from those seen with other antidepressants.

Conclusion

As prescribing to adults accounts for over 95% of an depressant use in the United Kingdom, our findir that SSRIs and tricyclic antidepressants have a simil risk profile with respect to suicide and non-fatal se harm is reassuring. It is possible, however, that ar adverse or protective effects are common to all class of antidepressants. Further research, based on larg randomised trials, should assess the long term ar short term risk and benefits of antidepressants ar compare these with non-pharmacological therapi for depression in adults.

We thank the ongoing dedicated contribution of clinical a support staff in the general practices, which supply data for t General Practice Research Database, and of the National Visi User Group; E M Bain for help in coding the severity of depr sion; Klaus Ebmeier for helpful comments on the classificati of the antidepressant drug classes; and members of t Medicines and Healthcare products Regulatory Agency Expe Working Group on SSRIs for comments on design, presen tion, and methods.

Contributors: See bmj.com

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Competing interests: The UK Committee on Safety Medicines established an expert working group to conduct

review of the safety of SSRIs. No members of the expert working group have financial interests in any of the companies that hold marketing authorisations for SSRIs. The MHRA funded the study and professional staff at the MHRA, including JM and LW, have been acting as secretariat to or observers on the expert working group's review. Neither JM nor LW have any personal financial interests in any drug product. DG, JC, and DA are members of the MHRA's expert working group on the safety of SSRIs, and DA is a member of the Committee on Safety of Medicines. They act as independent advisers, receiving travel expenses and a small fee for meeting attendance and reading materials in preparation for the meeting. DA has spoken on the methodology of adverse drugs reactions in HIV at a scientific meeting attended by several pharmaceutical companies and sponsored by GlaxoSmithKline (GSK). A honorarium was paid to her department. SE has no personal interests to declare. His department receives funding from many pharmaceutical companies, including GSK, but mainly for methodological research. SE has no direct involvement in any of this. The General Practice Research Database Division receives funding for services, including the conduct of commissioned research, from a wide range of public sector bodies and the pharmaceutical industry. CM and SR have no competing interests to declare.

Ethical approval: General Practice Research Database Scientific and Ethical Advisory Group.

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Subfecundity and neonatal mortality: longitudinal study within the Danish national birth cohort

Olga Basso, Jørn Olsen

Treatment for infertility correlates with adverse outcomes in pregnancy, especially in singleton deliveries.[1] A long time to pregnancy (subfecundity) also correlates with adverse outcomes,[2-4] but few studies evaluating treatment take subfecundity into consideration. We explored the association between time to pregnancy and neonatal death in the Danish national birth cohort.

Participants, methods, and results

We identified 27 624 firstborn singleton babies, born alive from the 24th week of gestation between March 1998 and December 2001, whose mothers were enrolled in the Danish national birth cohort.[4 5] Mothers had been interviewed during pregnancy (50% by the 16th completed week and 95% by the 25th) and asked about pregnancy planning and other factors.

Women who reported having planned or partly planned their pregnancy were asked how long it had taken them to conceive. If the answer was six months or longer, they were further asked whether they had received infertility treatment. We excluded 402 women reporting infertility treatment after less than one year of trying and 11 women with missing data on smoking. We analysed 27 329 births (with 66 deaths within 28 days of life (0.24%)). Age at death was recorded in the Danish birth registry.

We grouped women into five categories: up to two months of waiting time (reference); 3-12 months; >12 months, no infertility treatment; >12 months, treatment reported; and non-planners (including part planners). We examined the association between these categories and neonatal death through logistic regression, adjusting for mother's age, body mass index, smoking, and social class, the latter derived from the mother's job title.[4]

The risk of neonatal death increased with increasing time to pregnancy (table). Death between the 29th and the 365th day of life was not related to time to pregnancy (data not shown).

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Neonatal deaths (per 1000 births) as a function of time to pregnancy and treatment and crude and adjusted logistic regressions

Time to pregnancy or treatment	Deaths/births (per 1000)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
<3 months	13/8361 (1.55)	1.00	1.00
3-12 months	22/7944 (2.77)	1.78 (0.90 to 3.54)	1.76 (0.89 to 3.50)
>12 months	18/4142 (4.35)	2.80 (1.37 to 5.73)	2.82 (1.35 to 5.90)
No treatment reported	11/2104 (5.23)	3.38 (1.51 to 7.54)	3.32 (1.47 to 7.53)
Treatment reported	7/2038 (3.03)	2.21 (0.88 to 5.55)	2.32 (0.86 to 5.80)
Unplanned or partly planned	13/6882 (1.89)	1.22 (0.56 to 2.62)	1.14 (0.52 to 2.49)

*Adjusted for mother's age at delivery (<26 years, 26-30, 31-35, ≥36), smoking from conception to time of interview (no/yes), pre-pregnancy body mass index (<20, 20-24.9, 25-29.9, ≥30, missing), and social class (low, middle, high, missing). All covariates except age were self reported. When social class or body mass index were missing (4.8%), we included a separate category in the variable.

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Are selective serotonin re-uptake inhibitors associated with an increased risk of self-harm by antidepressant overdose?

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Abstract *Objective*: To investigate likelihood of self-harm by overdose with antidepressant drugs of different types by examining hospital admission data and poisons inquiries and relating them to prescribing.
Design: Retrospective analysis of prospectively collected data on overdose admissions, poisons inquiries and prescribing of antidepressants in Edinburgh and Scotland.
Setting: Poisons treatment unit of the Royal Infirmary of Edinburgh and its surrounding catchment for overdose cases and Scotland for poisons inquiries.
Participants: All patients admitted to the Royal Infirmary of Edinburgh between 1 January 2000 and 31 December 2002 with an overdose involving an antidepressant.
Main outcome measures: Overdose admissions (patients) in relation to prescribing in Edinburgh and poisons inquiries in relation to prescription rates in Scotland.
Results: There were 1656 admissions involving 1343 patients. The likelihood of admission for an individual patient in relation to volume of prescribing (likelihood ratio: 95%CI) in the catchment was somewhat smaller for amitriptyline (0.83:0.74–0.92) and sertraline (0.79:0.63–0.99), and somewhat greater for mirtazapine (1.99:1.57–2.51), trazadone (1.30:1.09–1.54) and venlafaxine (1.33:1.13–1.55). For poisons inquiries in Scotland, the excess for venlafaxine and mirtazapine was confirmed and likelihood of an inquiry lowest for selective serotonin re-uptake inhibitors (SSRIs).
Conclusions: There was no evidence of an excess likelihood of presentation with overdose with SSRIs, and the likelihood was reduced with sertraline. There was a small excess of both admissions and poisons inquiries for mirtazapine and venlafaxine. This is a concern in view of the increased toxicity of venlafaxine in overdose in comparison with SSRIs.

Keywords Selective serotonin re-uptake inhibitors · Self-harm · Antidepressant

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Introduction

Antidepressants developed over the past 40 years have revolutionised the management of depression. Patients with depression are at risk of suicide and self-harm. There has been concern that antidepressant drugs themselves may increase the risk of self-injury and suicide. Furthermore, there have been suggestions that such effects may be more likely with some drugs than others, particularly with respect to selective serotonin re-uptake inhibitors (SSRIs).

In 1990, some case histories were published suggesting that fluoxetine might increase suicidality in some patients [1]. A UK study in 1995–1996 suggested an excess risk of self-harm in association with SSRI prescribing [2], but overdose patterns change with time [3, 4]. The current position is confused as three recent papers illustrate. Hall et al. (2003) [5] have suggested from Australian mortality data that a reduction in suicides among the elderly may be linked to increased prescribing of SSRIs. Khan et al. (2003) [6] examined the USA Food and Drug Administration (FDA) summary reports of the controlled clinical trials for nine modern FDA-approved antidepressants. Of 48,277 depressed patients participating in the trials, 77 committed suicide. Based on patient-exposure years, their analysis could not support an overall difference in completed suicide risk between antidepressants and placebo-treated depressed

subjects, or between SSRIs and either other antidepressants or placebo suicide rates. The authors pointed out that patients recruited to such trials tend not to be suicidal at entry and are mild to moderately, rather than severely, depressed. Healy (2003) [7] considered that SSRIs increase suicide risk, particularly in vulnerable patients.

The issue was heightened in the UK in June 2003 with an announcement by the CSM recommending paroxetine not to be prescribed to treat depression in young people up to the age of 18 years, and attributing an excess risk (relative risk 1.5 to 3.2) of suicidal behaviour to the drug [8]. The manufacturer, at about the same time, added to the *Undesirable Effects* section of the Summary of Product Characteristics for paroxetine that, in their paediatric clinical trials, "self-harm, suicidal thoughts and attempted suicide" were among those adverse events which had occurred "at a rate of at least twice that of placebo" [9].

If SSRIs were associated in the adult population with an increased risk of self-harm in comparison with other antidepressants, then an excess likelihood of hospital admission arising from drug overdose might occur. In an attempt to address this issue, we have examined patterns of admission to our poisons treatment unit in Edinburgh of patients with self-harm who consumed antidepressants as part of their overdose. We have compared these with rates of prescribing in our catchment area. We have also examined Scottish inquiries to our poisons information systems and compared these with national prescribing in Scotland. We have used these measures to investigate potential differences between antidepressant classes and individual SSRIs in Edinburgh and across Scotland.

Methods

Hospital admission data were available from the Poisons Unit at the Royal Infirmary of Edinburgh. This manages all cases of deliberate self-harm presenting to hospital in the City of Edinburgh and surrounding region of East and Mid Lothian (population ~700,000). There is a 100% admission policy, reviews of which indicate 80–90% of cases are actually admitted. We excluded patients from other sources. All patients admitted under our care are recorded in a central hospital database. Anonymised data on admissions for the three calendar years 2000 to 2002 in which an antidepressant was taken as part of an overdose were obtained. Information on age, gender and antidepressant drugs ingested was extracted. A number of patients, 204, were admitted more than once: the analysis was confined to individual patients admitted with ingestion of individual antidepressants, rather than total admissions. Patients admitted on separate occasions with different antidepressant ingestions were counted under both drugs. We have also compared the frequency of recurrent admissions involving the same antidepressant in the same patient to assess any influence on repetitive self-harm.

The Lothian Health Board provided prescribing data (prescription items) for the years in question for Lothian general practitioners in our catchment, i.e. excluding West Lothian. Prescribing records do not link to individual patients, but document overall frequency of prescription items for individual drugs. Similar data were also available to us for the whole of Scotland from the Information and Statistics Division of the Scottish Common Services Agency. Data on defined daily doses is not available to us, but in Scotland prescriptions are most often for 1 month's supply of drugs. There is no suggestion in the prescribing data that this varies with newer antidepressants.

We compared admission rates to prescribing rates for antidepressants to derive likelihood ratios for individual antidepressants relative to the average for all antidepressants. For SSRIs, we also compared individual agents against the rest of the group. Finally, we examined the numbers of patients who re-present with an overdose involving the same drug as on a previous occasion within this 3-year period.

Separately, we examined poisons inquiries relating to overdoses with the three main classes of antidepressants received by our Poisons Information Service, BNF sections 4.3.1 tricyclics, 4.3.3 SSRIs and 4.3.4 others (flupenthixol, mirtazapine, nefazadone, reboxetine, tryptophan and venlafaxine) [10]. These were obtained in two ways: from telephone inquiries and accesses to our web-based poisons information database, TOXBASE [11]. Numbers of telephone inquiries are much lower than those to TOXBASE, which is the first-line information source for Scottish hospitals, and we concentrate on TOXBASE accesses in our analysis. Since these originate from the whole of Scotland, we have used national prescribing data to investigate the relationship between telephone and Internet accesses and prescribing volume.

Results

Hospital admissions

There were 1656 admissions involving 1343 patients (471 male, 872 female) during the years 2000–2002. As a whole, there was no age difference between those using SSRIs (median 31 years) and those using antidepressants (median 33 years).

Table 1 shows rates of admission for patients for individual antidepressants, as well as rates of prescribing and likelihood ratios with 95% confidence intervals. Trazodone, mirtazapine and venlafaxine have a likelihood ratio significantly greater than one, indicating a greater risk of presentation. Amitriptyline, doxepin, imipramine and sertraline have likelihood ratios significantly less than one, indicating a lower rate of presentation.

Rates of presentation with SSRIs, other than sertraline, were not statistically significantly different from the

average. In the catchment area, prescribing numbers and overdose rates with fluoxetine and paroxetine were remarkably similar (Table 1), while amitriptyline remained the most frequently prescribed antidepressant.

Re-presentation rates

Of the 270 patients who had taken paroxetine during their first presentation in this period, 51 re-presented with an overdose including the same drug on one or more subsequent occasions (18.9%). Of the 454 patients who took other SSRIs, 76 re-presented with the same drug (16.7%). There is no statistical difference in these percentages. Some of these patients also re-presented on other occasions with overdoses not including SSRIs. We cannot be sure whether they were still taking SSRIs therapeutically, and we have excluded these admissions from our analysis.

Poisons information inquiries

During the period 2000–2002, there were 1550 telephone inquiries and 13,417 TOXBASE accesses to information on antidepressants in the categories of interest. There was a close relationship between the numbers of telephone and TOXBASE accesses for antidepressants ($R^2 = 0.9674$). TOXBASE accesses were significantly lower for SSRIs than the other groups, but more likely for the category "other antidepressants" than for tricyclics and SSRIs (Table 2). Mirtazapine and venlafaxine accounted for 84% (1980 of 2355) of TOXBASE accesses and 88.5% (385,121 of 434,788) of prescription items for "other antidepressants".

Discussion

Studies of this type have inherent weaknesses. Patients may not actually be taking on a regular basis the drug they ingest in overdose and, in some cases, the drug may not be prescribed for them. We have not recorded data on patients receiving antidepressants who have taken an overdose not involving them, nor included patients who presented only with other types of deliberate self-harm but we have included patients whose self-poisoning was judged to be accidental. However, these factors should not produce systematic biases such that comparisons among drugs are invalid.

This study reflects experience in the largest clinical unit of its kind in the UK. The methods we have used address exposure (as reflected by prescribing volume), and risk (as admission numbers) and poisons inquiries.

Table 1 Numbers of patients admitted to the Royal Infirmary of Edinburgh (2000–2002) with an overdose involving an individual antidepressant, and numbers of prescription items in its catchment area; shown with likelihood ratios for this association and their 95% confidence intervals (note: likelihood ratio = 1 represents the overall average)

Antidepressant	Overdose patients	Lothian prescriptions	Likelihood ratio	95% Confidence interval
Tricyclics				
Amitriptyline	268	177,283	0.83	0.74–0.92
Clomipramine	29	13,993	1.13	0.79–1.62
Dothiepin	63	31,722	1.08	0.85–1.38
Doxepin	4	13,038	0.17	0.07–0.43
Imipramine	12	13,807	0.47	0.27–0.83
Lofepramine	29	19,170	0.83	0.58–1.18
Trazodone	120	50,341	1.30	1.09–1.54
SSRIs				
Citalopram	125	65,983	1.09	0.98–1.21
Fluoxetine	270	135,044	1.03	0.93–1.15
Paroxetine	270	158,278	0.93	0.84–1.04
Sertraline	68	46,998	0.79	0.63–0.99
Others				
Mirtazapine	66	18,151	1.99	1.57–2.51
Nefazodone	16	7196	1.21	0.75–1.96
Reboxetine	8	4718	1.16	0.59–2.29
Venlafaxine	140	81,320	1.33	1.13–1.55

Table 2 Numbers of TOXBASE accesses and prescriptions for the major antidepressant groups ("others" are flupenthixol, mirtazapine, reboxetine, tryptophan and venlafaxine) prescribed in Scotland. The likelihood ratios for the association are shown with 95% confidence interval. Mirtazapine and venlafaxine are also shown separately

Agent	TOXBASE accesses	Prescriptions	Likelihood ratio	95% Confidence interval
TCA	4606	1,111,145	0.99	0.96–1.01
SSRI	6456	1,660,511	0.93	0.91–0.94
Others	2355	434,788	1.29	1.20–1.34
Mirtazapine	561	93,854	1.42	1.31–1.54
Venlafaxine	1419	291,267	1.16	1.10–1.22

Since the referral pattern and admission protocols in this single-centre service have remained stable, the approach we have used allows comparison of different drugs in a defined population as demonstrated before when examining changes in prescribing behaviour and overdose patterns for antipsychotics [12].

Our data from Edinburgh show a lower risk of admission for amitriptyline. While this finding might be confounded by the use of this drug in the management of chronic pain, it is also likely to reflect a natural cautiousness in the prescribing of tricyclic antidepressants to patients deemed at high risk of self-harm, which is encouraging given the considerably greater toxicity in overdose associated with this group [13, 14].

Crucially we have found no evidence of either increased risk involving the SSRIs as a group or paroxetine individually—indeed sertraline was associated with a reduced risk of admission. Furthermore, we found no evidence of a greater risk of recurrence involving SSRIs. In contrast, overdose rates for mirtazapine, trazadone and venlafaxine were significantly higher than average. Worryingly, both in our clinical experience [15] and in that reported from national mortality statistics [13], venlafaxine appears to be associated with significantly more toxicity in overdose than other newer antidepressants. The differences we have found are small in absolute terms and do not necessarily indicate an effect on self-harm behaviour.

Inquiries to poisons information services are markers of clinical activity in managing acute overdose. We have previously shown for antipsychotics that the number of TOXBASE accesses is generally related to prescribing volume [12]. In this study, the relationship between accesses and prescription numbers was the same for tricyclics and SSRIs but significantly greater for "other antidepressants", principally mirtazapine and venlafaxine. This finding may confirm that the presentation rates for venlafaxine and mirtazapine are indeed greater, although there are other explanations, notably that doctors are less familiar with the effects of these drugs in overdose.

In conclusion, our data show that presentations to hospital involving an overdose of antidepressant drugs was not more likely than expected when SSRIs had been taken in relation to SSRI prescribing rates, and indeed was significantly less than expected for sertraline along with amitriptyline, imipramine and doxepin. However, admissions involving venlafaxine and mirtazepine were significantly more frequent than would be expected from the prescribing rates. This finding is a concern, given evidence of venlafaxine's greater toxicity in overdose, and the potential for patients to be switched from the SSRIs in general and paroxetine in particular in response to the current health scare about the drug and its class.

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The Seccat survey: I. The costs and consequences of alcoholism

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THE SECCAT SURVEY: I. THE COSTS AND CONSEQUENCES OF ALCOHOLISM

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Abstract — The SECCAT survey assessed the Socio-Economic Costs and Consequences of Alcoholism Treatment. Basic demographic and health service resource use data (for a previous 6-month period) were obtained for a cohort of 586 eligible patients who had had treatment at the Alcohol Problems Clinic (APC) in Edinburgh. The cohort was 75% male with a mean age of 46.0 years. Seventy-six per cent had an initial diagnosis of alcohol dependence and 21% alcohol abuse. Use of health services was highly variable. Thirty-six per cent agreed to be interviewed to provide data on their level of abstinence, on resource use, on quality of life (SF-36), on socio-economic characteristics and key adverse events. These 212 individuals had similar age and sex ratios to the full cohort, but alcohol abusers were under-represented. Nineteen patients reported no days of abstinence and 41 were abstinent over the whole 6-month period. Patients experienced a much poorer quality of life than a normal population in terms of all dimensions of the SF-36. The average total health care costs of the interviewed patients were £1134 of which 38% were related to treatment at the APC. Analysis suggests that alcohol-dependent patients make substantially more costly use of resources than abusers and experience a much poorer quality of life. No clear relationship of cost to degree of abstinence has been found. There is a clear and consistent relationship of SF-36 scores and drinking behaviour.

INTRODUCTION

The 1991 Health Survey for England suggests that 7% of men and 5% of women can be classified as problem drinkers [Office of Population Censuses and Surveys (OPCS), 1993]. It is widely reported that individuals with alcohol problems are a diverse group, from a wide range of social backgrounds, and that types of alcoholism vary considerably. Appropriate care often means individually tailored 'packages' of care, which to be effective need to be client-led, taking into account what is acceptable to the patient at a given time. Alcohol and alcoholism impose significant costs on the National Health Service (NHS). It has been estimated that in 1989 the cost of sickness absence associated with alcohol consumption was £779 million (Maynard, 1989). However, little is known about the overall magnitude of such costs, and even less about the social circumstances, quality of life and health service resource use of specific categories of patients. As a result, little is known about the potential cost-effectiveness of interventions aimed at this patient group, and there is a considerable problem to produce accurate cost and cost-effectiveness data given such a diversity of service provision (Godfrey, 1994).

This paper presents the findings of the SECCAT survey to assess the Socio-Economic Costs and Consequences of Alcoholism and its Treatment. The survey provides evidence of the socio-economic characteristics of a group of patients who had been treated for alcohol problems, their levels of abstinence, quality of life, key adverse events that they have suffered and the costs of providing health care and support to them. All the patients had had contact with the Alcohol Problems Clinic (APC) at the Royal Edinburgh Hospital (Lothian), chosen for its representative approach to the treatment of alcoholism. Service provision was available on an inpatient and outpatient basis and was directed at both the alcohol-dependent patient and those with milder

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forms of medical need, and ranged from intensive supportive therapy with individual counselling to a programme of detoxification with group therapy lasting 3 weeks, for a range of alcohol-related problems. Additional measures, such as supervised disulfiram therapy and antidepressants, were advocated as the need arose, and patients were encouraged to make contact with Alcoholics Anonymous and other voluntary agencies.

The paper first outlines the methods of data collection and costing used, and then describes the socio-economic circumstances of the full cohort. It then describes the limited socio-economic and the health service resource use data for the cohort as a whole, and the much fuller data available for those patients who agreed to be interviewed. Finally it presents two important sub-group analyses comparing patients in different diagnostic classifications and by levels of abstinence.

METHODS

The study surveyed a cohort of patients who had had contact with the APC. Referrals to the APC came chiefly from general practitioners (GPs). Other sources of referral included general psychiatrists, general hospitals, self-referrals and referrals from the courts, voluntary bodies and social work services. Ethical approval was sought and approved for the methods to be used in the survey. A case register was used to identify 685 patients who have been in contact with the APC during 1992. Case notes of these patients were checked to ensure that they satisfied the inclusion criteria for the survey: namely, that the patients had an alcohol problem and had been in contact with the APC for treatment at a point 12 months previously. Patients were excluded if they were of no fixed abode or had an address outside the Lothian Region. In total, 85 patients from the database were found to be ineligible. The remaining 600 patients were entered into the study and allocated a survey number. If the case notes indicated that the patient was in current contact with APC, their keyworker confirmed their most recent contact. In addition, the keyworker was asked if there was any reason why a patient should not be approached for the survey.

Patients were then written to and invited to return a reply-paid card stating whether or not they wished to take part in the survey. If no reply was received within 2 weeks, a further letter was sent. If after 2 weeks there was still no response, the patients' addresses were checked with their general practitioner. If the address was incorrect the patient was written to at their new address. For patients who were no longer in contact with the general practitioner (GP) recorded in their hospital notes, the name and address of their new GP along with their new address were obtained from primary care administration. These patients were then reapproached as above. If, following these procedures, patients did not reply, or declined to be interviewed and for patients who had died during the past 6-month retrospective time-frame, then the baseline information on the patient was completed in the case-record file (CRF) using data from the hospital case-record and additional information about NHS resource use from a questionnaire sent to the GP.

Patients who agreed to take part were then invited to attend a single interview, at which the CRF was completed. In addition, a questionnaire was sent to the patient's GP to confirm details of medical history, medication and to obtain information on NHS resource use. The process provided for all patients basic demographic data, clinical diagnosis (at time of initial contact) and information on some items of resource use. For patients who agreed to be interviewed, social circumstance, drinking behaviour in the previous 6 months, use of NHS resources including prescribed drugs, and the incidence of a variety of events relating to employment, the legal system and accidents was collected. During the interview, patients completed the UK version of the SF-36 health status questionnaire (Brazier *et al.*, 1992). The SF-36 measures health status according to eight dimensions: physical functioning; social functioning; role limitations due to physical problems; role limitations due to emotional problems; general mental health; energy/vitality; bodily pain; and general health perceptions. A score is derived for each dimension of between 0 (for poor health) and 100 (good health). Comparative norms from a survey of a UK population are available (Jenkinson *et al.*, 1993). In addition, the Alcohol Related Problems Questionnaire (ARPQ) (Chick *et al.*, 1988, 1991) was completed. The results of the ARPQ will be presented in a separate paper (Patience *et al.*, 1997).

Recruitment and interview of the patients took

Table 1. Unit cost and components of total cost

Component	Items	Unit costs (£)	Source
APC costs	Individual counselling session	36.25	Netten (1994)
	Group counselling session	3.65	Netten (1994)
	In-patient stay at APC	1422.30*	APC Edinburgh
	Home visit by APC staff	22.00†	Netten (1994)
GP costs	Visit to GP	7.62	Netten (1994)
	Visit to practice nurse	3.83	Netten (1994)
	Visit from GP	22.00	Netten (1994)
	Visit from practice nurse	7.89	Netten (1994)
Other costs	Non-APC counselling sessions	3.65	Netten (1994)
	Week in residential units	275.00‡	National Health Service in Scotland (1993)
	Outpatients visits	29.50	
	Non-APC inpatient day	200.00	
	Visit to A&E	57.00	
Drugs costs	Specific drugs prescribed	Specific cost	BNF; MIMS

APC = Alcohol Problems Clinic, Royal Edinburgh Hospital; A&E = Accident and Emergency department; BNF = British National Formulary (1994); MIMS = Monthly Index of Medical Specialities (1994).
*Average of the two programmes offered at the Unit (2 weeks).
†Costed as equivalent to GP home visit.
‡Mid-point of range of Edinburgh residential units.

place over 1 year, each month dealing with those who had been in contact 12 months previously. Of the 600 patients allocated a survey number, 212 agreed to be interviewed; 59 declined to be interviewed; 18 had died during the relevant period; 297 did not respond; 14 were eventually found to be ineligible. Thus for the purpose of subsequent analysis the full cohort is 586 (600 minus 14) patients. Data were collected for the 6-month period immediately prior to the interview date. For those not interviewed, the period was taken as 6 months prior to their being allocated an interview number. Where data were sought and obtained from more than one source (e.g. the patient and his GP), a predetermination was made for each item on the basis of an *a priori* likelihood of accuracy as to which source would be used in the analysis. For example, the GP was taken as the preferred source of data on medications.

For each individual, a total cost of health service contacts during the 6-month period was calculated. This calculation applied standard unit costs to the number of each type of contact for each individual, to estimate four component costs and the total cost. The make-up of the four components and the principal unit costs are summarized in Table 1. All drug prescriptions have been costed for the full 6-month period using prices from *Monthly Index of Medical Specialities* (June 1994) or *British National Formulary* (March 1994). Rather than making subjective decisions about causality, all health service resource use (including prescribed drugs), whether or not obviously related to their alcohol problem was costed.

RESULTS

Characteristics of the full cohort

The cohort consisted of 586 individuals and its demographic characteristics are shown in Table 2. The group is 74% male, has a mean age of 46.0 years and the most common diagnosis is alcohol dependence (DSM-III-R, 303.90) [DSM Classification of the American Psychiatric Association (1987)]. The cohort had had a mean (SD) length of contact with the APC of 4.48 (5.56) years. The median length of contact was 2.11 years, with an interquartile range of 0.57–6.16 years. The longest period of contact was nearly 30 years. Data on some aspects of health service resource use, in the 6-month survey period, is available for the full cohort from routine records. This is presented in Table 3. A wide range of usage is observed within the group, with some striking maximum values.

Table 2. Cohort demographics

Characteristic	Full cohort (586 individuals)	Interviewed group (212 individuals)	Non-interviewed group (374 individuals)
Sex			
Female	150	55	95
Male	436	157	279
Age			
Mean (SD) cohort age	46.0 (10.8)	48.3 (9.7)	44.5 (11.1)
Range	20–82	21–70	20–82
Disease classification (DSM III-R)			
Alcohol intoxication (303.00)	10	3	7
Alcohol dependence (303.90)	447	180	267
Alcohol abuse (305.00)	125	29	96
Missing data	4	–	4
APC contact			
Mean (SD) length of contact in years	4.48 (5.66)	5.15 (5.79)	4.08 (5.56)
Median length of contact in years	2.11	2.59	1.60
Proportion in current contact	24.8%	48.1%	11.4%
Missing data	11	–	11

APC = Alcohol Problems Clinic.

Table 3. Health service resource use: full cohort (586 individuals)

Resources	Total number of responses	Total number of non-zero responses	Number of contacts			
			Mean	Median (90% central range)	Minimum	Maximum
Individual sessions at APC	580	174	1.87	0 (0–6)	0	31
Group sessions at APC	582	62	2.28	0 (0–2)	0	150
Home visits by APC staff	582	20	0.18	0 (0–0)	0	22
IP admissions at the APC	582	54	0.11	0 (0–0)	0	2
Visits to GP	558	477	4.94	4 (0–10)	0	59
Visits to GP (alcohol related)	551	322	2.71	1 (0–7)	0	50
Visits to a practice nurse	551	72	0.40	0 (0–1)	0	51
Hospital OP visits (except APC)	547	167	0.75	0 (0–2)	0	28
Visits to A&E	551	124	0.37	0 (0–1)	0	12
IP admissions to a hospital or clinic (except APC)	551	92	0.24	0 (0–1)	0	5

APC = Alcohol Problems Clinic; A&E = Accident and Emergency department; IP = inpatient; OP = outpatient; GP = general practitioner.

An APC inpatient stay was recorded only for 54 patients (<10% of the cohort) with no patient being treated more than twice as an APC inpatient, but over the 6-month period at least one individual attended the APC for individual counselling 31 times and another attended 150 group sessions, i.e. more than five sessions per week. One patient made 59 visits to a GP. Two individuals made 12 visits each to accident and emergency departments.

A comparison can be made with data for 1992 for the population of Great Britain as a whole (OPCS, 1993). Nationally, the average number of contacts with a GP per 6-month period would only be ~2.5, approximately half that observed in this cohort. It would also appear that the rate of inpatient stays of this cohort is considerably higher than that of the population as a whole which had an average of only 0.06 inpatient stays per 6-month period.

Table 4. Health services resource use: comparison of interviewed and non-interviewed groups

Resources	Interviewed patients (212 individuals)* mean (SD)	Non-interviewed patients (374 individuals)† mean (SD)
Individuals sessions at APC‡	3.8 (5.92)	0.76 (2.86)
Group session at APC‡	5.93 (19.7)	0.2 (1.52)
IP admissions at the APC	0.18 (0.45)	0.06 (0.13)
Visits to GP	5.59 (4.76)	4.54 (5.40)
Hospital OP visits (except APC)‡	1.01 (2.42)	0.57 (1.52)
Visits to A&E	0.36 (0.79)	0.38 (1.21)
Inpatient admissions to a hospital or clinic (except APC)	0.28 (0.62)	0.22 (0.69)

*Due to missing data, observations for specific items range from 208 to 212.
†Due to missing data, observations for specific items range from 337 to 374.
‡Difference statistically significant ($P \leq 0.05$): calculated using the Wilcoxon rank sum test.
For abbreviations see Table 3.

These figures for the full cohort clearly indicate the higher use of health service resources made on average by alcoholics who have had recent contact with a clinic. However, they do not provide any indication as to which sub-groups make greater or lesser demands.

Characteristics of the interviewed group

The interviewed group of 212 individuals represented 36% of the full cohort. The sex ratios and ages of those interviewed (Table 2) reflect well those of the group as a whole, but alcohol abusers are under-represented, as are those who have not maintained contact with the APC.

Table 4 compares the use of those health service resources for which data were available from the APC routine data or from a questionnaire to GPs, of the interviewed group and the non-interviewed group. The interviewed group made significantly greater use of APC services, of visits to their GPs, and outpatient visits to hospital.

Column 1 of Table 6 shows that the mean (SD) costs of health care in the 6-month period for interviewed patients totalled £1134 (£1809), of which only 38% were costs at the APC.

The number of abstinent days has been used as an outcome measure in clinical trials and serves as a proxy for alcohol consumption. Interviewed patients were asked if there had been a period in the last 6 months when they had been completely abstinent and, if so, were helped to calculate the total number of abstinent days using the time-line follow back method (Sobell *et al.*, 1980). Forty-one patients were abstinent over the whole period. Nineteen patients had no days of complete abstinence. A graphical presentation of individual patient values for the number of abstinent days is shown in Fig. 1.

Figure 2 compares the subjective health status, as measured by the SF-36, of those interviewed with that of the UK population norms. These patients experience a much poorer health status on all dimensions than a normal population. (This effect is unchanged by age standardizing the comparison.)

Data were also obtained at the interview relating to the socio-economic circumstances and to the incidence of certain adverse events. Twenty-five per cent of the interviewed group were single or widowed, 27% married, 42% divorced or separated. Forty-five per cent were living alone, and 36% were in owner occupied accommodation. Only 26% were in full or part-time employment, whilst 37% were permanently sick/disabled or prematurely retired due to ill health. Comparison with data for Great Britain indicates that the proportion living alone is very high (national figure of 14% of the adult population) as is the proportion not in employment, where nationally $\sim$77% of men and $\sim$66% of women of working age might be expected to be employed (OPCS, 1994).

Those who were employed had, as a result of their alcohol problem, missed a mean (SD) of 10.2 (33.2) days of work with their employer's agreement and a mean (SD) of 6.8 (12.9) days where absence was not planned. There was a high incidence of legal events in the 6-month period: 23

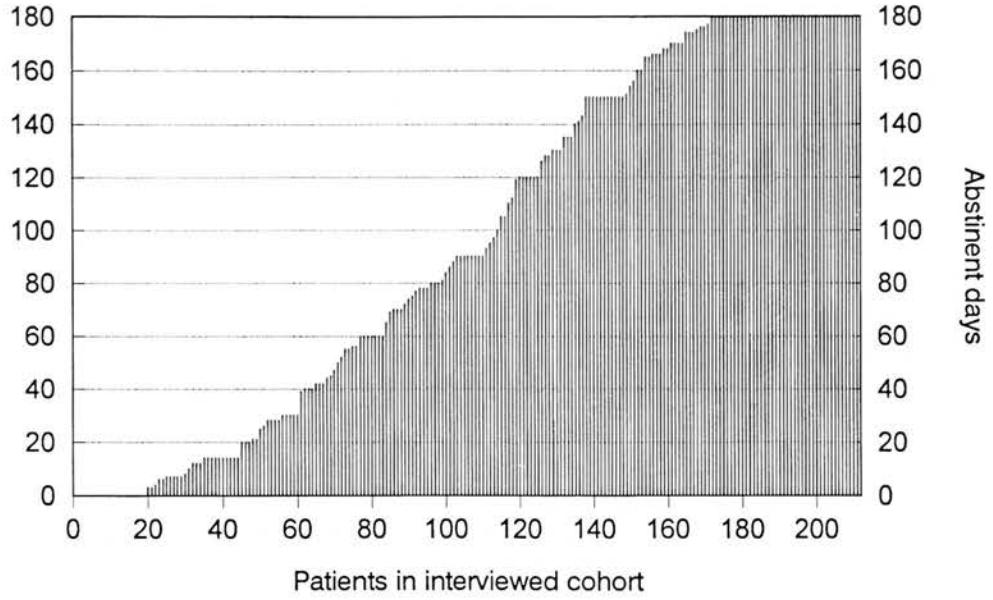

Fig. 1. Plot of individual patient values for number of abstinent days (in ascending order of value).

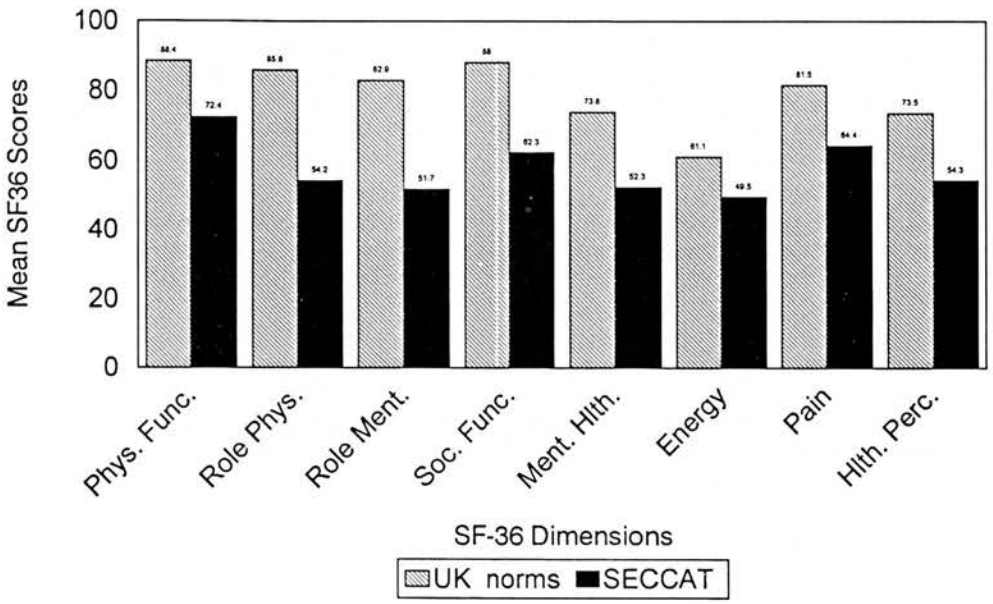

Fig. 2. SF-36: comparison of SECCAT data with UK norms.

individuals had been arrested at least once, 13 had been disqualified from driving, and 12 had been divorced or divorce proceedings were underway. More than 20% of the group had had an accident at home, compared with the rate of 2–4% which earlier national data from the 1989 *General*

Table 5. Health service resource use: number of contacts [mean (SD)]

Resources	All interviewed patients (212 individuals)	DSM-III-R category		Abstinence			
		Dependence (303.90) (180 individuals)	Abuse (305.00) (29 individuals)	Quartile 1:* most abstinent (54 individuals)	Quartile 2:* (56 individuals)	Quartile 3:* (47 individuals)	Quartile 4:* least abstinent (55 individuals)
Individual sessions at APC	3.80 (5.92)	4.13 (6.28)	1.93 (2.56)	3.72 (6.03)	4.21 (5.78)	4.47 (5.86)	3.29 (6.27)
Group sessions APC	5.93 (19.7)	6.37 (20.8)	3.79 (12.19)	6.23 (18.95)	10.36 (30.92)	4.14 (9.19)	2.98 (9.54)
Home visits by APC staff†	0.36 (2.27)	0.43 (2.44)	0.20 (0.81)	0.00 (0.00)	1.20 (4.23)	0.31 (1.14)	0.04 (0.27)
IP admissions at the APC‡	0.18 (0.45)	0.20 (0.46)	0.03 (0.18)	0.07 (0.26)	0.23 (0.47)	0.31 (0.60)	0.16 (5.62)
Visits to GP	5.59 (4.76)	5.72 (4.78)	4.85 (4.72)	5.52 (5.79)	5.38 (4.95)	6.03 (4.39)	5.62 (3.89)
Visits to a practice nurse	0.32 (1.24)	0.29 (1.24)	0.46 (1.26)	0.33 (0.99)	0.18 (0.43)	0.38 (0.71)	0.42 (2.09)
Home visits instigated by GP or practice nurse‡	0.26 (0.93)	0.23 (0.95)	0.39 (0.78)	0.13 (0.39)	0.46 (1.53)	0.39 (0.95)	0.07 (0.26)
Home visits by GP instigated by patient†	0.43 (1.26)	0.48 (1.34)	0.14 (0.44)	0.13 (0.52)	0.51 (1.03)	0.51 (1.14)	0.58 (1.92)
Hospital OP visits (except APC)	1.01 (2.42)	1.03 (2.50)	0.96 (2.06)	0.75 (1.04)	1.05 (1.95)	1.52 (4.53)	0.76 (1.36)
Visits to A&E§	0.36 (0.79)	0.37 (0.75)	0.20 (0.41)	0.15 (0.60)	0.35 (0.67)	0.45 (0.80)	0.49 (0.77)
Inpatient admissions to a hospital or clinic (except APC)	0.28 (0.62)	0.28 (0.55)	0.31 (0.96)	0.39 (0.88)	0.24 (0.51)	0.45 (0.96)	0.26 (0.49)

*The quartile split is inexact to ensure that, given the distribution of values, all patients with the same number of abstinent days are allocated to the same quartile rather than arbitrarily split at the true quartile boundary.
†Difference between abstinence sub-groups statistically significant ($P \leq 0.05$); Wilcoxon rank sum test.
‡Difference between DSM sub-groups statistically significant ($P \leq 0.05$); Wilcoxon rank sum test.
§Difference between abstinence sub-groups statistically significant ($P \leq 0.01$); Wilcoxon rank sum test.
For abbreviations see Table 3.

Table 6. Health service costs [£; mean (SD)]

Cost category	All interviewed patients (212 individuals)	DSM-III-R category		Abstinence			
		DSM-III-R 303.90 Alcohol dependence (180 individuals)	DSM-III-R 305.00 Alcohol abuse (29 individuals)	Quartile 1: most abstinent (54 individuals)	Quartile 2: (56 individuals)	Quartile 3: (47 individuals)	Quartile 4: least abstinent (55 individuals)
APC	429.14	474.38	137.44	260.51	497.06	614.42	364.52*
GP	52.73	55.01	40.49	46.17	52.64	56.09	57.21
Other	569.41	607.95	377.46	362.01	805.12	705.14	379.62
Drugs	82.70	84.72	76.25	114.30	87.88	70.02	60.25
Total	1133.98 (1809.46)	1222.06 (1878.13)	631.64 (1292.76)	782.99 (1265.47)	1442.70 (2138.27)	1445.67 (2165.73)	861.60* (1527.50)

APC = Alcohol Problems Clinic; GP = general practitioner.
* Difference between sub-groups statistically significant ($P \leq 0.05$); Wilcoxon rank sum test.

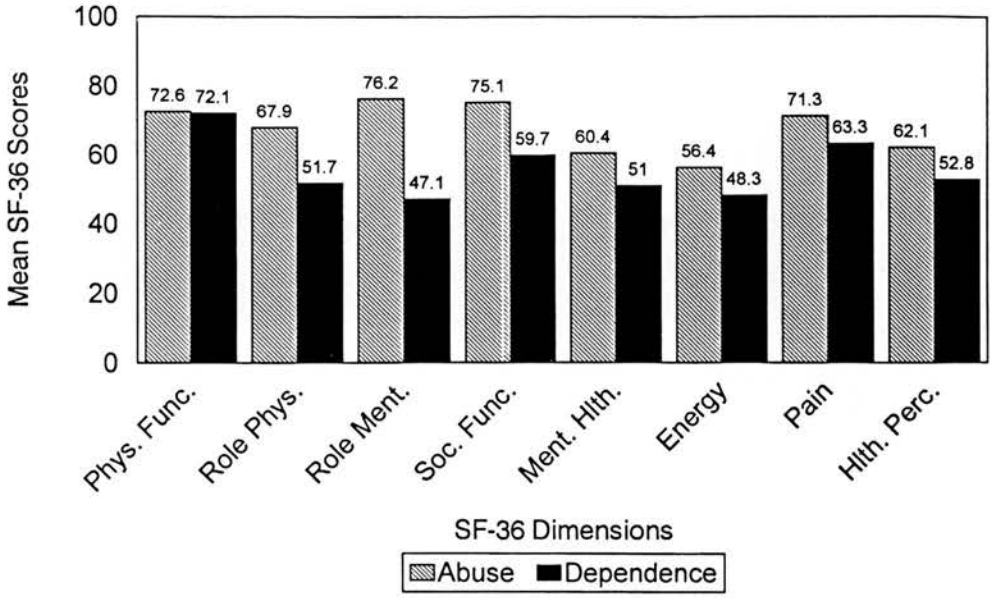

Fig. 3. SF-36: comparison of mean scores for DSM-III-R categories of 'alcohol abuse' and 'alcohol dependence'.

Household Survey suggests would be normal (OPCS, 1991). Thirteen per cent of those interviewed had been involved in accidents as pedestrians. Seventeen per cent of those working had had an accident at work. Thirteen per cent had taken an overdose or tried to harm themselves. (Despite these overall high incidence rates, the small absolute numbers prevent meaningful sub-group analysis of these data.)

Sub-group comparisons

Given the diversity of the groups, it was judged important to see whether resource use of quality of life varied according to diagnostic classification or to the degree of abstinence achieved in the 6-month period.

Diagnostic classification: abuse vs dependence. The comparison between diagnostic classifications relates to 209 individuals: the majority (180) were classed as alcohol-dependent (DSM III-R, 303.90), and 29 classified as alcohol abusers (305.00). The remaining three patients in the interviewed group had a clinical diagnosis of alcohol intoxication (DSM III-R, 303.00) and form too small a group for comparison.

Table 5 shows the mean number of health service contacts made by the two groups for each resource category. In most cases, alcohol-dependent patients average a higher number of health service contacts than alcohol abusers, although this is only statistically significant for inpatient visits ($P \leq 0.05$). For GP/practice nurse visits, abusers made more use than alcohol-dependent patients ($P \leq 0.05$). Table 6 shows the generally higher use of services made by alcohol-dependent patients, reflected in a higher average cost for this group. The difference is striking with average total health service costs of dependent drinkers almost double that of the non-dependent drinkers.

In terms of the SF-36, alcohol abusers score higher on every dimension than the alcohol-dependent group (Fig. 3). Dependent alcoholics exhibit very low scores on the 'role mental' and 'role physical' dimensions. Clearly individuals diagnosed as alcohol-dependent have a significantly lower subjective health status than alcohol abusers.

The usefulness of the clinical distinction between abuse and dependence has been questioned (Shuckit *et al.*, 1985). After following a group of alcoholics distinguished by DSM categorization for 1 year, the diagnostic criteria did not support different prognostic implications. The distinction is, however, important from an eco-

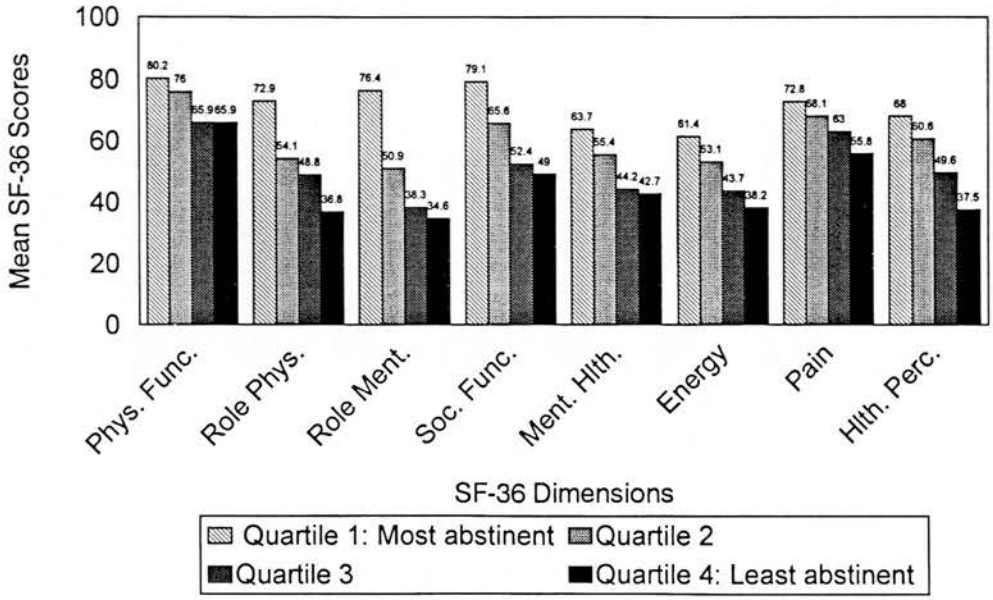

Fig. 4. SF-36: comparison of SECCAT mean scores for quartiles ordered by number of abstinent days.

nomic perspective. Alcohol-dependent patients impose significantly higher costs on the NHS and suffer much poorer health status.

Abstinent and non-abstinent drinkers. Table 5 also shows the resource use data for patients divided into quartiles according to their level of abstinence, as measured by the reported number of abstinent days in the 6-month period. This shows that the most abstinent group made significantly less use of emergency care, either in calling out their GPs or visiting Accident and Emergency. For other resource use, the picture is less clear, though there is a tendency for the middle quartiles to make greater use of services than the least or most abstinent groups. This tendency is confirmed in Table 6, which clearly shows that, whilst patients in quartiles 1 and 4 have similar mean total health service costs (£783 and £862 respectively), the costs of quartiles 2 and 3 are very much higher (£1443 and £1446 respectively). If the data are categorized slightly differently, separating out those 41 individuals who were completely abstinent (instead of quartile 1) and those 19 individuals who were never abstinent (instead of quartile 4) a similar pattern emerges, with the two extreme groups having very similar total costs of £735 (SD £1237) and £745 (SD £1828) respectively. Within the total costs, the one component that is statistically significantly different is that of the APC costs. APC costs are lowest for those who were completely abstinent or who were not at all abstinent during the 6-month period.

Univariate analysis of the relationship between abstinence days and total cost produced a positive but non-significant rank correlation coefficient (0.03, Spearman's *rho*). A plot of the relationship emphasized the absence of a linear relationship. While the plot was suggestive of a curvilinear relationship (with individuals at both extremes of the abstinence days distribution consuming similarly low levels of resources and those in the middle of the distribution consuming a greater number) a one-way analysis of variance was unable to detect such a relationship ($t = 0.324$, df = 1, $P = 0.75$). In summary, as most observations were clustered along the x-axis, it appears likely that whatever the number of abstinent days achieved, most patients incurred a similarly low level of costs.

Multivariate regression analyses looked at the relationship between average total cost as the dependent variable against the number of abstinent days and the number of controlled drinking months. The age of individuals was also included

as an independent variable and dummy variables were included for sex and disease classification. The number of abstinent days was positively related to total cost and significant ($t = 2.62$, df = 1, $P = 0.034$), whilst there was a negative and significant relationship between controlled drinking months and total cost ($t = 1.17$, df = 1, $P = 0.002$). Age was also negatively related to average total cost and this was significant ($t = 3.75$, df = 1, $P = 0.046$). The model explains, however, only 5% of the variation in the data (adjusted $R^2 = 0.056$).

Figure 4 compares the SF-36 scores according to levels of abstinence. There is a great difference in subjective health status, and a clear and consistent gradient on each of the dimensions. The sub-group comparison reveals a very striking difference in subjective health status with the abstinent group enjoying broadly normal health status levels.

DISCUSSION

This study sought very detailed information on drinking behaviour, health service resource use, quality of life and key events from interviews with patients who had been in previous contact with an alcohol problems clinic. Given the nature of the patient population, the low interview response rate of 36% was expected, and the comparison of the resource use data for the respondents with equivalent data for the full cohort shows again, not surprisingly, that the interviewed group is biased towards those with greatest clinic and health service contact, although the age–sex breakdowns are similar. The interviewed group under-represented patients with a diagnosis of alcohol abuse.

The design of the study attempted to strike an effective balance between the ideal and the attainable. A long-term cohort study prospectively following the course of intervention and subsequent outcomes for new patients would obviously have been preferable, rather than this cross-sectional retrospective review of those who have had previous contacts with the APC. But the former would have required a very long, expensive and intrusive study, which itself might have impacted on patient outcomes and behaviour. If such a study were in future to be seriously contemplated, the current data would provide a basis for determining necessary sample size and duration. Within this retrospective approach, it would have been attractive to obtain data on resource use over a longer-period (for example 1 year), but research on patient recollection of hospitalization indicates that memory begins to deteriorate rapidly after ~ 10 months (National Center for Health Statistics, 1965).

Despite the necessary design limitations, the interviews produced clear evidence of high rates of adverse socio-economic events and accidents, and striking data on the overall poor quality of life of patients, as measured by all dimensions of the SF-36 and its consistent relationship to abstinent days. The relationship of levels of abstinence and costs is more complex with both extremes of high and low abstinence associated with lower costs than those in between. Generally the diagnostic distinction between alcohol dependence and alcohol abuse appeared important. Alcohol-dependent patients made greater use of health service resources. Their health service costs as calculated here are on average double those incurred by abusing patients. There is also a clear distinction between the health status of dependent and abusing patients. As is customary in such studies, the estimates of cost incorporate average costs for the units of health care resources recorded on a patient-specific basis (Drummond *et al.*, 1987). No data were available on, for example, variation in length of counselling sessions. Allowing for such differences might well have slightly increased the between-patient variation in total cost.

Two implications may perhaps be drawn. First, alcohol dependence may be of greater significance than abuse in generating costs to the health service and imposing on the quality of life of patients. Studies of the natural history of the disease have shown that a progression from abuse to dependence occurs (Öjesjö, 1981). This emphasizes the costs that could be avoided in preventing the progression from abuse to dependence, and the need for effective therapies to achieve this. Second, whilst more effective treatment or support facilities for alcoholic patients may be unlikely to have a dramatic effect on the total health service costs of these patients in the short term, there would appear to be substantial scope for improving their quality of life, and reducing adverse socio-economics through achieving better control of their drinking. Longer-term follow-up might

confirm the finding of Holder and Blose (1992) that the cost of care for abstainers does decrease over time.

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Health Technology Assessment Report 3

Prevention of relapse in alcohol dependence

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With significant contributions from the Topic Specific Group
(see Appendix 1)

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1 EXECUTIVE SUMMARY

1.1 Background

1. The 1998 Scottish Health Survey included questions to estimate the scale of alcohol dependence in Scotland. It recorded that 10% of male drinkers and 3 – 4% of female drinkers replied affirmatively to one or more of three questions designed collectively to identify alcohol dependence. All three questions were answered affirmatively by 1% of male drinkers but less than 0.5% of female drinkers.

2. Untreated alcohol dependence results in levels of drinking which substantially increase the risk of stroke, cirrhosis of the liver, brain damage and several forms of cancer and are associated with increased mortality.

3. Following initial detoxification of people with alcohol dependence, a longer-term programme of treatment is required to prevent relapse into heavy drinking and dependence. A number of different psychosocial and pharmacological interventions are available to prevent relapse. These are the focus of this Health Technology Assessment.

4. The Plan for Action on Alcohol Problems was published in January 2002 (Scottish Advisory Committee on Alcohol Misuse (SACAM), 2002) and covers a wide range of social, economic and clinical aspects of the misuse of alcohol in Scotland, including chronic heavy drinking. This Health Technology Assessment provides policy makers, planners and those working in the field of prevention of relapse in alcohol dependence with information required to implement a part of the plan. Local Alcohol Action Teams should take account of this advice when preparing the local strategies to be published in April 2003, that are required by the Plan for Action.

5. People with established alcohol dependence are likely to require treatment mainly within Tier 3 (for people with more complex needs) or Tier 4 (for people with highly specialised needs) of the Scottish Executive's Alcohol Problems Support and Treatment Framework. Thus, this Health Technology Assessment will be of primary interest to those concerned with these specialist tiers. However, aspects of prevention of relapse may happen in Tier 1 (services for the whole community) or Tier 2 (local services that identify and respond to people with alcohol problems). In 2003, the Scottish Intercollegiate Guidelines Network (SIGN) will publish a guideline on the management of harmful drinking and alcohol dependence in primary care.

6. There is no single definition of alcohol dependence used by clinical trial investigators, although certain basic features tend to be shared. Rigid adherence to any single criterion would have forced many studies to be discarded and so in this Health Technology Assessment, when possible, the pragmatic criterion that any process of detoxification had been undergone was preferred.

1.2 Objectives of this Health Technology Assessment

The objectives of this Health Technology Assessment were to answer the following questions:

1. Which treatment or combination of treatments (pharmacological and psychosocial) will yield the maximum maintenance of recovery amongst the population of those with alcohol dependence who have undergone detoxification?

2. What is the most effective and efficient approach to delivering the individual interventions (or combination of interventions) taking into account the different risk groups, locations, durations of treatment, etc?

1.3 Health Technology Assessment evidence

1. This Health Technology Assessment used systematic literature searching to identify evidence published in scientific literature. It also used evidence submitted by professional groups, patient groups, manufacturers, other interested parties and experts and commissioned primary research with patients to elicit their views and preferences.

2. For clinical effectiveness, a number of comprehensive reviews of treatment for alcohol problems and reviews of specific interventions were consulted. Studies particularly relevant to people with alcohol dependence were extracted from these reviews. Additional relevant studies were identified and an analysis was carried out to estimate the effects of treatment in a form suitable for input to the Health Technology Board for Scotland economic model.

3. The patient issues component used published scientific literature, materials from Alcoholics Anonymous, and a qualitative study of patient attitudes commissioned by the Health Technology Board for Scotland.

4. The economic evaluation critically appraised the economic models contained in the literature. The Health Technology Board for Scotland developed a simple, transparent model to combine the clinical effectiveness and epidemiology data with the costs of therapies and diseases in order to inform the cost effectiveness estimates of four psychosocial and three pharmacological therapies to prevent relapse in people who are alcohol dependent.

5. The current provision of services for prevention of relapse in alcohol dependence in Scotland was assessed by two postal surveys. One of these was targeted at National Health Service specialist services and the other at non-National Health Service providers.

1.4 Clinical effectiveness

1. A number of psychosocial interventions were found to be of value in preventing relapse in alcohol dependence. The total combined success rates, in terms of abstinence or controlled drinking at the trial end (varying between six months and beyond one year), in trials of those psychosocial treatments judged effective, was 42% for patients in the intervention groups and 26% for those receiving control treatments. In common with clinical trials in many other areas of medicine, these may overestimate the absolute benefits attainable in everyday clinical practice.

2. The Health Technology Board for Scotland meta-analysis suggested similar, statistically significant, beneficial effect sizes for four types of psychosocial treatment. The odds ratios for abstinence or controlled drinking at the end of the clinical trial compared with patients offered control treatments were: Behavioural Self-Control Training (odds ratio=1.75, 95% confidence interval 1.02, 3.02); Motivational Enhancement Therapy (odds ratio=1.88, 95% confidence interval 1.28, 2.77); Marital/Family Therapy (odds ratio=1.94, 95% confidence interval 1.37, 2.73); and Coping/Social Skills Training (odds ratio=2.11, 95% confidence interval 1.53, 3.92).

3. Behavioural Self-Control Training showed benefit when compared with control interventions. However, the only trial which focused on the unique defining features of Behavioural Self-Control Training and controlled for the more general features of Cognitive Behavioural Therapy did not show a benefit. Thus, there is no proof of superiority over other Cognitive Behavioural Therapy based approaches.

4. There is mixed evidence for Motivational Enhancement Therapy. It shows efficacy over ineffective controls. However, it was slightly less effective than Alcoholics Anonymous based treatment in outpatients in Project MATCH. This may be due to the short course of treatment given. It is suggested that Motivational Enhancement Therapy might be provided first, if such a relatively low intensity approach has not already failed, and more intensive therapy then given if necessary.

5. Although Marital/Family Therapy has shown a beneficial effect it should be recognised that this approach is only usually feasible in those with relatives willing to invest substantial effort in the treatment and with the consent of the patient. Thus, it is an option for treatment of only some patients. An exception to this is the Community Reinforcement Approach, which has been shown to be effective when a contractual element with non-family members has been tested.

6. Trials of Brief Interventions have failed to show any benefit in patients with established alcohol dependence.

7. Acamprosate and naltrexone are pharmacological treatments intended to reduce relapse. The meta-analysis suggested statistically significant beneficial effects for both treatments: acamprosate (odds ratio=1.73, 95% confidence interval 1.36, 2.20); and naltrexone (odds ratio=1.46, 95% confidence interval 1.12, 1.90). The combined success rates, in terms of abstinence or controlled drinking at the trial end (varying between three months and one year), in trials of these treatments was 34% for treated patients and 25% for those receiving placebo treatments. These may overestimate absolute benefits attainable in clinical practice.

8. Disulfiram, which causes unpleasant symptoms when taken with alcohol, was found to be ineffective if taken without supervision to ensure compliance. One good clinical trial and some substantiating evidence supports the use of supervised oral disulfiram.

9. All the evidence for effectiveness of pharmacological treatments is obtained from studies in which they were adjuncts to 'counselling'. Thus, the psychosocial treatment should preferably be organised prior to starting medication.

10. Within a specialist unit, protocols should be available for all treatment options to ensure standardised and consistent treatment. These protocols should be closely based on methods that have proven effective in clinical trials.

11. Evidence suggests that practical help with problems such as housing, debt and claiming benefits is likely to contribute to control of alcohol problems. Thus, close liaison with local authority services such as social work and housing and groups able to deliver such help is essential.

12. Encouragement to attend Alcoholics Anonymous meetings has been shown to have benefit. Explanation of the aims and philosophy of Alcoholics Anonymous during treatment will allow patients to make an informed choice. For benefit to be obtained from Alcoholics Anonymous, as with other psychosocial treatment approaches, people with alcohol dependence should not be pressurised to attend.

13. The effectiveness of interventions for prevention of relapse delivered by the Councils on Alcohol, and some other non-statutory services, has not been tested in clinical studies. Where counsellors are practising treatments that have been shown to be effective in other settings there is likely to be benefit.

1.5 Patient issues

1. Method of treatment, treatment awareness and access, involvement in choice of treatment and follow up were identified as key patient issues.

2. It is important that both the person who is alcohol dependent and his or her doctor understand and agree the purpose of treatment and review this understanding.

3. In reply to the Health Technology Board for Scotland survey, only 36% of National Health Service specialist services carrying out psychosocial interventions

indicated that they had patient information sheets or leaflets for any of these interventions. It is recommended that such information should be available for all interventions.

4. A qualitative study has been undertaken for the Health Technology Board for Scotland, to explore patients' treatment preferences and also to elicit factors which were felt to prevent relapse to drinking. The aim was to describe the experiences and preferences of individuals for pharmacological or psychosocial interventions, or a combination of both, for the treatment for alcohol dependence. This was achieved by undertaking in-depth one-to-one interviews with 45 patients in three Trusts in NHSScotland.

5. Issues to emerge from this qualitative research include:
- participation in residential or day case relapse services may currently depend on the way services are structured locally, rather than patient choice
- lack of understanding of terms such as Cognitive Behavioural Therapy and Motivational Enhancement Therapy need to be recognised in communication with service users
- participants valued activities such as coping skills training, assertiveness training, anger management, stress/anxiety management, relaxation exercises and rehearsing difficult situations within a safe environment
- views about pharmacological interventions differed greatly. Some people identified a role for acamprosate in providing confidence about not being tempted to drink, while others doubted whether acamprosate reduced the sense of craving. However, those who felt the benefits were convinced.
- most people who had no experience of taking disulfiram said this was because they would not trust themselves not to drink while taking it
- all who took these pharmacological interventions believed that the pharmacological and psychosocial interventions were complementary
- women who had experienced 'women only' group work had a preference for women only groups, but conversely men may have a preference for mixed sex group work
- individual therapy sessions may be valued for the depth of work they enable
- flexibility of times and venues was valued
- a Helpline number given to people when they were discharged from inpatient treatment in one Trust was valued
- all participants in this sample of National Health Service attenders recognised that Alcoholics Anonymous works well for many people, but most of them felt that it was not suitable for them
- awareness of services other than Alcoholics Anonymous may be low and may require better promotion.

6. Additionally, the study, the literature and consultation comments indicate that awareness of different services and treatments may be low among health professionals and service users and require better promotion and discussion to identify treatment preferences. A shared understanding and mutual agreement regarding the purpose of treatment is important between a person who is alcohol dependent and his or her doctor.

7. Letters from services users of residential 12-step settings tended to emphasise the benefits of residential treatment and Alcoholics Anonymous.

8. It is clear from the results of clinical studies that all interventions are of limited effectiveness. It is therefore worth providing a range of options of proven efficacy. Treatment should be individualised taking account of patients' expectations, needs and wishes with the understanding that these needs may change and the treatment plan should adapt to this.

1.6 Economic evaluation

1. The economic evaluation compared the costs and consequences of seven therapies in comparison to a standard care package. The relevant outcomes were disease states, these being alcohol dependence, alcoholic psychosis (including alcohol-related brain damage), liver cirrhosis, epilepsy, chronic pancreatitis, cancer, stroke and death.

2. For each therapy, the costs and consequences for 1000 patients complying with the therapy were modelled and compared with the costs and consequences for 1000 patients receiving a standard care package. This involved:
- defining and costing each intervention
- applying the clinical effectiveness odds ratio for the intervention to the epidemiology for the cohort, to calculate the number of patients likely to be in the various disease states
- calculating the costs to NHSScotland of the disease states
- calculating an incremental cost or saving per additional abstinent patient.

3. The results show that each of the four psychosocial interventions (Coping/Social Skills Training, Behavioural Self-Control Training, Motivational Enhancement Therapy and Marital/Family Therapy) and acamprosate produce net *savings* per incremental abstinent patient. This means that the cost of the intervention is less than the savings it affords to NHSScotland. These savings arise because the improved abstinence rate results in a lower incidence of diseases, thereby saving inpatient hospital stays and other disease-related costs.

4. Naltrexone and unsupervised oral disulfiram have a net cost per abstinent patient but are judged to be cost effective in comparison to standard care. Sensitivity analysis shows that the ranking of therapies is robust.

5. A limitation of the model is the absence of data on relapse rates beyond the relatively short trial periods. There are also concerns about generalising from trials to treating patients in a Scottish setting. Further research and evidence is therefore needed to give more definitive estimates of the long-term effectiveness of all the therapies in a Scottish setting.

1.7 Organisational issues

1. Randomised controlled trials testing matters related to the organisation of specialist alcohol services are scarce. Thus, recommendations with regard to organisational issues also take account of clinical expert judgement, economic evaluation, patients' needs and preferences, surveys of existing services and relevant policy documents.

2. Alcohol dependence is a relapsing condition and the need for ongoing treatment, even after a number of unsuccessful interventions, should be recognised.

3. Alcohol services are highly suited to 'joint working', as recommended by the Joint Futures Group, involving specialist mental health and social work addiction services and non-statutory agencies with joint resourcing and management of community care services.

4. Certain subgroups such as young people, the homeless and those with comorbid mental health problems, have special service needs and providers should ensure that the service is accessible to all and responsive to differences in users' needs.

5. NHS specialist alcohol services should be multidisciplinary community (and day hospital) based services with the option of specialist inpatient/residential care. Consolidation of services may be necessary to allow for a concentration of expertise and resources for inpatient services for example.

6. Specialist services must make themselves aware of mutual help (Alcoholics Anonymous) and non-statutory agencies operating in their area and coordinate their approach, making this information available to individuals within their care. Informing patients about Alcoholics Anonymous and non-statutory agencies should be part of the overall strategy for prevention of relapse.

7. In specialist settings it will usually be the case that abstinence will be the goal for severe dependence, where controlled use is rarely sustainable and especially when there is evidence of alcohol-related organ damage. Controlled use of alcohol may be an appropriate treatment goal for those with less severe alcohol problems. If controlled use or harm minimisation is the considered preferred goal of the individual, there must still be options for intervention e.g. referral to a non-statutory agency or outpatient motivational sessions.

8. The National Health Service survey identified gaps in the core provision of services for inpatient/residential facilities and for staffing. In addition to the core services, it is good practice for specialist services to make arrangements for continuing care of service users. For example, service users value follow up, such as a phone call, when they miss appointments.

9. An improved information collection system is required. Information and Statistics Division is currently developing the National Alcohol and Information Resource for use by those who plan and provide services. Local services should liaise with Information and Statistics Division regarding methods of recording and collecting information.

10. A regularly updated comprehensive directory of alcohol services including residential treatment would be beneficial. This should be useable by all participating agencies and where available provide accurate outcome data as well as a greater understanding of progress through the treatment system.

11. The financial implications of implementing the recommendations presented in the organisational and patient issues sections of this Assessment Report amount to £2.5 million per annum.

1.8 Discussion

1. This Assessment Report addresses the problems of prevention of relapse in people who are alcohol dependent and have undergone detoxification and are newly abstinent.

2. The focus of this Assessment Report is the service delivered by NHS specialist staff and the evidence reviewed is largely drawn from studies carried out in a specialist setting. Extrapolation from any of the Health Technology Assessment conclusions to other settings should be undertaken with caution. Advice on management of alcohol problems by primary care professionals is available from the Scottish Intercollegiate Guidelines Network (SIGN).

3. This Health Technology Assessment views alcohol dependence from a health perspective. However, no effective service can ignore the societal aspects of drinking alcohol. The existence of a spectrum of drinking from the socially acceptable, and even encouraged, to the socially unacceptable and dangerous necessitates an unbiased self-assessment by the person before treatment will even be sought. Thus, judgmental attitudes concerning alcohol dependence may delay some people in seeking help. In consequence, weight has been given in this Health Technology Assessment to perceptions of service users and the message that any alcohol treatment service must be approachable cannot be emphasised too highly.

4. The long-term health consequences of harmful drinking have been reviewed using sources drawn from published literature. This analysis revealed the extensive damage caused to the health of people who drink beyond defined limits. The increased risk of several types of cancer, liver disease, brain damage and of death from many causes show clearly the importance of identifying and effectively treating alcohol dependence at an early stage.

5. The quality of evidence regarding effectiveness of interventions is not high. Most studies of psychosocial interventions are performed by skilled enthusiasts. Furthermore they generally involve small, and

necessarily unblinded, trials. The assumption that other specialists can consistently achieve similar results in everyday practice is not obviously justifiable. Hence, very stringent criteria have been imposed in the cost-effectiveness analyses to test the robustness of the Health Technology Assessment conclusions on this point. Similar remarks apply to acamprosate and naltrexone which show unexpected variations in efficacy between studies.

6. The concern that it might be difficult to reproduce in clinical practice the effectiveness seen in clinical trials has led to several conclusions with respect to the importance of therapist training, access to expert psychological advice and the existence of robust quality assurance measures. It is stressed that the complex nature of psychosocial interventions and the important role of therapist qualities in their delivery make these measures an essential element in ensuring a consistent and effective service.

1.9 Recommendations

1. Behavioural Self-Control Training, Motivational Enhancement Therapy, Marital/Family Therapy and Coping/Social Skills Training are clinically and cost-effective psychosocial interventions and are recommended treatment options for the prevention of relapse in alcohol dependence.

2. Brief Interventions are not recommended, as trials in people with alcohol dependence have failed to show any benefit. However, the Scottish Intercollegiate Guideline Network (SIGN) will recommend Brief Interventions for hazardous drinkers (a less severely affected group than those who are considered to be alcohol dependent).

3. Other psychosocial interventions are not recommended as their clinical effectiveness is unproven.

4. Acamprosate and supervised oral disulfiram are treatment options recommended as adjuncts to psychosocial interventions. Naltrexone does not have a Marketing Authorisation for the treatment of alcohol dependence in the United Kingdom and is not recommended for routine use in NHSScotland.

5. Alcohol services should aim to reduce the delay between detoxification and interventions for the prevention of relapse. This would be facilitated by joint working between specialist mental health services, primary care, social work addiction services and non-statutory agencies, as recommended by the Joint Futures Group.

6. Acamprosate or supervised oral disulfiram should usually be initiated by a specialist service. The specialist service will: ensure that the patient meets the criteria for suitability; ensure the assessment of the motivation and ability of the patient to use the medication correctly; monitor efficacy; and ensure that adjunctive psychosocial treatment is organised. Usage should be in accordance with the Summary of Product Characteristics, and should also be reviewed regularly during the first 12 weeks after initiation of treatment, at which stage transfer of prescribing to the general practitioner may be appropriate, even though specialist care may continue (shared care).

7. Introduction to Alcoholics Anonymous and non-statutory agencies such as local Councils on Alcohol (Alcohol Focus Scotland) should be part of the overall strategy of specialist NHS services for the prevention of relapse. As with other psychosocial treatments, attendance is most likely to be beneficial if it is an informed voluntary decision.

8. People who are alcohol dependent should be informed about treatment choices. Their needs, preferences and social circumstances should be considered. As a result, the choice of interventions should be a shared decision between the health professional and the patient.

9. NHS specialist services should contact people who drop out of treatment programmes and offer them another appointment.

10. Health professionals should provide patient information, including leaflets, which should be used to support discussion between health professionals and patients about the most appropriate treatment option.

11. Written information about the range of available services should be readily accessible to people with alcohol problems, their families, carers and to health professionals, especially general practitioners. Alternative formats such as cartoons or audio-visual material should be used to support discussions with people who have low reading skills or poor concentration. Alcohol Action Teams could coordinate information requirements.

12. A regularly updated comprehensive directory of alcohol services and accommodation should be developed for the benefit of NHSScotland staff, patients and their families, friends and carers.

13. Shorter, less intensive interventions (such as Motivational Enhancement Therapy) might be provided first, following the principle of 'stepped' care, if the history suggests that such a relatively low intensity approach has not already failed. Non-response will indicate the need to move to more intensive treatment.

14. Recurrent relapse should not be a barrier to re-referral. If a particular intervention is unsuccessful for an individual, it is important to recognise that other treatments may be more suitable and that further options should be explored.

15. Core services should provide the full spectrum of treatment options, including access to beds for NHS inpatient or private/non-statutory residential treatment. This might be achieved economically by sharing of services across Trusts and Boards provided that access is carefully considered.

16. To ensure equity of access for the heterogeneous group of people with alcohol dependence, the provision and standard of alcohol services should be consistent throughout NHSScotland.

17. Specialist NHS services should make provision for the continuing care of each individual.

18. Certain subgroups of people with alcohol dependence such as those in rural communities, young people, the homeless, those with comorbid mental health problems and those in the criminal justice system can encounter unique difficulties in accessing specialist services. Providers should make reasonable efforts to ensure that the needs of every alcohol-dependent person can be accommodated somewhere within the spectrum of service provision.

19. Providers should develop services for the relatives, carers and dependants of people with alcohol dependence.

20. Joint training of staff from NHS and non-statutory services is recommended to help ensure that all staff are trained to uniform standards and equipped with the necessary skills to deliver the recommended interventions.

21. Interventions should be carried out in accordance with standardised protocols by staff trained to agreed national standards.

22. Measures should be in place to ensure that psychosocial treatments are delivered to consistently high standards over time. The delivery of these interventions should be as similar as possible to that which has been shown effective in clinical trials. As these have involved delivery by clinical psychologists, the skills of such professionals should be used at least in supervision of treatment delivery and in training in methods of delivery.

23. The Plan for Action (Scottish Advisory Committee on Alcohol Misuse, 2002) requires each Alcohol Action Team to draw up, publish by April 2003, and subsequently implement, a local strategy covering at least three years. These strategies should take account of these recommendations.

24. An improved information collection system is required to ensure that the requirements of these recommendations are fulfilled. Development of the National Alcohol and Information Resource (NAIR), currently being undertaken by the Information and Statistics Division, should take these requirements into account.

25. In order to assess the long-term clinical course of alcohol dependence following treatment in Scotland, measurement of simple, verifiable outcomes such as further detoxification over a period of, for example, five years would prove useful. Long-term treatment success rates in terms of abstinence or controlled drinking should be reported.

26. More research is needed regarding the benefits of different settings for psychosocial interventions in order to determine the most effective and efficient approach to delivering the interventions. It has not been established whether group therapy is more effective than individual therapy, or whether an inpatient, outpatient or day unit setting is most conducive to treatment success. It is unclear if there is a correlation between the effectiveness of interventions and the length, frequency or intensity of treatment. In particular, the impact on effectiveness of multiple psychosocial treatments for one individual is not established.

27. Acamprosate (and naltrexone) have given unusually variable results in clinical trials in specialist settings, with some trials having shown no treatment effect. Possible explanations have been suggested but these require corroboration by prospective studies. Given the variability of effect even in specialist settings, any extrapolation to use in primary care requires new clinical trial evidence of effectiveness.

28. A trial of supervised oral disulfiram has shown a convincing reduction in drinking while on the drug but no study has demonstrated that this results in an increased likelihood of ongoing abstinence or controlled drinking. Such a study is needed to inform clinical practice.

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PREDICTORS OF RELAPSE TO HARMFUL ALCOHOL AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Abstract — Background: End-stage alcoholic liver disease (ALD) is a common indication for liver transplantation. Outcomes may be limited by return to harmful drinking. Previous studies have identified few predictors of drinking relapse. **Aim:** This study examined novel postulated predictors of relapse to drinking. **Method:** The case notes of all patients transplanted for ALD at the Royal Prince Alfred Hospital from 1987–2004 were reviewed. Pre-transplant characteristics were rated by a psychiatrist independent of the transplant team, blind to the outcome. Outcomes were rated by a second independent alcohol treatment specialist also blind to the pre-transplant ratings. **Results:** Of 100 patients, 6 died before discharge from hospital, 4 had <6 months follow-up, 18 relapsed to harmful drinking, 10 drank below harmful levels, and 62 remained abstinent after a mean of 5.6 years follow-up. Univariate analyses identified six potential pre-transplant predictors of return to harmful drinking. These were a diagnosis of mental illness (of which all cases were of depression), the lack of a stable partner, grams per day consumed in the years before assessment for transplant, reliance on 'family or friends' for post-transplant support, tobacco consumption at time of assessment, and lack of insight into the alcohol aetiology. Duration of pre-transplant abstinence and social class by occupation did not predict relapse. A multivariate model based on the above characteristics correctly predicted 89% of the outcomes. **Conclusion:** A model based on readily defined behaviours and psychosocial factors predicted relapse to harmful drinking after transplant for ALD. This model may improve assessment and post-transplant management of patients with advanced ALD.

Alcoholic liver disease (ALD) is a common cause of cirrhosis of the liver and is also a common indication for liver transplantation. Following early uncertainty, it is now widely accepted that the overall clinical outcomes of liver transplantation for carefully selected patients with ALD are similar to those of other forms of liver disease (Lucey *et al.*, 1992; Haber *et al.*, 1999; Bjornsson *et al.*, 2005). However, relapse after transplant to harmful use of alcohol remains a concern and can lead to significant problems. Up to 40% of those receiving a liver transplant will return to consuming alcohol (Bird *et al.*, 1990; Lucey *et al.*, 1997; Gish *et al.*, 2001; Pageaux *et al.*, 2003; Lim and Keeffe, 2004). Up to 20% drink heavily (Pageaux *et al.*, 2003; Lim and Keeffe, 2004), which can lead to recurrent ALD (Pageaux *et al.*, 2003), graft failure due to non-compliance with immunosuppression treatment and other serious alcohol-related harms including death (Cuadrado *et al.*, 2005).

Orthotopic liver transplantation is a highly resource intensive treatment with access typically limited by availability of suitable donor livers. The identification of those patients likely to experience the maximum sustained benefit is very important. Specific and objective selection criteria have been sought without success to date. A minimal period of 6 months pre-transplant abstinence from alcohol is an objective measure widely adopted as it provides adequate time to demonstrate cessation of alcohol use and also provides the opportunity for many patients to recover adequately so as to no longer require transplantation. However, this 'six month rule' has been criticized as being arbitrary and the pre-transplantation duration of abstinence is a poor predictor of outcome (Weinrieb *et al.*, 2000; Neuberger *et al.*, 2002; Lim and Keeffe, 2004). Lucey *et al.* (1992) proposed that four factors defined risk of post-transplant relapse to heavy drinking (insight, stable partner, stable housing, stable employment). Subsequent research from several groups has shown that pre-transplant assessment does not predict the minority who return to heavy drinking after successful transplantation (Lucey *et al.*, 1997; Mackie *et al.*, 2001; Bjornsson *et al.*, 2005). However, DiMartini *et al.* (2001) reports predictive data in a study of 36 patients surviving transplantation for ALD. Post-transplant use of any alcohol was significantly associated with prior non-alcohol substance use, presence of a first-degree relative with alcoholism, prior alcohol rehabilitation but not with prior psychiatric history. Diagnosis of alcohol dependence by an addiction psychiatrist was the only pre-transplant factor assessed, which predicted return to harmful drinking (Smyth *et al.*, personal communication).

The relevance of factors associated with relapse in addictions outside the transplant context remains unclear. Prognostic factors of interest include insight, presence of psychiatric comorbidity, stability of relationships, housing and employment, maintenance of abstinence while physically well enough to drink, and expansion of social role with abstinence. Rather than any consumption of any alcohol, the outcome variable of interest was harmful alcohol consumption as the latter is of greater clinical significance. The aim of this study was to test the value of these parameters as predictors of relapse to harmful drinking after liver transplantation for ALD.

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METHODS

The study protocol was approved by the Ethics Review Committee of Central Sydney Area Health Service (RPA Zone). The Australian National Liver Transplant Unit is based at Royal Prince Alfred Hospital and maintains a prospective database of all liver transplants, which includes the underlying aetiology for liver disease. The standardized pre-operative checklist did not include the specific questions we wished to look at, covering medical and demographic items. Accordingly, the notes of all patients who received a liver transplant with a record of alcoholic cirrhosis as either the primary or secondary diagnosis were reviewed.

From study of the literature, consultation with the transplant team, including the liaison psychiatrist and the substance misuse specialist who had interviewed a proportion of the patients, a list was prepared of candidate predictors of post-transplant drug and alcohol misuse, which was refined to include only the items for which the pre-transplant assessment and medical records would provide data. Some pre-transplant variables of possible interest were not included because data were not consistently recorded, e.g. alcohol rehabilitation experience and family history of alcoholism.

A psychiatrist (M.K.) who was blind to the post-transplant outcome examined the pre-transplant hospital notes for all information recorded of relevance to the candidate predictors of outcome (Table 1). All patients had had a discussion with the transplant team about their alcohol use, and the need for life-long abstinence from that point was routinely stressed. Only when it was noted specifically that motivation or insight was a concern was that patient given a negative score for that binary variable. Where there had been no mention of concern, the patient was rated by M.K. as 'positive'. A senior alcohol specialist (J.C.), who was blind to the pre-transplant ratings, examined the post-transplant notes to rate outcome. Neither had met the patients or had any role in the treatment of the patients, nor in the transplant unit. In two instances where post-transplant data were equivocal, further information was obtained from an outside specialist who had treated the patient since the transplant.

As a measure of inter-rater reliability, the assessments made on eight patients by a third rater (M.H.) were compared with the ratings made by M.K. and J.C.

Table 1. The predictor variables

Addiction variables
- Grams per day of alcohol when drinking (in the pre-transplant assessment years)
- Number of days abstinent before transplant
- ICD 10 diagnosis of dependence present or not: diagnosis recorded in the records, or any history of withdrawal symptoms, including an alcohol-related seizure
- Insight into cause of liver failure—did the patient believe the cause was alcohol?
- Motivation to stop drinking as assessed by addictions specialist or others
- Any drug misuse and amount per day
- Ever injected
- Tobacco use (cigarettes per day at time of final transplant assessement)

Psychosocial variables
- Housing stability—more than 2 years in current address
- Committed cohabiting spouse or partner
- Family or friends named as primary support, as stated by the patient
- Previous employment (coded as professional, blue collar, or unemployed)
- Diagnosis of any mental illness: a pragmatic definition based on any record made by the physician of a diagnosis *and* specific treatment for that illness
- Post-alcohol lifestyle. This was registered as illness lifestyle—i.e. no other meaningful occupation such as return to work or home activities or voluntary work during the period of abstinence prior to liver failure and transplantation

Assessment factors
- Early or late assessment—due to medical condition of patient—assessment may not have included consultation with addictions or psychiatry specialist
- Consensus of opinion—did every consultant involved offer the clear opinion to go ahead with transplant or were doubts raised

Outcome variables

Our primary outcome variable was the incidence of return to harmful drinking. The definition of harmful drinking was drinking with recorded medical or social harm, or drinking above 140 g ethanol/week. 'Harm' included evidence of ongoing abnormal liver tests consistent with alcohol, which could not be accounted for by other factors despite investigations and careful consideration of organ rejection and medication. None of the case records includes results of breathalyser tests, or blood or urine ethanol. In our analysis, those who drank below harmful limits are included with the abstainers. Any record or evidence of post-transplant drinking was noted.

Statistical analysis

Univariate tests of significance between the two outcome groups were conducted using cross-tabulations and Chi-squared tests for categorical variables (continuity corrected), with appropriate attention to small cell sizes. Mann–Whitney *U*-tests were used for continuous variables. Stepwise logistic regression analysis (forward conditional) was conducted to identify significant predictors to harmful drinking. The Statistical Package for the Social Sciences (SPSS Version 13 for Windows, Chicago, IL) was used for all analyses.

RESULTS

There were 100 patients between 1987 and 2004 who received liver transplants for ALD alone or with a diagnosis of chronic viral hepatitis. Three patients were transplanted twice, owing to complications unrelated to substance misuse, making a total of 103 such transplants. The numbers of patients transplanted for ALD increased as the years went by. Between 1987 and 1990, there were only 3; from 1991 to 1994, 14; from 1995 to 1998, 26; from 1999 to 2002, 30; and from 2003 to 2004, 30.

Six died at or soon after the transplant, and four had less than 6 months of follow-up at the time of the ratings and were not included in the study. Of the remaining 90, 18 (20%) relapsed to harmful drinking and another 10 drank below harmful levels up to the date of the study (total drinkers 28, 31%; Fig. 1). Of the 26 patients who had ever used illicit drugs prior to transplant, 22 of whom had injected, 10 (38%) resumed illicit drug use post-transplant, and 2 (9.1%) resumed injecting. Of those who consumed illicit drugs post-transplant four were also harmful drinkers and six were abstainers from alcohol. Of the abstainers and non-harmful drinkers, 67 were male (81%); of the 18 harmful drinkers, 15 were male (83%).

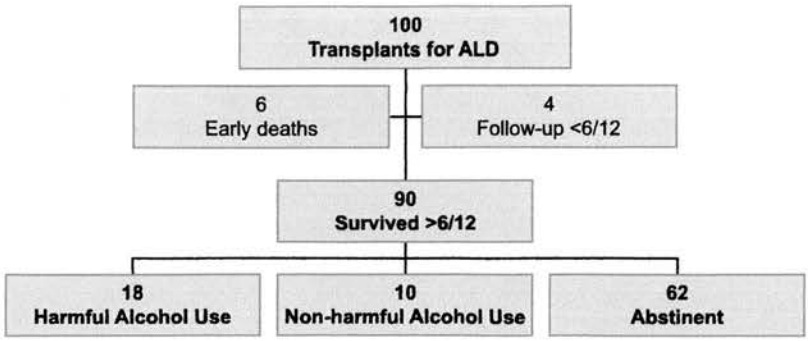

Fig. 1. Overview of study results.

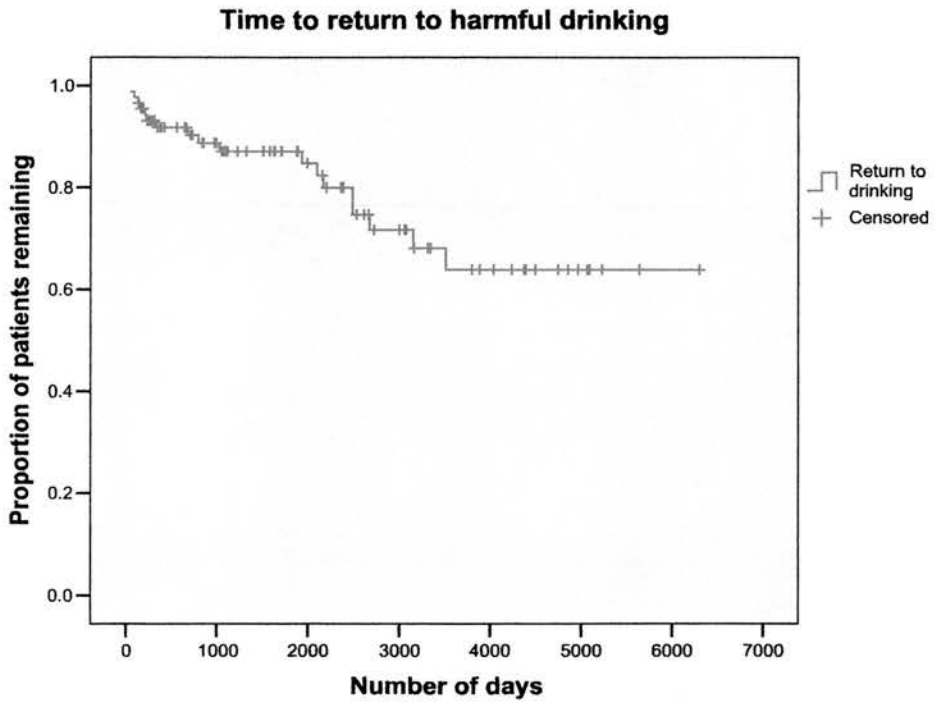

Fig. 2. Cumulative survival to time to first record of harmful drinking following transplant (days).

The time to a record in the casenotes of harmful drinking post-transplant varied from 60 days to over 10 years (Fig. 2). Fifty percent of relapses were recorded within the first 2 years. The mean duration of follow-up was 5.6 years, suggesting the duration of follow-up was sufficient to detect most relapse events. Relapse to harmful drinking emerged as very serious for several patients. One patient had a drink drive offence, another's drinking led to his partner leaving, one patient developed life-threatening alcoholic pancreatitis, and one man died on the waiting list for a second transplant liver having once again developed ALD.

Inter-rater reliability

In all eight cases there was complete agreement between raters on all pre-transplant and outcome variables.

Univariate analysis

The characteristics of interest as possible predictors of relapse among these 90 patients are shown in Table 2. A series of univariate tests, showed that tobacco consumption at the time of assessment, the presence of mental illness diagnosis prior to transplant, lack of a stable partnership, and tobacco consumption were significantly associated with post-transplant harmful drinking. In addition, there were a number of variables approaching significance. These were a lack of insight into alcohol as the main aetiology of liver failure, lack of a meaningful abstinent lifestyle, unstable housing, grams per day of alcohol consumed when drinking in the years before the assessment for transplant, late referral for transplant assessment, and a lack of consensus concerning suitability amongst the transplant team. The presence of stated family or friend

Table 2. Univariate analysis of pre-transplant risk factors for harmful alcohol consumption post-transplant

Pre transplant variable	None/not harmful drinking $N = 72$	Harmful drinkers $N = 18$	Significance P-value[a]
Alcoholic cirrhosis—primary diagnosis *n* (%)	44 (61%)	7 (40%)	0.089
Age at transplant mean (SD) (median)	50.8 (7.2) (50.5)	47.5 (5.8) (48.5)	0.101
Days from transplant to outcome assessment mean (SD) (range)	2022 (1689) (143–6302)	2195 (963) (635–4175)	0.246
Addiction behaviours			
Ethanol per day [g; mean (SD)]	135 (67)	188 (109)	0.077
No. of days abstinent before transplant mean (SD) (range)	686 (680) (120–3650)	697 (642) (60–2190)	0.940
Abstinent <1 year pre-transplant *n* (%)	22 (30%)	7 (39%)	0.499
ICD 10 diagnosis of dependence *n* (%)	19 (26%)	6 (33%)	0.556
Insight: poor *n* (%)	17 (24%)	9 (50%)	0.055
Motivation: doubtful *n* (%)	12 (17%)	6 (33%)	0.114
Any drug misuse *n* (%)	19 (26%)	7 (39%)	0.295
Ever injected *n* (%)	15 (21%)	7 (39%)	0.111
Tobacco use per day (median) (range)	1 (0–60)	10 (0–50)	0.026
Psychosocial			
Housing unstable *n* (%)	10 (14%)	6 (33%)	0.054
No partner *n* (%)	16 (22%)	9 (50%)	0.019
No family/friend support *n* (%)	14 (19%)	1 (6%)	0.157
Previous occupation			0.669
Blue collar *n* (%)	49 (69%)	11 (61%)	
Professional *n* (%)	18 (25%)	5 (28%)	
Unemployed *n* (%)	4 (6%)	2 (11%)	
No 'post-alcohol lifestyle' *n* (%)	36 (50%)	13 (72%)	0.053
Previous diagnosis mental illness *n* (%)	3 (4%)	4 (22%)	0.011
Transplant assessment factors			
Late assessment	4 (5.6%)	4 (22.2%)	0.079
Consensus—doubt	10 (14.%)	6 (33.%)	0.054

[a]Continuity correction used for 2 × 2 tables.

Table 3. Final regression model

Variables entered in final model	Coefficient β	Standard error	P-value for use in model	Odds ratio	95% confidence intervals for Exp β	
					Lower	Upper
Grams per day alcohol	0.009	0.005	0.059	1.009	1.000	1.018
Mental illness	2.005	1.026	0.051	7.424	0.993	55.485
Partner	–2.611	0.823	0.002	0.073	0.015	0.368
Family/friends	3.669	1.444	0.011	39.16	2.314	663.792
Cigarettes/day	0.061	0.025	0.016	1.063	1.012	1.116
Insight	–1.770	0.754	0.019	0.170	0.039	0.748
Constant	–4.079	1.681	0.015	0.017		

support correlated with harmful drinking outcome (see Discussion).

Multivariate analysis

A stepwise logistic regression analysis showed that a model based on six pre-operative predictor variables accounted for 52% of the variance in outcome ($P < 0.0001$). All the hypothesized predictor variables were significant and were included in the following order (Table 3):

(i) grams per day alcohol before assessment for transplant;
(ii) mental illness diagnosis;
(iii) stable relationship;
(iv) family or friends support;
(v) tobacco use per day;
(vi) insight into alcohol aetiology.

The multivariate model correctly classified the outcome of 89% of patients (Table 4). Ten of the twelve who the model predicted would return to harmful drinking did so, indicating that the positive predictive value was 83%. Two were incorrectly predicted to return to harmful drinking. Of the 77 cases where the model predicted no return to heavy drinking, 8 cases relapsed indicating that the negative predictive value was 90%.

Table 4. Classification of outcome by model at step 7

Observed	Predicted: Drinking status: Abstinent/not harmful drinking	Predicted: Drinking status: Harmful drinking	% correct
Abstinent/not harmful drinking	69	2	97.2
Harmful drinking	8	10	55.6
Overall percentage			88.8

DISCUSSION

This study has demonstrated that pre-transplant assessment of patients with ALD is able to identify patients at particular risk of returning to harmful consumption of alcohol post-transplant. The predictors of outcome were those that could be defined by the transplant hepatologist without specialist skills in addiction medicine, or psychiatry. A comprehensive structured assessment battery was not in place in the service studied; a role for routine use of such batteries is not yet established. The model predicted the presence or absence of relapse in 89% of cases. There is evidence that relapse to alcohol use adversely impacts on survival. The findings of this study should be replicated in a different transplant population before being incorporated into transplant assessment protocols. Additionally, prospective identification of the group at greatest risk of post-transplant substance use problems creates the opportunity for additional intervention to prevent relapse and its associated adverse clinical events.

Strengths and limitations

The strengths of the study design are that we had independent blind raters who assessed clinically relevant outcomes with a relatively large sample size for a single centre study. The study looked strictly at recorded material and was not influenced by any knowledge or personal involvement in any clinical care. The outcome ratings were done by an expert in alcohol problems with experience in detecting alcohol abuse using all clinical indicators. Harmful drinking, not 'any drinking' was used as the outcome of interest; this is a more clinically relevant outcome measure. It avoids making assumptions of whether low-level drinking may or may not lead to later harm, although it may be noted that only one-third of post-transplant drinking was rated as 'non-harmful'. The focus for this study was the clinical records made by clinicians performing routine care, yielding a measure of clinically significant relapse. This may have been less sensitive than any self-reported alcohol consumption, but was likely to be more specific by focussing on clinically important use of alcohol. It did not include subclinical alcohol consumption and thus reduced 'noise' in the data. Self-reports of consumption, unreliable in many contexts, may be especially unreliable when, as in a transplant unit, the patient had given a vow to abstain. However it is possible that relying only on case records will miss some cases of return to heavy drinking, which have not aroused clinical suspicion, despite frequent close monitoring by the transplant and community teams of both clinical and laboratory parameters, and regular communication between transplant clinicians and the patients carers.

Similarly, the date of recording of harmful drinking does not necessarily indicate the date harmful drinking commenced, because it may have been hidden for some time. Nonetheless, it is striking that the majority of relapses occurred early, and therefore interventions even only in the first post-transplant year would be likely to help reduce the total relapse rate. However, as almost half the relapses occurred after the first 2 years, close monitoring of an at risk group should be sustained long term.

The model

Our findings indicate that if each patient is assessed and given a score according to these variables it is possible to predict with a fair reliability the patients who are vulnerable to a return to harmful drinking. It is important to validate these findings in a different transplant population before applying the model more widely. This study has also shown that no single predictor, when used on its own, predicted relapse with any reliability. The diagnosis of mental illness, the lack of a stable partner, and tobacco use were individually significant; however, the increase in relapse risk was modest. The illnesses recorded were, in the event, all cases of depression of varying severity, all with previous treatment. However, depression is a condition that can respond to psychiatric treatment, and relapses can be prevented, if treatment is available and accepted. These findings do not suggest that a history of depressive illness should be an exclusion from transplant, but an indication for specific assessment and outpatient monitoring.

Entry to the transplant waiting list is based on consensus decision from a weekly meeting of transplant clinicians. The clinical opinion of transplant psychiatrist and substance misuse physician is included in this process. The present statistically significant findings have emerged despite the possibility that the more extreme scorers on these parameters would already have been excluded from transplantation, thus biasing the study against identifying predictive factors. This helps to support the validity of the identified factors. Even though these findings are statistically impressive, it is important to place them in the appropriate clinical context. The transplant team would not wish to refuse transplantation on the basis of a wrong prediction that the candidate will return to harmful drinking. This would have occurred on 2 of 12 occasions based on a model using these predictors. Indeed, 8 of 18 relapses occurred in those predicted to be at low risk according to our model. Moreover, many relapses were not life threatening. Once identified, most patients responded to further interventions and reduced their drinking.

Comments on individual predictors

The finding that average consumption in grams per day during heavy drinking periods during the years before the assessment for transplant correlates positively with the risk of relapse may say something important about the recording of alcohol consumption data. Studies that have found that pre-transplant consumption was not a predictor of relapse may have used weekly consumption or some other averaging method, which blurred the importance of heavy session drinking as a predictor of harm (Miller *et al.*, 2005).

Unlike in the Edinburgh follow-up study (Smyth *et al.*, personal communication), the presence or absence of a diagnosis of previous alcohol dependence was not often stated in the notes. The reason may be that relatively few patients receive assessment by an addictions specialist so more of those who relapsed may have met the criteria for dependence than we have shown. Previous studies have found that a significant number of patients transplanted for ALD never met criteria for dependence (Lucey *et al.*, 1992).

Looking further at the factors that contributed to our predictor model, we suggest that the evaluation of insight into cause

of illness and motivation to change may be valuable for every candidate during the pre-transplant assessment. The level of insight described in this study is relatively modest and future research might evaluate this in greater detail to include insight into personal limitations and treatment needs. This should also, ideally, be a time for planning long-term support and an illness-free and addiction-free lifestyle.

The stated presence of family and friend support correlated with return to drinking, which seems counter-intuitive. One explanation is as follows. The pre-transplant patient is asked to name a support network and if he/she does not have a cohabiting partner, may identify 'family or friend support'. A number of patients named former spouses who agreed to give specific support for a limited time period—for example, the acute post-operative period. The same applied to parental or other family support where a patient planned to move temporarily into a family or friends' home during the early recovery period. However, this is also the time that they are least likely to resume drinking. The years after the acute illness has passed are likely to be more risky (Fig. 2) and in some of the cases where 'family and friends' support' had been named, perhaps the least supported.

It was noteworthy that pre-transplant tobacco use was a predictor of post-transplant alcohol use. This association might reflect the presence of a greater tendency to substance misuse in general. In our centre, transplant candidates are strongly encouraged to stop smoking in view of the association with a range of adverse events post-transplant including post-operative respiratory complications, vascular complications (Pungpapong *et al.*, 2002), and osteoporosis (McCaughan and Feller, 1994). It is not surprising that those who continue to smoke against advice may be at risk of other therapeutic non-adherence. Post-transplant smoking has recently been shown to adversely impact on clinical outcomes (Dimartini *et al.*, 2005). Thus, smoking is both a marker of the risk of returning to alcohol consumption and a significant clinical problem per se.

The duration of abstinence prior to transplantation was not a predictor. Our transplant centre generally adopts the six-month rule and accordingly only six cases were transplanted with less than 6 months abstinence. Nonetheless, the finding is consistent with other studies that have found that other factors are more important predictors of outcome than the duration of abstinence taken in isolation (Weinrieb *et al.*, 2000). Finally, we wish to underline that, in this sample, social class measured by occupation did not predict outcome, either in univariate analysis or after adjustment for other variables.

In conclusion, we have found that a multivariate model based on four adverse factors (presence of documented mental illness, level of alcohol consumption, continuing tobacco use, and the need to rely on friends or family for support) and two protective factors (presence of a cohabiting partner and insight into the aetiological role of alcohol) was able to predict the likelihood of relapse to harmful alcohol consumption after liver transplantation for ALD in 89% of cases. Similar factors are known to influence the prognosis of alcohol dependence outside the transplant context (Neuberger *et al.*, 2002), but this is the first study to identify pre-transplant factors that can predict return to harmful alcohol consumption after successful transplantation. The detailed psychosocial assessment plays a role in predicting outcome after liver transplant for ALD in terms of harmful drinking. The factors highlighted in this report can be assessed by non-specialist staff, but assessment by an addictions specialist may also be valuable because several of these factors may be amenable to change. Additional research should be directed towards validating these findings in other transplant populations, applying them prospectively to enhance pre-transplant assessment and case selection, and in designing pre-transplant and post-transplant monitoring and intervention programmes to minimize the relapse rates and attending harms to transplant patients and the community.

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20

Doctors with emotional problems: how can they be helped?

JONATHAN CHICK

Introduction

Mortality statistics in many countries show three conditions from which doctors tend to die more frequently than the general population: *suicide*, *liver cirrhosis* (much of which in the Western world is alcohol-related), and *accidents*. The first two, and perhaps the accidents also given the vagaries in the certification of suicides, point to psychiatric illness.

Studies of the *suicide rate in physicians* are not completely unanimous in finding an excess, and methodological problems in interpreting the occupational mortality data are described by several authors (e.g., Arnetz *et al.* 1987; Roy 1985). In the UK, however, the standardized mortality rate (SMR) for suicide in doctors has remained high throughout the twentieth century, except for the 1930s, when the national suicide rate increased dramatically during the economic depression. It is currently twice the rate for other professionals. In Sweden, the suicide rate in male physicians is not raised in comparison with the general population but is raised in comparison to others in the population with higher education (Arnetz *et al.* 1987).

Women physicians are at even greater risk of suicide than are men. Pitts *et al.* (1979) studied the information about cause of death in American physicians during the period from 1967 to 1972, and found that the suicide rate in the 751 female physicians who had died was 6.52 per cent, four times higher than the rate for white women over the age of 25. The recent 10 year prospective Swedish study found an SMR for female physicians of 5.7 (Arnetz *et al.* 1987).

Murray (1977) found that overall *psychiatric hospitalization rates* for Scottish male doctors were more than twice those of Social Class I controls. This difference was accounted for by the excess in the diagnoses of drug dependence, alcoholism, and depression. Studies of hospitalization in Canada, the US, and England and Wales have found the same pattern.

The *cirrhosis mortality* SMR in doctors has fallen in the UK recently, from 350 in 1962, to 311 in 1970–2, and yet further, to 115, in 1982–3 (OPCS 1986). The possibility that hepatitis B exposure might have accounted

cirrhosis rate in nurses, and thus alcoholism has usually been deemed to be the cause. No studies of trends in physicians' alcoholism morbidity rates are available to indicate whether perhaps by drinking less alcohol in recent years British doctors have lowered their incidence of this condition. An explanation for the fall in their cirrhosis death rate could conceivably be that alcoholic doctors now have a better outcome than two decades ago, and this will be discussed below.

Differences between specialties

The weight of the evidence in North American studies is that the suicide rate is higher among psychiatrists than among doctors who choose other areas of work. However, the well-conducted Swedish study already mentioned found that out of the 30 physician suicides over a 10 year period, surgeons had the highest relative risk (Arnetz *et al.* 1987).

Alcoholism, however, does not seem to be the prerogative of the psychiatrist. Murray (1976) found that only 6 per cent of the psychiatrists referred to the Maudsley Hospital in London were diagnosed as alcoholic, compared to 33 per cent of surgeons and 37 per cent of general practitioners. Extraversion and gregariousness are predictors of alcoholism when college samples are followed up, and perhaps psychiatry tends to recruit less of these personality types than surgery or general practice.

The causes of psychiatric illness in doctors

There is data to support both 'selective recruitment' (medicine attracts some vulnerable individuals) and an 'exposure' factor (stress, or other aspects of the work or of a doctor's life) to explain increased psychiatric illness in doctors.

The Harvard sophomore study of 268 college students was able to follow up 46 men who later went on to medical school, and chose 79 controls (fellow students) who did not (Vaillant *et al.* 1972). In the repeated interviews in the next three decades, doctors, especially those involved in direct patient care, were more likely than controls to report being unhappily married, to abuse drugs, and to have psychiatric treatment. These problems were associated with having had an unsatisfactory childhood, and greater instability at college, rather than any particular stress related to medical practice. It was concluded that there is a vulnerable minority among medical students, who may enter the profession as an attempt to be involved in caring relationships to compensate for their own unsupported childhoods and instability: 'It is in the physician with a barren childhood who is feeling overly burdened by dependent patients that trouble arises' (Vaillant *et al.*

Waring (1974) similarly concluded that family history, life experience, and personality before entering medical school, accounted for much of the psychopathology seen in doctors. A report in 1869 of the future careers of 1000 graduates of St. Bartholomew's Hospital Medical School, London, led James Paget to note that, of the 56 pupils who had 'failed entirely', 10 had done so 'through the continuance of the same habits of intemperance or dissipation, as had made us, even while they were students, anticipate their failure' (Collier and Beales 1989). Today male medical students do not report more alcohol consumption than other young men, though women medical students do drink more than their female peers (Collier and Beales 1989).

It seems to be only among women medical students that a higher than expected suicide rate is found. Surveys of medical students find that, compared to employed people of the same age in the general population, symptoms of anxiety and depression are more commonly reported by female and perhaps slightly less so by male students (reviewed in Surtees and Miller 1990). If a comparison is made with other undergraduate populations, such as law, pharmacy or dental students, it is seen that other disciplines also have a stressful rite of passage (Roy 1985). A higher rate of stress symptoms than in the general population also continues to be seen after graduation (Firth-Cozens 1989).

Part of the high doctors' suicide rate often found in the literature may be accounted for by their greater knowledge of lethal methods, as with pharmacists. Another undoubted contributary factor is alcoholism, follow-up studies of alcoholic physicians finding high rates of suicide (Roy 1985). For example, Murray (1976) followed 36 alcoholic doctors over five years and found that four had died by their own hand.

The American Medical Association (1987) gathered information from the colleagues, friends, and relatives of 142 doctors who died of suicide between 1982 and 1984, and compared this with information about 101 physicians matched for age and sex who had died of other causes. Most (94 per cent) were thought to have taken their lives because of mental pain, and some (26 per cent) also because of physical pain. There was a trend, not statistically significant, for the doctors who died of suicide to have had more difficult, emotionally draining patients in recent years. Alcohol and drug abuse were factors, as were previous psychiatric illnesses. Many (42 per cent) had been seeing a mental health specialist at the time of death, suggesting either an underestimating of the risk of suicide by therapists, or perhaps that there was an intractable chronic illness for which it was difficult to find a cure (58 per cent had been hospitalized for psychiatric treatment more than once). Physicians who had died of suicide were more likely to be thought of as critical of others, and highly critical of themselves. They tended to have fewer social supports. Alcohol abuse and depression were

The ready availability of drugs is an obvious explanation for the increase in drug dependence among doctors. There are a number of reasons put forward to explain why alcoholism is, or has been at least until recently, common in doctors. As well as usually being able to afford alcohol, some doctors work with little supervision, or in work settings in which there is no superior to comment on failing performance.

However, there are, of course, some aspects of work with patients which can lead to great anxiety, or despair, and which may lead either to use of drugs or alcohol as an escape, or to depression. Contact with death can disturb a doctor even after many years of practice. The fear of making mistakes, or having made a mistake, is something many doctors know. A patient's legal complaint, or a negligence investigation, can have a profound effect on a doctor's self-confidence, and his mood, as he or she goes through the phases of constant rumination on what happened, of anger, of fear of losing his professional authority or even losing his livelihood. Depression can arise when the work is unsatisfying because of the pressure of sheer numbers of patients to be seen, when feelings of being taken for granted by patients or the managing authority may fester and lead to demoralization or resentment.

Stress related to work has been studied in detail in contemporary British general practice by Branthwaite and Ross (1988). Questionnaires returned from 408 of 632 doctors revealed that 56 per cent experienced uncertainty or insecurity in their work, 38 per cent social isolation, 38 per cent poor relationships with other doctors, and 22 per cent disillusionment. These negative comments were more frequent in doctors who worked alone or in small groups, perhaps without support staff, and who had large practice lists.

Doctors' marriages may not be as supportive as they could be, if the diversion of energy and time away from the marriage and into helping patients has fostered resentment or loss of self-esteem in the spouse, with a deterioration of communication and loss of expressed affection. Doctors' wives sometimes feel profoundly neglected, a sad matter which also shows in the high suicide rate in wives of doctors compared to wives of other professionals reported by Sakinofsky (1980) in the UK.

Arnetz *et al.* (1987) found that women with higher education have an elevated suicide rate, approaching that of women doctors. This suggests that suicide among female physicians may be partly related to factors common to all women who aim for a career, such as the strain of combining the roles of wife, mother, and profession. The divorce rate is higher for women than men doctors (Lorber and Ecker 1983). Depression seems to be more common in female than male junior doctors and the contributants to this discrepancy have recently been discussed (Godlee 1990). A UK study of women junior doctors found that the most frequent stressors described were overwork and conflict between career and personal life. However, there was

also a high correlation between emotional disorder, the reporting of a poor relationship with the consultant, and worry over making clinical decisions (Firth-Cozens 1990).

Asking for help

'There were many dismal stories about practitioners whose competence to practise had plainly been impaired by illness, often psychiatric, but who soldiered on to the distress of their families and to the alarm of their colleagues' (Rawnsley 1985). There is an expectation felt by doctors themselves that they should not need help, that they should be able to sort out their own problems—'Physician heal thyself'. This is probably especially true in the UK, where in many sections of society, seeking psychological help is seen as weakness. This perpetuates *denial* of the illness. Being on the receiving end of help or advice is something many doctors find difficult, but airing this feeling may help a doctor cross the first hurdle.

Medical knowledge is no barrier to a doctor developing disabling hypochondriasis, when palpitations and dizziness are in fact due to the panic attacks of the anxiety or depressive state he or she will not acknowledge. Severe depressive illness may involve profound loss of insight. However, with drug and alcohol problems there are other dimensions to the denial which prevents seeking help. There is the fear of moral stigmatization. There is also the reluctance to admit any course of action which may lead to having to make a decision to reduce or terminate a habit which has been or still is enjoyable or felt as a necessary aid to coping.

Family and colleagues of the drug- or alcohol-abusing doctor may be drawn into *covering up*. Colleagues may turn a blind eye, even though their resentment grows as extra work accumulates for them. Lateness, unreliability, the smell of alcohol at work, tremor at the operating table—these signs are dismissed as 'stress'. No one wants to confront him or her. The spouse perhaps feels guilty and is just as afraid of the stigma of acknowledging an alcohol problem as the drinker. Colleagues are easily put off by the drinker making them feel like a wet blanket, spoiling the fun, or like meddlesome interferers who should mind their own business. Or there is a misplaced belief that 'loyalty' must override other considerations. An eminent surgeon's alcoholism was described thus (Strega 1978):

> . . . the extent of his drinking was acknowledged throughout the hospital. The subject was rarely discussed openly and then only with a mixture of jocularity ('Guess what he did next?') and hopelessness ('Well, how could I stop him?'). Nothing it seemed could threaten his inviolability, supported as he was by a pyramid of housemen, registrars, lecturers and research fellows. If one man had stepped out of line the whole fragile construction would have fallen; but whether out of loyalty to the gifted surgeon he once was or whether out of fear for the power of a referee, nobody moved a muscle.

It can take courage and compassion to act to help a sick colleague to get well.

Persuasion/coercion

Colleagues think that reason will eventually prevail. When it does not, and the miracle they pray for does not happen, and anger and resentment are allowed to build up, there is eventually a crisis leading to violent rejection perhaps with little understanding. Complaints are made. The doctor loses his reputation, perhaps his career; his alcoholism or depression gets much worse; suicide may seem a way out (Crawshaw *et al.* 1980).

At this point, when disciplinary action is considered, the employing authority, the General Medical Council (UK), the State Board (US) or other board of accreditation, may require the doctor to have a psychiatric or medical assessment and follow recommended treatment. However, if family and colleagues or managers had acted sooner, matters need not have gone so far.

Records should be kept of specific events which have led to the conclusion that the individual must get treatment. The timing for approaching a colleague who appears to be ignoring a psychiatric illness or an addiction sometimes needs to be planned. Occasionally, an approach will only be successful when there has been a further incident. The approach should be at a time when he or she is sober. Colleagues, administrator, and family, and perhaps other friends might be brought together, so that their voice, expressing caring as well as facing reality, is united. Under this co-ordinated pressure, the sick doctor may find it harder to refuse to take the next step, which might be, for example, to see his or her own general practitioner, to see an adviser recommended by the national or regional specialty colleagues, or to go for a psychiatric assessment. One should not expect or accept promises: these will be futile, especially with addictions.

Establishing at this point an agreement about openness between the parties concerned can later be invaluable: the doctor may otherwise suffer in the way 'special patients' suffer, because of the smoke-screen of excessive secrecy—dead of night phone calls giving information, 'which on no account is to be passed on'. The colleagues or employer should state that they will pass the information they have to the assessing psychiatrist. This reduces the chance that the individual deceives the specialist into passing him or her as fit and well.

It may be easier for unwell doctors to agree to assessment, or to seek treatment, outside their own district. Doctors are sceptical, and competitive, by nature and by training. They may not welcome advice to see 'old so and so', whose failings they have smiled at for years, or who is a personal

friend. But it may be necessary for colleagues to insist explicitly that treatment is followed, because doctors are notorious in not even following advice they would give to their own patients (and, of course, in addiction, deciding that they will treat themselves, sometimes self-medicating in an alarming way).

The medical profession in many countries has procedures, before disciplinary procedures are instigated, of helping a sick doctor find his way to treatment. In British NHS hospitals there is the 'three wise men' arrangement, which a doctor can approach for advice about an at-risk colleague. However, there may be a stage in the evolution of a problem at which a sick doctor might be receptive to advice from outside rather than from within his own region. In the UK, a national body has been created by the Royal Colleges and the British Medical Association which any doctor seriously concerned about the effects of illness or the fitness to practise of a colleague may contact (The National Counselling and Welfare Service for Sick Doctors, tel. 071 580 3160; the Overseas Doctors Association, tel. 061 236 5594). A national adviser from within the same specialty as the patient may then contact the doctor concerned. In the US, similar hot-lines exist on a statewide basis, often run by county medical societies.

The role of the General Medical Council and accreditation boards

In the UK, the General Medical Council (GMC) controls doctors' licences to practise. Allegations of serious professional misconduct, and criminal convictions, are notified to the Council. If this raises in any way the question of ill health, or if the GMC receives information suggesting ill health, there is a screening procedure which can greatly minimize the doctor's anxiety, because legal proceedings are averted and there is no publicity. The first two years of a similar 'diversion' programme, instituted by the Californian Board of Medical Quality Assurance, were described by Gualtieri *et al.* (1983). By the second year, self-referral, albeit often instigated by peers, was a more usual route of making contact than official disciplinary action.

Procedures which allow diversion from disciplinary action enable the doctor to continue to practise, as long as he or she accepts that his behaviour is monitored. The GMC require that a supervisor acceptable to the doctor and to the GMC screener is nominated, who will obtain information and perhaps arrange to see the doctor at short notice. In addition, reports at regular intervals are required from the doctor's therapist to confirm compliance with treatment. These reports would include, for example, urine specimens in a drug abuser, markers of drinking, such as serum gamma-glutamyl transferase, and mean red cell volume in an alcoholic, or serum lithium in a manic-depressive doctor who had agreed to that form of treatment.

Assessment is the beginning of therapy

Although doctors are trained to accept psychiatric conditions as illnesses, they are often personally very sensitive to the stigma associated with psychiatric treatment. Although this should be recognized by the treating psychiatrist, it is usually best not to deviate from customary practice. Consultations should be at normal hours and at the usual clinic. The doctor's own family physician should be involved as normal. Secrecy does not facilitate good therapy.

Seeing one's condition as illness, be it anxiety state, depression, or addiction, rather than moral weakness, reduces shame and guilt: this is not incompatible with the tenet that the individual is responsible for taking appropriate steps to get well and stay well.

It is best to treat the sick doctor as an intelligent layman, and not assume that he or she knows all about psychiatric illness (although there may be an attempt to convince one of that!). The doctor's self-esteem will be at a low ebb and use of jargon and display of knowledge and experience is understandable at this point.

The interview should begin by inquiring what the individual's own worries are. It may be despair about work and inability to cope with the demands; a complaint about the marriage; the drink–driving offence which alerted the GMC; or simply anger at being told to go for a psychiatric examination. Information which is available from colleagues or employer should be discussed and consent obtained to speak to the spouse, 'to have your partner's views of how best I can help'.

If the presenting complaint would normally indicate a physical examination and blood tests, these should be done. For suspected alcohol problems, one should look for physical signs of heavy drinking, such as tremor of the fingers, mouth, and tongue; hepatomegaly; and excessive capillarization of the face or conjunctivae, or even spider naevi. The following must be checked: liver function tests, mean cell volume, and urinalysis for benzodiazepines (alcoholic doctors often self-medicate to disguise anxiety and withdrawal symptoms).

Treatment

After agreeing to treatment, the doctor may well try to terminate this prematurely. This is best averted by a warm, trusting relationship with a psychiatrist who is prepared to set limits and adhere to good clinical practice. Helpful pressure to ensure that the doctor stays in treatment and attends follow-up can be brought to bear by the doctor's colleagues or employing authority (perhaps the occupational health physician or medical personnel staff) or the GMC if it has been involved.

The doctor may need help to accept that it is appropriate to take time off work, and not to feel guilty towards colleagues or patients. Decisions about admission to hospital for treatment should be the same as for other patients. Sick doctors have been successfully treated as in-patients in the hurly-burly of NHS wards (and their subsequent comments on life in these wards can be illuminating and helpful—Anon. 1990). Similarly, decisions about physical treatments should be made as for other patients: drugs or perhaps ECT for depression, or perhaps disulfiram for relapsing alcoholism (supervised by spouse, colleague or the employer's occupational medicine department).

Psychotherapy

This may be especially relevant in two areas: the marriage, and the management of work stress. The doctor may have neglected *the emotional needs of the family*. The spouse may have years of resentment and when asked to help feels: 'Where were you when I needed support?' Addictions and depression can lead to the individual becoming solitary and self-absorbed, another cause of hardening of the partner's attitudes or demoralization.

Communication with the spouse may be helped by joint sessions in which each is encouraged to express needs and to practise being a better listener. Relearning to give and receive in the relationship will take time. As recovery begins, it is important that the patient has realistic expectations of the time it can take for the family to respond, to avoid disappointment. Playing down how hurt the family have been is part of the denial of the illness.

To have more time and energy for the family, as well as to 'cherish' him- or herself, will entail setting limits on the emotional drain of work. Therapist and patient may need to evolve guidelines for *managing stress*:

- accepting time constraints, and therefore setting boundaries to work demands;
- deciding on methods for managing difficult patients (general practitioners have patients who can be demanding, sometimes even threatening and frightening);
- finding a way to accept imposed administrative changes and only fighting those battles that are really important;
- accepting that one is expected to be 'good enough' rather than perfect;
- delegating work to others;
- not letting a 'problem' burgeon in the mind into a 'catastrophe';
- not harbouring resentments;
- rebuilding self-esteem, by taking satisfaction in successes, rather than dwelling on failures.

Monitoring progress

This is especially important when alcohol or drugs are involved. During an eight year study of the Oregon programme for helping impaired physicians on probation, the majority of whom had alcohol and/or drug problems, outcome was best (96 per cent 'improved') in those physicians who entered the programme after a procedural decision had been made that the out-patient phase of treatment would be closely monitored by random blood and urine tests. Those who had entered in the years before monitoring was instituted had not done as well (64 per cent 'improved') (Shore 1987). Close monitoring was one helpful factor proposed by Shore *et al.* (1984) when they found that alcohol and drug-abusing doctors discharged from the Mayo clinic had a better prognosis (83 per cent favourable outcome) than other discharged patients also drawn from fairly high socioeconomic groups (62 per cent favourable outcome).

If supervision is agreed to, early return to work should be encouraged, so that credibility is quickly re-established.

Relapse in addiction

One must expect and accept initial relapse in alcohol and drug abusers. The doctor's family, colleagues, and employers should be encouraged to take action as soon as relapse is noted, otherwise the addict will learn that concealment works. It is reasonable for colleagues or employer to agree a limit to the number of relapses within, say, the first year. They cannot be expected to soldier on for years with no improvement in the individual.

Mutual-help groups

These groups, of which Alcoholics Anonymous is by far the most widely distributed, can be of great help. A considerable number of doctors can testify that attendance at such meetings does not damage a doctor's reputation. In many countries it is now possible to link a drug or alcohol dependent physician to a national or regional 'doctor's and dentist's group'. The non-judgemental, empathic welcome the physician receives from such a group helps greatly in reducing stigma, and can help him or her accept the need for complete abstinence. That recovery can indeed be facilitated is suggested by a survey conducted amongst the 100 members of a UK regional group for alcoholic doctors which had been running for eight years (Lloyd 1990). Seven died, still in the throes of their addiction, and five had died but had been abstinent. Two had retired somewhat early. However, 76 were well and still practising. The survey only reviewed those who had continued in contact with the group for at least six months, and those who did not adhere to the group may have had a poor prognosis for other reasons. Nevertheless, Lloyd (1990) is probably correct to point out that the outcome of this sample was very considerably better than that UK sample of alcoholic doctors admitted to psychiatric hospital studied 20 years earlier by Murray (1976), amongst whom 12 per cent had died due to alcohol and only 42 per cent were in recovery, after a similar length of follow-up.

Clinical guidelines

1. Courage and compassion, not covering-up, are needed to help colleagues with emotional problems to accept responsibility and get the help they need.
2. Coercion, if supportive, can be constructive.
3. It is important to ensure that the sick doctor does not just make promises or pay lip-service to seeking help, but participates actively in treatment.
4. The dialogue with the physician–patient should be as with an intelligent layman, without assuming extra knowledge, and should commence with the problems as perceived by him or her.
5. Secrecy should be avoided.
6. The psychiatrist, non-judgemental and empathic, may need to set limits and prevent too early discontinuation of therapy.
7. Doctors with alcohol and drug problems should have their progress monitored, using objective markers, and if they agree to this could be able to return to work soon.
8. The family should be involved in treatment.
9. One should look at methods for managing work stress more efficiently.
10. Encouraging contact with a mutual-help group can be beneficial.

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Scottish Intercollegiate Guidelines Network

The management of harmful drinking and alcohol dependence in primary care

A national clinical guideline

September 2003

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Harmful drinking and alcohol dependence are common conditions which contribute considerably to morbidity, mortality and burden to the NHS, as well as causing social harm:

- in the Scottish population, at any one time 250,000 people report symptoms of mild alcohol dependence, and 16,000 report moderate to severe symptoms[1]
- deaths attributed to alcohol misuse more than doubled between 1990 and 1999 and they continue to rise[2]
- alcohol dependent patients consult their general practitioners (GPs) about twice as frequently as other patients in a practice[3,4]
- alcohol dependence and alcohol related diagnoses have been rising among patients discharged from Scottish general hospitals[2]
- Accident and Emergency (A&E) attendance surveys conducted in Glasgow[5] and Edinburgh[6,7] have noted a high burden to the A&E service of problems related to serious alcohol misuse
- there is widespread variation in practice, interest, knowledge and experience in dealing with alcohol dependence amongst healthcare professionals in primary care.[8]

1.2 DEFINITIONS

1.2.1 UNIT OF ALCOHOL

One "unit" in the UK usually means a beverage containing 8 g of ethanol, eg a half pint of 3.5% beer or lager, or one 25 ml pub measure of spirits. A small (125 ml) glass of average strength (12%) wine contains 1.5 units *(see Annex 1 for a list of the alcohol content of a range of beverages)*.

1.2.2 HAZARDOUS DRINKING

The term hazardous drinking is widely used. It is synonymous with "at-risk drinking" and can be defined as the regular consumption of:

- over 40 g of pure ethanol (5 units) per day for men
- over 24 g of pure ethanol (3 units) per day for women.

These figures derive from population studies showing the relationship of self reported levels of drinking to risk of harm. It is arbitrary which point on the risk curve is deemed to merit a warning.[9-13] Other authorities have quoted weekly recommended upper limits for alcohol consumption of 21 units per week for men and 14 units per week for women.[14]

Consuming over 40 g/day alcohol on average doubles a man's risk for liver disease, raised blood pressure, some cancers (for which smoking is a confounding factor) and violent death (because some people who have this average alcohol consumption drink heavily on some days). For women, over 24 g/day average alcohol consumption increases their risk for developing liver disease and breast cancer.[9-12] These studies used self reported consumption figures.

The term hazardous drinking is also used loosely to cover those who have experienced minimal as opposed to serious harm.

1.2.3 HARMFUL DRINKING

Harmful drinking is defined in the International Classification of Diseases (ICD-10) as a pattern of drinking that causes damage to physical (eg to the liver) or mental health (eg episodes of depression secondary to heavy consumption of alcohol).[15] The diagnosis requires that actual damage should have been caused to the mental or physical health of the user.

1.2.4 ALCOHOL DEPENDENCE

Alcohol dependence is defined as a cluster of physiological, behavioural, and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviours that previously had greater value.[15] A central characteristic is the desire (often strong, sometimes perceived as overpowering) to drink alcohol. Return to drinking after a period of abstinence is often associated with rapid reappearance of the features of the syndrome (priming).

A definitive diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

- a strong desire or sense of compulsion to take alcohol
- difficulty in controlling drinking in terms of its onset, termination or level of use
- a physiological withdrawal state when drinking has ceased or been reduced (eg tremor, sweating, rapid heart rate, anxiety, insomnia, or less commonly seizures, disorientation or hallucinations) or drinking to relieve or avoid withdrawal symptoms
- evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses (clear examples of this are found in drinkers who may take daily doses sufficient to incapacitate or kill non-tolerant users)
- progressive neglect of alternative pleasures or interests because of drinking and increased amount of time necessary to obtain or take alcohol or to recover from its effects (salience of drinking)
- persisting with alcohol use despite awareness of overtly harmful consequences, such as harm to the liver, depressive mood states consequent to periods of heavy drinking, or alcohol related impairment of cognitive functioning.

1.3 POPULATION COVERED BY THE GUIDELINE

This guideline pertains to patients with alcohol dependence, hazardous or harmful drinking, in primary care (general practice and community nursing) and among those attending, but not admitted from, A&E Departments.

The guideline does not address some specific situations:

- patients already in specialist care
- patients admitted to general or psychiatric hospitals
- driving
- drinking related to vocational or professional issues eg for van drivers, surgeons or teachers with alcohol problems
- adolescents with an alcohol problem
- child safety
- the management of alcohol related organ damage
- treatment of carers and family members of patients with an alcohol problem.

A health technology assessment has been performed by NHS Quality Improvement Scotland on the prevention of relapse in alcohol dependence in specialist settings, which complements this guideline *(see Annex 8)*.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor, following discussion of the options with the patient, in light of the diagnostic and treatment choices available. It is advised however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.5 REVIEW AND UPDATING

This guideline was issued in 2003 and will be considered for review as new evidence becomes available. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

2 Detection and assessment

2.1 CLINICAL HISTORY

There is evidence from clinical and epidemiological studies of a relationship between heavy drinking and certain clinical presentations (injuries, physical and psychiatric illnesses, frequent sickness absence) and social problems (*see Annex 2*). There are some signs at physical examination recognised by experts as linked to heavy drinking, such as injuries (including in the elderly), tremor of the hands and tongue, and excessive capillarisation of the facial skin and conjunctivae.[16,17] The exact association between these signs and actual heavy drinking has not been thoroughly investigated. 4

Research suggests that most people are not offended by being asked about their alcohol consumption and will give a reliable account if there is no sanction anticipated.[18,19]

D **Primary care workers should be alerted by certain presentations and physical signs, to the possibility that alcohol is a contributing factor and should ask about alcohol consumption.**

2.1.1 THE ACCURACY OF SELF ASSESSMENT

Although evidence is not consistent, patients in research projects tend to report consumption that correlates with blood tests and is fairly close to that reported by their family.[20] It is not known if this is true for UK primary care consultations, where the GP may be perceived by the patient as having several roles, and where fears of employment, legal or insurance consequences affect what patients disclose to the GP. 2+

Severely dependent drinkers may not want to admit a pattern of drinking, which they prefer to continue, or feel they cannot alter. Shame or guilt may lead some drinkers to minimise their reported consumption.[21]

☑ While most patients are factual about their drinking, the primary care team should recognise that some will under-report their consumption at times.

2.2 SCREENING FOR ALCOHOL DEPENDENCE AND THOSE AT RISK

There is a large volume of good quality evidence indicating that appropriate screening helps the detection and treatment of alcohol problems *(see Annex 2 for a list of alerts)*. This evidence has consistently shown that screening using the Alcohol Use Disorders Identification Test (AUDIT) is effective within primary care, A&E, pre- and antenatal settings. The AUDIT is more sensitive in the detection of hazardous drinking than CAGE (attempts to **C**ut back on drinking, being **A**nnoyed at criticisms about drinking, feeling **G**uilty about drinking, and using alcohol as an **E**ye-opener; positive answers to two or more = probable alcohol dependence), unless CAGE is supplemented with questions on maximum daily and total weekly consumption (CAGE plus two).[22-33] 1++ 2++ 2+

The scoring procedure for AUDIT can be difficult to memorise, and the questionnaire itself can take five minutes to complete. Abbreviated versions of AUDIT are preferred by many primary care workers, and accuracy is only slightly diminished. These include the Fast Alcohol Screening Test (FAST; *see Annex 3*), which is a thirty second version of the AUDIT and the Paddington Alcohol Test (PAT; *see Annex 4*).[22,31] TWEAK and T-ACE are abbreviated screening tools found to be particularly appropriate for A&E and obstetric settings.[25,26]

B **Abbreviated forms of AUDIT** *(eg FAST)*, **or CAGE plus two consumption questions, should be used in primary care when alcohol is a possible contributory factor.**

C **In A&E, FAST or PAT should be used for people with an alcohol related injury.**

B **TWEAK and T-ACE** *(or shortened versions of AUDIT)* **should be used in antenatal and preconception consultations.**

When a patient registers with a GP, a medical history is taken which includes questions on alcohol consumption.[34] A screening questionnaire at this point is a useful tool for identifying hazardous drinking.

☑ When new patients register with a GP they should be asked about weekly and maximum daily alcohol consumption, or an appropriate screening tool should be used.

The screening and brief interventions algorithm shown in Box 1 in section 3.1 is based on the UK Alcohol Forum guidelines for the management of alcohol problems in primary care and general psychiatry[35] and is a useful tool to aid decision making.

2.3 BIOLOGICAL MARKERS OF ALCOHOL PROBLEMS

2.3.1 MARKERS OF ALCOHOL PROBLEMS

Elevations in mean red blood cell volume (MCV), serum gamma glutamyl transferase (GGT) and carbohydrate deficient transferrin (CDT) are markers of heavy drinking in preceding weeks. The difficulty in assessing their accuracy as diagnostic tests has been that self reported consumption is used as the "gold standard" but sometimes a biological marker may be more accurate than a self report.[36-38]

False positive results occur with GGT and MCV due to other causes of elevation. False positive MCV can occur as a result of vitamin B12 deficiency, folic acid deficiency, thyroid disease or chronic liver disease. False positives with GGT are due to other causes of liver disease or enzyme induction including some drugs. CDT is normal in mild to moderate liver disease. It may be raised in severe liver disease, but otherwise gives few false positives. If elevated due to alcohol, it remains elevated for several weeks after consumption has reduced. It will not detect a recent relapse. CDT may be a more accurate marker of very recent (past two weeks') drinking than GGT.[39,40] 2+

As CDT measurement is not available within Scotland, it is recommended only when there is clinical difficulty in interpreting a normal or an abnormal GGT or other liver test result. King's College Hospital, London accept serum samples by post for CDT assay.

Biological tests are of less value than self reports for screening with the intention of intervention. They have their greatest role where patients have a reason for minimising (or, less commonly, exaggerating) their consumption, and in monitoring patients' progress in reducing their drinking.

Even though these tests have limited sensitivity and specificity, if elevated in a given patient, they may help motivate a patient to reduce drinking and they are then useful in monitoring change in consumption.

2.3.2 BLOOD ALCOHOL CONCENTRATION

Blood alcohol concentration (BAC), normally measured by reference to breath alcohol, can contribute to screening[41] and is valuable for monitoring patients during detoxification in the community, as well as following progress thereafter. Breathalysers permit estimates to be made of very recent alcohol consumption and are often used by specialist nurses in the community. A breathalyser is a useful item of equipment in a Health Centre and in A&E. 2+

Saliva alcohol tests also give a reliable estimate of BAC.[42,43]

B **Biological tests are useful when there is reason to believe that self reporting may be inaccurate.**

☑ Biological tests are useful to motivate patients to review their drinking and to consider change.

☑ Biological tests should be used to monitor patients' progress in reducing their drinking.

☑ A&E departments and health workers regularly dealing with alcohol problems in the community should have access to a breathalyser.

2.4 PRESENTATION IN CRISIS

Patients presenting in crisis may place the primary care team in difficult situations. There is no evidence on how best to approach these encounters. This section discusses some possible common sense solutions.

2.4.1 PATIENT IN CRISIS

Suicidal threats or demands for immediate but undefined "help" require assessment, preferably within the surgery or by the out-of-hours service. Listening to the patient's concerns may help to alleviate the pressure on the healthcare professional to take additional action. Immediate admission is rarely indicated or possible but, if suicidal ideation persists it may be needed, in which case referral to psychiatric services is appropriate.

2.4.2 DRUNK PATIENTS ON THE TELEPHONE, OR IN PERSON, EXPRESSING THREATS

Physically threatening behaviour should be dealt with by calling the police.[44] Drunk patients should be listened to politely and with courtesy, as showing frustration may inflame the situation. The patient may respond to being listened to politely and may be gently encouraged to go home. Drunk patients on the telephone can be disruptive to surgery function and also out-of-hours services as they may block the line. Having given due consideration and advice on who to contact when the patient is sober, it may be appropriate to terminate the call. At times, it may be quicker to see these patients.

2.4.3 DOMESTIC ABUSE

The domestic violence/abuse liaison officers at police stations provide advice to victims of domestic abuse and can put them in touch with support systems, whether or not they wish to prosecute their partner. Sometimes the police arrest and charge the aggressor, even if the victim will not give evidence. The victim may need to be removed to a place of safety such as a refuge.

2.4.4 ORGANIC BRAIN DAMAGE

Community management of patients with organic brain damage can be difficult. They often do not attend appointments. The community nursing team may be able to offer advice and support to the patient. A community care assessment by the social work department may be needed. If drinking continues to be problematic, sometimes patients will agree to an arrangement with their family or their social worker such that, at any one time, they only have access to small amounts of their money.

3 Brief interventions for hazardous and harmful drinking

Within the literature, the terms "brief" and "minimal" interventions cover a range from one five minute interaction to several 45 minute sessions. The major positive studies discussed in this section typically consist of one interaction lasting between five and 20 minutes, sometimes with one brief follow up contact.

The acronym FRAMES[45] captures the essence of the interventions commonly tested under the terms "brief intervention" and "motivational interviewing":

- **F**eedback: about personal risk or impairment
- **R**esponsibility: emphasis on personal responsibility for change
- **A**dvice: to cut down or abstain if indicated because of severe dependence or harm
- **M**enu: of alternative options for changing drinking pattern and, jointly with the patient, setting a target; intermediate goals of reduction can be a start
- **E**mpathic interviewing: listening reflectively without cajoling or confronting; exploring with patients the reasons for change as they see their situation
- **S**elf efficacy: an interviewing style which enhances peoples' belief in their ability to change.

This guideline uses "brief intervention" throughout to cover short duration interventions which use the FRAMES style. The efficacy studies on brief interventions quoted have almost always excluded alcohol dependent patients because they were deemed inappropriate for this intervention.

3.1 BRIEF INTERVENTIONS IN GENERAL PRACTICE

There is consistent evidence from a large number of studies that brief intervention in primary care can reduce total alcohol consumption and episodes of binge drinking in hazardous drinkers, for periods lasting up to a year. There is limited evidence that this effect may be sustained for longer periods. All groups under study reduced alcohol consumption, but those with brief interventions did so to a greater extent than those in control groups. Very brief interventions (5-10 minutes) may have a similar effect to extended interventions (20-45 minutes or several visits), although the evidence is not consistent.[46-57] 1++ 1-

Studies have varied in whether the intervention is given on the day of detection or later, without revealing a preferred timing. Some successful studies have used a booster contact (a follow up intervention at a later date).[58,59]

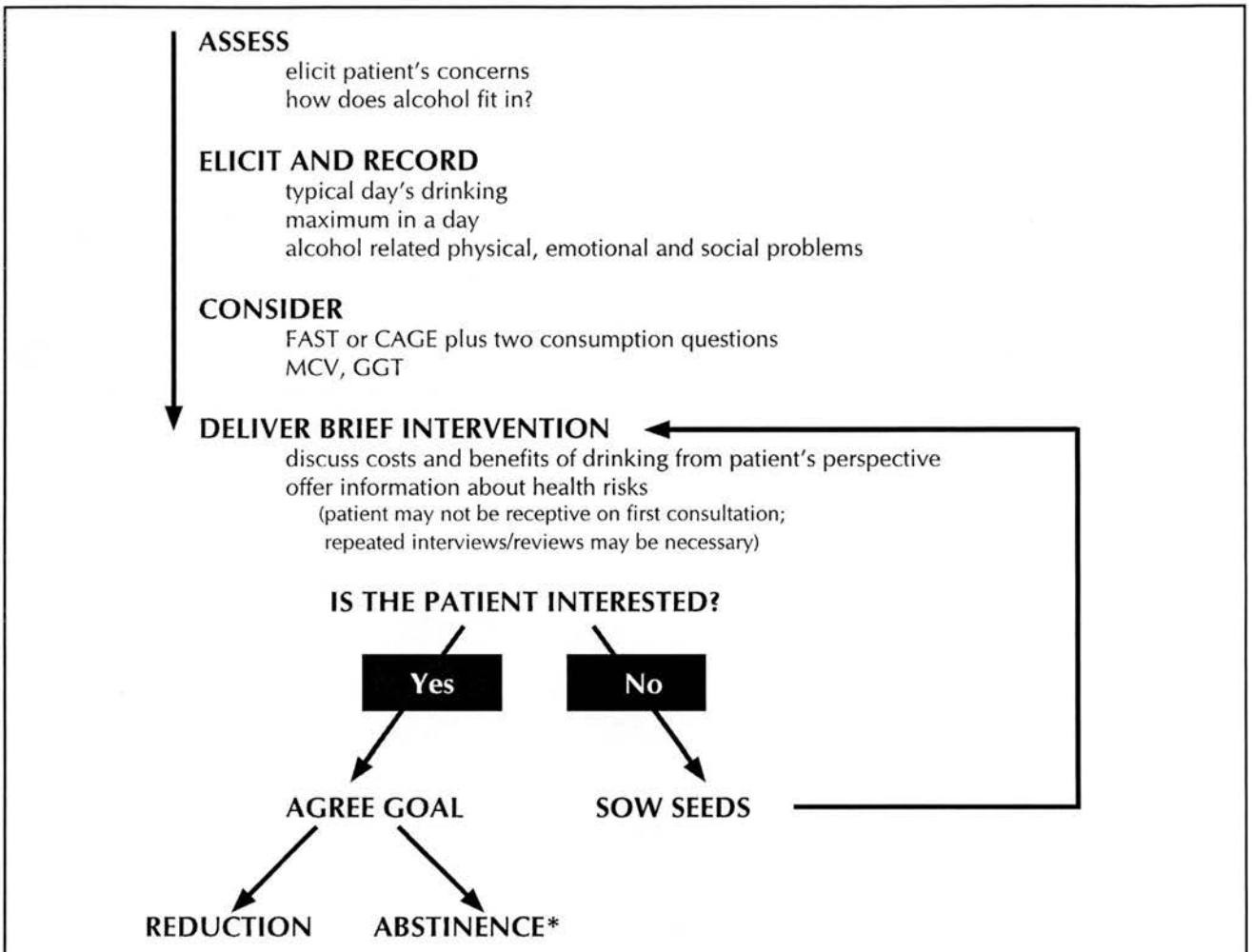
There is some evidence that the use of written media such as booklets or leaflets enhances the efficacy of brief interventions.[60]

The optimum type of intervention is still to be defined. Sometimes "advice" is given, while at other times the style of interaction epitomised in "motivational interviewing" has been used. Additionally, the comparative value of opportunistic intervention, versus intervention after population screening is not clear.

Data on follow up beyond one year are very limited.[61] One study found that the effect had disappeared at 10 years.[62] Another found a continuing small effect at four years.[63] A 10-16 year follow up of a sample recruited in a screening project found that intervening had reduced mortality, but the original intervention comprised sessions repeated regularly over up to two years – much more than a brief intervention.[64] 1- 3 4

The evidence does not support the use of brief interventions for more severely affected patients seeking treatment.[57] A brief intervention is effective at the point when the hazardous or harmful drinker is newly identified (ie an opportunistic encounter).[54] This may be during attendance for a related or even unrelated illness or injury, at health screening for employment or insurance purposes, or at the time of registering with the practice *(see Box 1)*.

Box 1: Screening and brief interventions



Assisting goal of reduction	Assisting goal of abstinence
Elicit patient's concerns	Enlist support of family and friends Consider use of local alcohol services
Regular review to offer encouragement	Plan medically assisted withdrawal if indicated, at home or in hospital Recommend Alcoholics Anonymous, especially if other support for abstinence is lacking
Monitor (see or telephone patient; information from family/GGT)	Consider specific pharmacotherapy: acamprosate (reduces intensity of and response to cues and triggers to drinking) and/or disulfiram (deterrent) Initiate active intervention if other psychiatric problems (depression/anxiety) persist >2 weeks
Reassess with patient the costs and benefits of change	Monitor (see or telephone patient; information from family/GGT)

*** Absolute indications for abstinence:**
- alcohol related organ damage
- severe dependence (eg morning drinking to stop the shakes or previous failed attempts to control drinking)
- significant psychiatric disorders

Relative indications for abstinence:
- epilepsy
- social factors (eg legal, employment, family)

Based on the UK Alcohol Forum guidelines for the management of alcohol problems in primary care and general psychiatry.[35]

The effectiveness of brief interventions has been reported as number needed to treat (NNT) of 7-9. That is between seven and nine patients will need to be given a brief intervention in order to achieve a reduction of drinking to within non hazardous levels in one patient.[54,56,63] 1++ 1+

This compares favourably with treatment for other medical conditions (eg the use of statins to prevent cardiovascular mortality following myocardial infarction over trial duration, NNT = 30-90[65] or the use of antihypertensive therapy to prevent a cardiovascular event within five years, NNT = 40-125).[66]

In research studies of brief intervention, patients were recruited by screening all attenders at the practice, or all those on the practice list. Of attenders screened, less than 5% met criteria and entered the treatment arm.[54,58,67-70] Thus, at an NNT of eight, 1000 patients would need to be screened for around six patients to show clear benefit. For this reason, primary care professionals should rely on case detection based on clinical presentation, with judicious use of questionnaire tools where there is suspicion, rather than the screening of whole populations.

A
- **General Practitioners and other primary care health professionals should opportunistically identify hazardous and harmful drinkers and deliver a brief** *(10 minute)* **intervention.**
- **The intervention should, whenever possible, relate to the patient's presenting problem and should help the patient weigh up any benefits as perceived by the patient, versus the disadvantages of the current drinking pattern.**

3.1.1 TRAINING

Training healthcare providers in the use of structured interventions enhances the efficacy of brief interventions.[71]

Training practice nurses at health centres in screening and delivering brief interventions has the potential for increasing the availability of these services, but more research is needed to verify this.[71]

There are well documented difficulties in disseminating research findings to primary care providers. Research on implementing screening and brief alcohol intervention showed personal meetings to effect most behaviour change in GPs, but ongoing telephone support to be the most cost effective measure.[72-74]

Training is required in order to deliver effective brief interventions.

D **Training for GPs, practice nurses, community nurses and health visitors in the identification of hazardous drinkers and delivery of a brief intervention should be available.**

3.2 BRIEF INTERVENTIONS IN THE ACCIDENT AND EMERGENCY SETTING

A few studies have been conducted of brief interventions to non-admitted A&E patients. One involved the use of a routine follow up letter to patients advising attendance at alcohol counselling services. The letter appeared to be useful in encouraging a significant minority of people to attend appropriate specialist services.[75] The use of follow up correspondence may be a low cost intervention which could produce positive results but more research is needed in this area. 1+

Another study delivered an onsite intervention to adolescents presenting with alcohol problems and showed a positive effect of a single intervention in this patient group.[76] This study has limitations in its design and only applies to a limited subset of A&E attenders. 1-

A third study compared standard care, motivational interviewing or motivational interviewing plus a booster session 7-10 days later.[59] This study recruited injured patients who screened positive for harmful or hazardous drinking. At one year follow up, the "motivational interviewing plus booster session" group reduced their alcohol related injuries by 30% more than those who received standard care. There was no difference between standard care and a motivational interview offered at the time without the booster session. The interventions were delivered by research staff trained in motivational interviewing. 1+

In A&E departments where brief interventions are offered by busy A&E staff, uptake of such interventions by patients may be very low.[77]

When conducted by specially trained and allocated staff offering and arranging follow up, brief intervention can be beneficial. There is insufficient evidence however, to recommend routine brief intervention alone in A&E.

☑ Patients who screen positive for harmful drinking or alcohol dependence in A&E should be encouraged to seek advice from their GP or given information on how to contact another relevant agency.

3.3 BRIEF INTERVENTIONS IN THE ANTENATAL SETTING

Advice from the Health Education Board for Scotland (now NHS Health Scotland) is that light, occasional drinking during pregnancy (one or two units once or twice a week) is not likely to do any harm.[78] Heavy drinking is associated with miscarriage, and sometimes with serious effects on the baby's development.[78] Some authorities recommend complete abstinence during pregnancy (the US National Institute on Alcohol Abuse and Alcoholism: http://www.niaaa.nih.gov/publications/brochure.htm).

Two studies have been identified which looked at brief interventions in the antenatal setting. One study, in women of childbearing age identified by screening as "at-risk drinkers", compared giving the patient a booklet without additional advice with two 15 minute physician consultations that incorporated a workbook, a drinking agreement and drink diary cards. Both groups reduced consumption with the physician intervention group reducing consumption to a greater extent. Differences overall were significant but the magnitude of difference between groups was small. Subjects who became pregnant however, showed the greatest reduction.[53] 1+

A study of women receiving antenatal care compared an "alcohol consumption assessment only" group with a brief intervention group. Both groups reduced their drinking during the rest of the pregnancy, but differences in reductions by group were not statistically significant. Those who received the brief intervention maintained higher rates of abstinence.[79]

B **Routine antenatal care provides a useful opportunity to deliver a brief intervention for reducing alcohol consumption.**

3.4 EFFECTIVENESS OF MOTIVATIONAL INTERVIEWING

Motivational interviewing (a non-judgemental interviewing style which avoids confrontation, helps the individual weigh up the pros and cons of change, and enhances self efficacy) is a style which is helpful in brief interventions (*see Annex 5*).[80] A systematic review showed that motivational interviewing has a significant effect on reducing alcohol consumption in the primary care setting.[81] There is no evidence to support a confrontational style of interviewing. 1+

B **Motivational interviewing techniques should be considered when delivering brief interventions for harmful drinking in primary care.**

☑ Staff who deliver motivational interviewing should be appropriately trained.

4 Detoxification

4.1 INTRODUCTION

Detoxification refers to the planned withdrawal of alcohol. Alcohol withdrawal carries risks and requires careful clinical management.

The choice of timing for a preplanned detoxification is important, in relation to the patient's commitment and medium term plans. Detoxification should be seen as the first step towards achieving abstinence.

4.2 PRIMARY CARE DETOXIFICATION VERSUS INPATIENT DETOXIFICATION

A comparison between community and inpatient detoxification of alcohol dependent patients found no difference in the number of patients remaining sober six months later.[82] At least three out of four such patients can be detoxified successfully in the community.[82] 1++

No studies of outpatient detoxification using medication were identified where fits occurred but studies had, appropriately, excluded patients with a history of withdrawal seizures or with impending delirium.[83]

Home detoxification does not appear to have any clinical advantages but may offer cost savings.[82-85] There are too few reports to be able to show rare serious events and publication bias may contribute to the current favouring of home detoxification as the first line. 1++ 1+ 2-,3

There is evidence that many patients prefer home detoxification.[86] 2+

Community detoxification is an effective and safe treatment for patients with mild to moderate withdrawal symptoms. Personnel involved in detoxification may include GPs, community psychiatric nurses, primary care nurses and community pharmacists. There are resource implications, including the cost of a breathalyser.

☑ Where community detoxification is offered, it should be delivered using protocols specifying daily monitoring of breath alcohol level and withdrawal symptoms, and dosage adjustment.

☑ Every GP practice (and out-of-hours service) would benefit from access to a breathalyser for use in the acute situation and for follow up.

☑ Intoxicated patients presenting in GP practices, out-of-hours services and A&E, requesting detoxification should be advised to make a primary care appointment and be given written information about available community agencies.

See Annex 6 for advice to give to patients who undergo home detoxification.

4.2.1 SITUATIONS WHERE INPATIENT DETOXIFICATION WOULD BE ADVISED

The following list is based on expert opinion and comprises validated and best practice contraindications to managing withdrawal at home:[35]

Hospital detoxification is advised if the patient:

- is confused or has hallucinations
- has a history of previously complicated withdrawal
- has epilepsy or a history of fits[87]
- is undernourished
- has severe vomiting or diarrhoea
- is at risk of suicide
- has severe dependence coupled with unwillingness to be seen daily
- has a previously failed home-assisted withdrawal
- has uncontrollable withdrawal symptoms
- has an acute physical or psychiatric illness
- has multiple substance misuse
- has a home environment unsupportive of abstinence.

4

☑ If admission to hospital is unavailable or the patient refuses, specialist opinion should be sought to aid risk assessment.

4.3 PHARMACOLOGICAL DETOXIFICATION

4.3.1 WHEN IS MEDICATION FOR WITHDRAWAL INAPPROPRIATE?

Cessation of drinking is unlikely to be complicated in milder dependence.[35]

Medication may not be necessary if:

- the patient reports consumption is less than 15 units/day in men / 10 units/day in women and reports neither recent withdrawal symptoms nor recent drinking to prevent withdrawal symptoms
- the patient has no alcohol on breath test, and no withdrawal signs or symptoms.

4

Among periodic drinkers, whose last bout was less than one week long, medication is seldom necessary unless drinking was extremely heavy (over 20 units/day).[35] Patients need to be informed of the likely symptoms if medication for withdrawal is not given. Annex 7 may be used to assist in deciding whether medication for withdrawal and admission are necessary.

D **When medication to manage withdrawal is not needed, patients should be informed that at the start of detoxification they may feel nervous or anxious for several days, with difficulty in going to sleep for several nights.**

4.3.2 THE EFFICACY OF BENZODIAZEPINES IN DECREASING ALCOHOL WITHDRAWAL SYMPTOMS

A body of evidence, based on randomised controlled trials (RCTs), has shown that benzodiazepines are currently the best drug group for alcohol dependence detoxification. The studies are of variable quality, with some reporting on small numbers of patients. Although the evidence is mostly derived from inpatient studies, the conclusions are generalisable to primary care.[88-92]

1++
1+

Benzodiazepines can cause temporary cognitive slowing and may interfere with learning and planning.[93] This, and the need to avoid benzodiazepine dependence, are reasons for keeping the length of treatment to a maximum of seven days.

A **Benzodiazepines should be used in primary care to manage withdrawal symptoms in alcohol detoxification, but for a maximum period of seven days.**

4.3.3 LONGACTING VERSUS SHORTACTING BENZODIAZEPINES

There is insufficient consistent evidence to make a recommendation about the use of longacting versus shortacting benzodiazepines.[88,94-96] | 1+ 2+, 4

4.3.4 MISUSE OF BENZODIAZEPINES

All benzodiazepines have a potential for misuse, but diazepam is the benzodiazepine most associated with misuse and alcohol related fatality.[97,98] If used in community detoxification, diazepam requires supervision to avoid misuse.[99] Chlordiazepoxide has a more gradual onset of its psychotropic effects and therefore may be less toxic in overdose. These factors probably contribute to chlordiazepoxide being less often misused and having less 'street' resale value. | 3 4

D **For patients managed in the community, chlordiazepoxide is the preferred benzodiazepine.**

4.3.5 THE ROLE OF CLOMETHIAZOLE IN PRIMARY CARE ALCOHOL DETOXIFICATION

Although clomethiazole (former name chlormethiazole) is an effective treatment for alcohol withdrawal, there are well documented fatal interactions with alcohol which render it unsafe to use without close supervision.[90,98,100-103] | 1+ 3 4

D **Clomethiazole should not be used in alcohol detoxification in primary care.**

4.3.6 DO ELDERLY PEOPLE REQUIRE DIFFERENT PHARMACOLOGICAL MANAGEMENT?

Physical illness sometimes increases the risk of delirium in the elderly, but otherwise there is no difference between alcohol withdrawal symptoms in the elderly, or the amount of benzodiazepine required for detoxification, as compared to younger patients.[104,105] Nevertheless, the risk of accumulation of a drug in the elderly patient needs to be considered. | 2+

C **Provided attention is paid to any acute or chronic physical illness, elderly patients should be managed the same way as younger patients.**

4.3.7 ANTIEPILEPTIC MEDICATION

There is insufficient evidence to support the use of antiepileptic medication as the sole treatment for the management of alcohol withdrawal or in the prevention of alcohol withdrawal seizures.[106,107] | 1+

B **Antiepileptic medication should not be used as the sole medication for alcohol detoxification in primary care.**

☑ People with a history of alcohol related seizures should be referred to specialist services for detoxification management.

4.3.8 ANTIPSYCHOTIC DRUGS

Antipsychotic drugs have been shown to prevent delirium but increase the incidence of seizures.[88] | 1+

B **Antipsychotic drugs should not be used as first line treatment for alcohol detoxification.**

☑ Delusions and hallucinations due to alcohol withdrawal, which would indicate the need for antipsychotic drugs, should be managed by specialist services.

4.3.9 SYMPTOM-TRIGGERED DOSING

Although there are studies of the efficacy of symptom-triggered dosing and/or loading dosing in inpatients, there is no evidence regarding the use of these methods in primary care.[92,108-110] Tapered fixed dose benzodiazepine regimen is likely to be as effective in primary care. | 1+ 2+

☑ Tapered fixed dose regimen of a benzodiazepine is recommended for primary care alcohol detoxification, with daily monitoring whenever possible.

4.4 THE ROLE OF VITAMIN SUPPLEMENTS IN DETOXIFICATION

There are very few high quality studies on which to base recommendations in this area. To do such studies now would be inappropriate.

4.4.1 TREATMENT OF ACUTE WERNICKE-KORSAKOV SYNDROME

Detoxification may precipitate Wernicke's encephalopathy *(see Box 2)*, which must be treated urgently with parenteral thiamine.[111] There is a very small risk of anaphylaxis with parenteral vitamin supplementation. This is less likely with the intramuscular route. There has been one case of anaphylaxis solely attributable to intramuscular Pabrinex since 1996.[112] 4

Box 2: Pointers to diagnosis of Wernicke-Korsakov syndrome

Signs of possible Wernicke-Korsakov syndrome in a patient undergoing detoxification
▪ confusion ▪ ataxia, especially truncal ataxia ▪ ophthalmoplegia ▪ nystagmus ▪ memory disturbance ▪ hypothermia and hypotension ▪ coma

One RCT has examined the role of parenteral vitamin supplements in inpatient alcohol detoxification using memory function as the outcome.[113] This study was done in people who did not have Wernicke-Korsakov symptoms. 1+

☑ Any patient who presents with unexplained neurological symptoms or signs during detoxification should be referred for specialist assessment.

D **Patients with any sign of Wernicke-Korsakov syndrome should receive Pabrinex in a setting with adequate resuscitation facilities. The treatment should be according to British National Formulary *(BNF)* recommendations and should continue over several days, ideally in an inpatient setting.**

4.4.2 TREATMENT OF THOSE AT RISK OF WERNICKE-KORSAKOV SYNDROME

There is no published evidence and conflicting expert opinion on the treatment of malnourished patients, and the specification and treatment of "at-risk" patients (those with diarrhoea, vomiting, physical illness, weight loss, poor diet), with the majority of experts recommending parenteral vitamin supplementation during detoxification.[111] 4

For the malnourished patient in the community, intramuscular Pabrinex given in the GP surgery, A&E department, outpatient clinic or day hospital is indicated if facilities for treating anaphylactic reactions are available, such as in any setting where routine immunisations take place.

☑ Patients detoxifying in the community should be given intramuscular Pabrinex (one pair of ampoules daily for three days) if they present with features which put them at risk of Wernicke-Korsakov syndrome.

4.4.3 ORAL SUPPLEMENTATION

No studies were identified that have looked at oral thiamine and its benefit to memory in either the recovering alcoholic or those who continue to drink in general practice. Absorption is diminished when patients continue to drink and should be given in divided doses to maximise absorption. The BNF recommended dose for treatment of severe deficiency is 200-300 mg daily.[114]

☑ Patients who have a chronic alcohol problem and whose diet may be deficient should be given oral thiamine indefinitely.

4.5 THE PREFERRED SETTING FOR TREATING DELIRIUM TREMENS

Delirium tremens is defined here as withdrawal symptoms complicated by disorientation, hallucinations or delusions. Autonomic overactivity is a potentially fatal aspect of this condition.

A Clinical Resource and Audit Group (now part of NHS Quality Improvement Scotland) good practice statement on delirium tremens recognises the serious medical aspects of this syndrome and recommends that local protocols for admitting patients with delirium tremens are used.[87]

4

Although the proportion of such patients seen by psychiatrists varies across Scotland, the majority of cases are treated by the acute medical service. This is because there is often a coexisting medical condition such as pancreatitis, pneumonia or other infection and there may be life threatening complications.

D **Local protocols for admitting patients with delirium tremens should be in place.**

5 Referral and follow up

5.1 WHO TO REFER, AND TO WHOM

Specialist treatments for alcohol problems are effective. A health technology assessment from NHS Quality Improvement Scotland concluded that specialist services are effective for relapse prevention if offering behavioural self control training, motivational enhancement therapy, family therapy/community reinforcement approach and/or coping/communication skills training *(see Annex 8)*.[115] 1++

General Practitioners are able to manage more patients with alcohol related problems if they perceive that they are working in a supportive environment which includes access to help with difficult patients.[116] 4

Research aiming to predict which patients will do better with which type of specialist treatments has given few leads. The GP's decision where to refer a patient should be guided in large part by the patient's choice. Some predictors however, have emerged: patients who are angry at the initial assessment appear to do better, in the short term, if given motivational interviewing.[117,118] 1+
Patients with psychiatric disorders ('dual diagnosis') tend to do better if referred to specialist psychological or psychiatric services than to 12-step Alcoholics Anonymous (AA) groups.[119] 2++
Patients referred to specialist care, who live or work in environments where there is a lot of drinking and little support for abstinence, may do better in a service which offers consultations which emphasise the 12-step AA approach, rather than specialised psychological therapy.

One underpowered study found no advantage to specialist treatment over general practice management in the UK.[120] Two North American studies have shown that milder alcohol dependence can sometimes be successfully managed without specialist care.[121,122] However, brief primary care intervention has usually excluded alcohol dependent patients who should, in general, be referred for specialist care. 1-
1+

A **Access to relapse prevention treatments of established efficacy should be facilitated for alcohol dependent patients.**

5.1.1 PATIENTS WITH ALCOHOL RELATED PHYSICAL DISORDER

American studies have shown that for patients with alcohol related physical disorders, integrated medical care and addiction treatment gives a better outcome than when the two services are separate.[122,123] If this is extrapolated to the NHS, it suggests that these are patients for whom particularly good links between the alcohol agency and medical care should be nurtured or where the treatment of the alcohol problem should be based as much as possible in primary care. 1+
4

B **When the patient has an alcohol related physical disorder, the alcohol treatment agency should have close links with the medical and primary care team.**

5.1.2 STEPPED CARE

Stepped care[124] (in a tiered treatment service[2,125]) occurs when treatment is chosen where possible to match the patients' needs and wishes and cause least disruption to their family and their work. More intensive treatment is only required if the outcome is unsatisfactory. 4

D **The principles of stepped care should be followed for patients with alcohol problems and dependence.**

5.2 WAITING TIME TO REFERRAL

Two case control studies and one cohort study found that increased waiting times made attendance at specialist clinics less likely.[126-128] None found a link between delay in referral or waiting time for assessment with ultimate outcome of treatment. 2+

5.3 MONITORING

Low intensity monitoring over the course of one to three years has been shown to reduce the severity of relapses.[129,130] This may be done by telephone or a brief appointment. In these studies, benefit may have been partly due to earlier rereferral to specialist services. 1+

B **Primary care teams should maintain contact over the long term with patients previously treated by specialist services for alcohol dependence.**

5.4 EFFECTIVENESS OF LAY SERVICES

5.4.1 ALCOHOLICS ANONYMOUS

The health technology assessment from NHS Quality Improvement Scotland supports the appropriate use of AA.[115]

Alcoholics Anonymous believes that alcohol dependence is a chronic and progressive illness without cure, for which total abstinence is the only solution. Alcoholics Anonymous is widely available and entirely self-funding, but there is limited formal evidence of efficacy from randomised studies. It is a network of support including advice for individuals in crisis. Their members are willing to help primary care teams link patients with AA. 2+

C **Alcohol dependent patients should be encouraged to attend Alcoholics Anonymous.**

5.4.2 OTHER LAY AND NON-STATUTORY SERVICES

Motivational interviewing and coping skills training for relapse prevention have been shown to be effective when delivered by psychologists.[131] Counselling by lay and non-statutory agencies is available in most of Scotland (eg by Councils on Alcohol) but has not been evaluated in controlled studies.[132] These agencies welcome referrals from NHS primary care. The evidence for efficacy of client-centred counselling for alcohol dependence is conflicting. Less defined counselling and education appear to be ineffective. Day care/drop-in centres are available in certain areas. 2+

D **If patients are referred to a lay service, agencies where lay counsellors use motivational interviewing and coping skills training should be utilised.**

5.5 EFFECTIVENESS OF MEDICATIONS TO PREVENT RELAPSE

The health technology assessment by NHS Quality Improvement Scotland included meta-analyses of the efficacy and cost effectiveness of medications for relapse prevention and found evidence of efficacy for disulfiram (supervised) and acamprosate.[115] This was also the conclusion of a health technology assessment by the Swedish Council on Technology Assessment in Health Care[106] and a literature review for the Aberdeen Health Economics Research Unit.[32]

Other meta-analyses support these findings[133,134] as does the joint guideline of the US Agency for Healthcare Research and Quality/American Society of Addiction Medicine (2002). Acamprosate is believed to act by modulating disturbance in the gamma-aminobutyric acid /glutamate system associated with alcohol dependence, reducing the risk of relapse during the postwithdrawal period. It is a safe drug with few unwanted side effects, and is not liable to misuse. Its value is in the first months after detoxification. Acamprosate is not effective in all patients so its efficacy should be assessed at regular appointments, and the drug withdrawn if there has not been a major reduction in drinking. Where it appears to be effective, good practice suggests prescribing for 6-12 months. The studies were conducted in specialist centres where psychosocial treatment was offered. It is an assumption that, as long as there is a system of monitoring compliance and efficacy, these data are applicable to primary care. 1++ 1+

B **Acamprosate is recommended in newly detoxified dependent patients as an adjunct to psychosocial interventions.**

☑ Acamprosate will usually be initiated by a specialist service within a few days of successful detoxification. If a specialist service is not available, the GP should offer acamprosate, monitor its efficacy and provide links to local support organisations.

Disulfiram's function is to deter the patient from resuming drinking. If taken regularly there is an unpleasant reaction when alcohol is consumed. It has unwanted effects in some patients, and carries special warnings. The health technology assessment by NHS Quality Improvement Scotland found some support for the use of supervised disulfiram and none for its non-supervised use. [115] If used, it should be offered for six months in the first instance, with regular review. Supervision is agreed by the patient to increase the likelihood that the medication is taken even at times of ambivalence. 2+

C **Supervised oral disulfiram may be used to prevent relapse but patients must be informed that this is a treatment requiring complete abstinence and be clear about the dangers of taking alcohol with it.**

☑ Disulfiram supervision may be undertaken by the spouse, healthcare or support worker, or the workplace representative if appropriate.

Naltrexone, although supported by the above reports, and used by specialists in Scotland, is not licensed in the UK for the treatment of alcohol dependence.

5.6 TREATING ALCOHOL DEPENDENCE AND ANXIETY OR DEPRESSION

In patients with an alcohol problem, there is good evidence that most anxiety and depression resolves with standard treatment for alcohol dependence.[133,135-138] 1+

For patients with panic disorder and social phobia, there is no consistent evidence of extra benefit of cognitive behavioural therapy beyond the simultaneous treatment for the alcohol problem.[139,140] 1+

In detoxified patients with definite depressive illness, antidepressants improve depressive symptoms and in some studies drinking outcomes.[133,135-138] The strongest effect is with fluoxetine, although this treatment seems to reduce the beneficial effect of cognitive behavioural therapy in the type of patients characterised by early onset and prominent social problems.[141] Therefore caution should be exercised in prescribing selective serotonin reuptake inhibitors (SSRIs) to patients characterised by early onset of alcohol problems and antisocial behaviour. 1+

There is insufficient evidence that antidepressants improve drinking outcomes in non-depressed patients.

B **Patients with an alcohol problem and anxiety or depression should be treated for the alcohol problem first.**

B **If depressive symptoms persist for more than two weeks following treatment for alcohol dependence, consideration should be given to using an SSRI or referring for counselling or specialist psychological treatment along with the relapse prevention treatment.**

☑ **If severe anxiety symptoms persist for more than two weeks in abstinent patients, consideration should be given to using an SSRI, or referring for specialist psychological treatment along with the relapse prevention treatment.**

5.7 TREATING ALCOHOL DEPENDENCE WHEN OTHER PSYCHIATRIC ILLNESS IS PRESENT

Patients with comorbid schizophrenia/schizoaffective disorder and substance misuse benefit from motivational interviewing, cognitive behavioural therapy and family interventions aimed at decreasing their dependence.[143-146] These patients are best treated by specialist services. | 1+ 2+ 4

Disulfiram may be used with caution in these patients bearing in mind drug interactions.[147] | 4

B **Patients with psychotic disorder and alcohol dependence should be encouraged to address their alcohol use and may benefit from motivational, cognitive behavioural, family and non-confrontational approaches.**

☑ Patients with psychoses should be referred for psychiatric advice.

5.8 EFFECTIVENESS OF ALTERNATIVE THERAPIES

Information on outcomes following use of alternative therapies was found only for acupuncture and transcendental meditation. RCTs and systematic reviews have not demonstrated an effect for acupuncture in the treatment of alcohol dependence.[148-150] | 1+ 1- 4

A review of transcendental meditation[151] (plus the accompanying erratum[152]) reports that this may be useful as an adjunctive treatment for people with an alcohol or drug dependence. The studies included in this review were heterogeneous and patient selection criteria were not reported. | 4

There is insufficient evidence to make any recommendations about the use of acupuncture, transcendental meditation or other alternative therapies in treating patients with an alcohol problem.

6 Advising families

The drinker's family may seek advice on how they should intervene when the drinker is not motivated to change. "Detaching with love" (one of the principles by which Al-Anon members lessen the risk of harm to their own mental health resulting from living with a drinker), or simple confrontation, are less likely to get the drinker to change or seek help than using an approach based on community reinforcement and family training (CRAFT).[153,154] Although not tested in primary care, the method can be taught to non-specialists. 1+

CRAFT instructs the family or "committed significant other" to reinforce, by encouragement or other rewards, any changes or statements that the drinker makes towards stopping or reducing the drinking, and to do nothing to enable or reward drinking. The treating team lays down the groundwork for rapid availability of outpatient treatment for the drinker in the event that he or she opts to begin therapy. The family are prepared from the beginning to recognise and respond safely to any potential for domestic violence during the introduction of what may be a new way of reacting to the drinker and the drinking.

The family are helped to:

- understand the nature of alcohol dependence
- improve communication with the drinker
- selectively apply or withdraw reinforcement, to amplify non-drinking
- apply pressure without bickering or recrimination
- learn stress reduction and gain more reward in their own life
- use effective methods and optimal times for proposing treatment entry to the drinker, such as restricting key messages to moments of sobriety, and exploiting alcohol related crises
- support the drinker through treatment.

The following recommendation has been extrapolated from the above trials.

C **The primary care team should help family members to use behavioural methods which will reinforce reduction of drinking and increase the likelihood that the drinker will seek help.**

7 Information for discussion with patients and carers

The following points were drawn up by the guideline development group to reflect the issues likely to be of most concern to patients and carers. These points are provided for use by health professionals when discussing alcohol problems with patients and in guiding the production of locally produced patient information materials.

7.1 PATIENT FEARS AND PERCEPTIONS WHEN PRESENTING WITH AN ALCOHOL PROBLEM

Research carried out by System Three Social Research,[2] and the SIGN patient involvement project, commissioned by the Scottish Executive, has identified recurrent themes of concern to patients presenting with an alcohol problem.

There is a widespread acceptance that the GP is the most appropriate first point of contact once a patient has decided to seek help. However, there are considerable fears or reservations associated with seeking such help even where a good relationship exists with the GP. Such fears include:

- the normal shyness or hesitancy associated with a condition perceived to be "shameful"
- being labelled an "alcoholic"
- jeopardising one's work by admitting to having an alcohol problem
- being concerned that children may be taken into care
- not being treated seriously or being told to "pull yourself together".

Other general points to emerge from the SIGN research and the literature:

- continuity of personnel providing support is essential as establishing trust is very important
- speed of referral is also very important as, once the difficult decision to seek help has been made, it needs to be followed up quickly or this positive attitude may evaporate
- there are wide differences in understanding of the terms "alcohol misuse", "alcohol problems" and "alcoholic". A common usage is for alcohol misuse to mean "beginning to impinge on normal life" and alcoholism to mean the above plus "a need or compulsion to drink" *(see section 1.2 for medical definitions)*
- there is confusion regarding what constitutes the standard unit of alcohol
- patients may have heard of Alcoholics Anonymous but will rarely have any knowledge of its methods or operations
- there is widespread belief that there are substantial facilities for sufferers from drug abuse but very little for those with alcohol problems.

7.2 KEY MESSAGES FOR PATIENTS

Problems with alcohol are suffered by people in varying degrees, ranging from occasional excess consumption to an addiction or dependence, which may affect the person and their whole lifestyle. Patients often progress from mild misuse of alcohol to more extreme stages so it is important to try to address any problem at an early stage, seeking medical assistance where necessary.

7.2.1 EFFECTS ON THE PERSON

At a personal level alcohol misuse has many effects including:

- anxiety, which often leads to a compounding of the problem
- health problems caused by the alcohol consumption itself including liver and brain damage and other serious conditions such as epilepsy and heart disease
- consequential health problems caused by the effects of alcohol such as malnutrition, injuries and gaps in memory
- difficulties in sustaining employment.

7.2.2 EFFECTS ON THE FAMILY

Having a family member with an alcohol problem can seriously affect the family, where family members and friends can become anxious, depressed or alienated.

Financial problems caused by the purchase of alcohol, coupled with reduced earnings potential also impact on the family.

7.2.3 HELP AVAILABLE FROM THE PRIMARY CARE TEAM

The range of advice, treatment and referral available from the GP and the primary care team includes:

- initial discussion and support
- advice regarding non-hazardous drinking levels and ways to reduce drinking
- counselling and therapy for the individual
- counselling and therapy for the family
- treatment options including medication to relieve the physical effects of stopping drinking and to help to reduce the incidence of drinking in the longer term
- referral to a specialist nurse, often within the practice, for individual help
- referral to another agency for clinical care with information about treatment options available
- referral to a voluntary agency for lay counselling
- link with a mutual help association such as Alcoholics Anonymous
- longer term support and monitoring.

☑ It should be stressed to patients that stopping or cutting down their drinking can only result from their own decision to do so. Any treatment, from whatever source, can only be an aid to taking this decision and following it through.

7.3 ORGANISATIONS WHICH PROVIDE USEFUL INFORMATION

AL-ANON
Mansfield Park, Unit 6, 22 Mansfield Street
Glasgow, G11 5QP
24h telephone service: 0141 339 8884
Website: www.al-anonuk.org.uk
Support for families and friends of alcoholics

Alcoholics Anonymous
National helpline: 0845 76 97 555
Website: www.alcoholics-anonymous.co.uk

Alcohol Concern
Waterbridge House. 32-36 Loman Street
London, SE1 0EE
Tel: 020 7922 8667 (Information Team)
Email: info@alcoholconcern.org.uk
Website: www.alcoholconcern.org.uk
Provides information on a wide range of alcohol related subjects. Alcohol Concern does not operate a helpline.

Alcohol Focus Scotland (formerly the Scottish Council on Alcohol)
2nd floor, 166 Buchanan Street
Glasgow, G1 2LW
Tel: 0141 572 6700, Fax: 0141 333 1606
Email: admin@sca-online.co.uk
Website: www.alcohol-focus-scotland.org.uk

Down Your Drink
Online program for reducing drinking
Website: www.downyourdrink.org.uk

National Alcohol Information Resource
Information and Statistics Division
Trinity Park House
Edinburgh, EH5 3SQ

NHS 24
Tel: 08454 24 24 24
Website: www.nhs24.com

NHS Health Scotland (formerly the Health Education Board for Scotland)
Woodburn House, Canaan Lane
Edinburgh, EH10 4SG
Tel: 0131 536 5500, Fax: 0131 536 5501
Website: www.hebs.org

8 Implementation, audit and further research

8.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of local NHS organisations and is an essential part of clinical governance. It is acknowledged that not every guideline can be implemented immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

8.2 KEY POINTS FOR AUDIT

- Are primary care workers opportunistically identifying people with an alcohol problem and delivering appropriate brief interventions?
- At new patient registration in general practice, what is the proportion of completed sections on alcohol consumption?
- Are staff delivering treatments such as motivational interviewing according to recognised methodology?
- Are there local protocols for alcohol withdrawal management in place and in use?
- Does the practice have access to a breathalyser?

A brief instrument which has been used in audit of outcomes is the Alcohol Related Problems Questionnaire.[155]

8.3 RECOMMENDATIONS FOR RESEARCH

Further high quality research in a representative population group is needed to:

- establish the effectiveness of routine brief intervention in the A&E setting
- compare outcomes for in/outpatient detoxification
- study the use of oral vitamin preparations in primary care, and whether subsequent Wernicke-Korsakov syndrome, neuropathy or cerebellar damage is delayed/prevented
- appraise alcohol policy initiatives in order to ascertain the cost effectiveness of such treatments, and of "brief interventions"
- simplify screening tools
- study the efficacy of alternative therapies in treating patients with an alcohol problem.

9 Development of the guideline

9.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals, and patient organisations, funded by NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

9.2 THE GUIDELINE DEVELOPMENT GROUP

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Mr Walter Simpson	*Lay Representative*
Dr Richard Watson	*General Practitioner, Glasgow*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive. Guideline development and literature review expertise, support, and facilitation were provided by the SIGN Executive.

9.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Healthstar, Cinahl, PsychINFO, Alcohol and Alcoholism, and the Cochrane Library. The year range covered was 1995-2001. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, the UK Health Technology Assessment programme, the NIAAA Alcohol and Alcohol Problems Science Database (ETOH), and the US National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group. All selected papers were evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

9.4 CONSULTATION AND PEER REVIEW

9.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 29 April 2002 and was attended by around 150 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

9.4.2 SPECIALIST REVIEW

The guideline was also reviewed in draft form by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to this guideline.

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9.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an Editorial Group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The Editorial Group for this guideline was as follows:

Dr David Alexander	*Scottish General Practice Committee*
Dr Keith Brown	*Royal College of Psychiatrists*
Professor Gordon Lowe	*Chair of SIGN*
Dr Lesley Macdonald	*Faculty of Public Health Medicine*
Dr Safia Qureshi	*SIGN Programme Director*
Dr Sara Twaddle	*Director of SIGN*
Dr Bernice West	*National Nursing, Midwifery, Health Visiting Advisory Committee*

Each member of the guideline development group then approved the final guideline for publication.

9.5 ACKNOWLEDGEMENTS

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Annex 1
Alcohol content of some beverages

Beverage type		Alcohol by volume (%)	Measure	Alcohol content (units)
Beers/lagers	Barbican	0.02	440ml	<0.01
	Kaliber	0.05	Pint	0.03
	Tennents LA	1.2	440ml	0.5
	Mild/light beers (various brands)	3.1	Pint	1.8
	Best bitter (various brands)	3.5	Pint	2.0
	Skol	3.6	Pint	2.0
	McEwans/Labatt	4.0	Pint	2.3
	Guinness draft stout	4.1	Pint	2.3
	Grolsch	5.0	440ml	2.2
	Premium beer/lager (various brands)	5.0	Pint	2.8
	Stella Artois	5.2	330ml	1.7
	Lowenbrau Pils	6.0	440ml	2.6
	Hofmeister Special	9.0	440ml	4.0
	Kestral Super	9.5	440ml	4.2
Ciders/Perries	Strongbow LA	0.9	330ml	0.3
	Woodpecker	3.5	Pint	2.0
	Strongbow	4.5	1000ml	4.5
	Old English	5.5	Pint	3.1
	Strongbow Super	8.0	Pint	4.5
	Diamond White	8.2	275ml	2.3
	Strong White Cider	8.4	1000ml	8.4
Spirit based drinks with mixers (alcopops)	Hooch	4.7	330ml	1.6
	WKD Original Vodka Blue or Iron Brew	5.5	330ml	1.8
	Smirnoff Ice	5.5	275ml	1.5
	Bacardi Breezer	5.4	275ml	1.5
	Metz Snapps (Black, Still or Original)	5.4	275ml	1.5
	Vodka Red Square (Barrs Irn Bru)	5.5	275ml	1.5
	Aftershock	40.0	700ml	28.0
Vodka Hooch	Lemon/Apple/Orange/Hoopers Hooch	4.7-5.1	330ml	1.6-1.7
Shooters (addition to main drink)	Jelly Pots	15.0	47ml	0.7
	Sidekick	20.0	30ml	0.6
	Aftershock	40.0	30ml	1.2
	Frostbite	50.0	30ml	1.5
	Absinthe	75.0	30ml	2.3
Wines	Various brands	9-14	750ml	6.8-10.5
A purchased glass of wine can vary from 125 to 250 ml and can contain 1.1-3.5 units per glass depending on % alcohol. A small (125ml) glass of average strength (12%) wine contains 1.5 units.				
Fortified Wines and similar	Cinzano bianco/Buckfast	14.7	750ml	11.0
	Croft Original Sherry	17.5	750ml	13.1
	Cockburn's Port	20.0	750ml	15.0
Spirits	Gordons Dry Gin/Smirnoff Vodka	37.5	700ml	26.3
	Bacardi White Rum	37.5	700ml	26.3
	Bells Whisky/Martell cognac brandy	40.0	700ml	28.0
	Captain Morgan's dark rum	40.0	700ml	28.0
A purchased measure of spirit is 25 or 35 ml. A 25ml measure of 40% spirit contains 1 unit of alcohol.				
Liqueurs	Bailey's Irish Cream	17.0	350ml	6.0
	Archers Peach Schnapps	23.0	700ml	16.0
	Apricot Brandy/Crème de Menthe/Malibu	24.0	700ml	16.8
	Pernod/Cointreau/Drambuie	40.0	700ml	28.0

Formula: the amount of alcohol (in units) = volume (in litres) x percentage alcohol

Note: there are 1,000 ml in 1 litre and 1 pint = 568 ml.
The information in this table has been adapted from three sources: the Medical Council on Alcoholism,[14] Alcohol Focus Scotland and the Portman Group.

Annex 2
Clinical presentations where the role of alcohol should be considered

Hazardous drinking and alcohol dependence present in many ways. The following presentations should alert clinicians to the possibility that alcohol may be involved:

Social

- marital disharmony and domestic violence
- neglect of children
- criminal behaviour such as driving offences, breach of the peace, shoplifting
- misuse of the emergency telephone services
- unsafe sex
- financial problems

Occupational

- repeated absenteeism, especially around weekends
- impaired work performance and accidents
- poor employment record

Psychiatric

- amnesia, memory disorders and dementia
- anxiety and panic disorders
- depressive illness
- morbid
- alcoholic hallucinosis
- treatment resistance in other psychiatric illnesses and as a factor in relapse
- repeated self harming

Physical

- multiple acute presentations to A&E with trauma and head injury
- dyspepsia, gastritis, haematemesis
- diarrhoea and malabsorption
- acute and chronic pancreatitis
- liver abnormalities from deranged liver function tests, through hepatitis, to fatty liver and cirrhosis
- cardiac arrhythmias
- hypertension and stroke
- cardiomyopathy
- peripheral neuropathy, cerebellar ataxia
- impotence and problems with libido
- withdrawal seizures and fits starting in middle age
- falls and collapses in the elderly
- blood dyscrasias such as low platelet count and white cell count (neutrophils)
- acne rosacea, discoid eczema, psoriasis, multiple bruising
- cancers of mouth, pharynx, larynx, oesophagus, breast and colon
- acute and chronic myopathies
- unexplained infertility
- gout

Annex 3

The Fast Alcohol Screening Test (FAST) for the detection of probable hazardous drinking[31]

For the following questions please circle the answer which best applies.

1 drink = 1 unit = $^1/_2$ pint of beer or 1 glass of wine or 1 single spirits

1. **MEN: How often do you have EIGHT or more drinks on one occasion?**
   WOMEN: How often do you have SIX or more drinks on one occasion?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

Only ask Questions 2, 3 & 4 if the response to Question 1 is "Less than monthly" or "Monthly"

2. **How often during the last year have you been unable to remember what happened the night before because you had been drinking?**

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

3. **How often during the last year have you failed to do what was normally expected of you because of drink?**

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

4. **In the last year has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?**

No	Yes, on occasion	Yes, on more than one one occasion

Scoring is quick and can be completed with just a glance at the pattern of responses as follows:[156]

Stage 1
The first stage only involves question 1.
If the response to question 1 is never then the patient is not misusing alcohol.
If the response to question 1 is Weekly/Daily or Almost Daily then the patient is a hazardous, harmful or dependent drinker. Over 50% of people will be classified using just this one question.
Only consider Questions 2, 3 & 4 if the response to Question 1 is Less than monthly or Monthly.

Stage 2
If the response to Question 1 is Less than monthly or Monthly then each of the four questions is scored 0 to 4. These are then added resulting in a total score between 0 and 16. The person is misusing alcohol if the total score for all four questions is 3 or more.

Score Questions 1, 2 & 3 as follows:	Score Question 4 as follows:
Never = 0	No = 0
Less than monthly = 1	Yes, on one occasion = 2
Monthly = 2	Yes, on more than one occasion = 4
Weekly = 3	
Daily or almost daily = 4	

In summary, score Questions 1, 2 & 3: 0,1,2,3,4. Score Question 4: 0,2,4
The minimum score is 0
The maximum score is 16
The score for hazardous drinking is 3 or more.

Annex 4
The one minute Paddington Alcohol Test (PAT)[157]

Please complete for ALL A&E PATIENTS where there is any INDICATION OF ALCOHOL MISUSE: eg assault, head especially facial injury, fall, non-specific gastrointestinal problem, "unwell", fit, blackout, collapse, insomnia, sweating, hypo/hyperglycaemia, palpitations, chest pain, gout, rashes, depression, overdose; note **REPEAT** attendance (perhaps with unexplained symptoms) and **DELAYED** attendance >4 hours (perhaps intoxicated at the time of "incident").

Remember the elderly presenting with: falls, confusion, incontinence and self neglect.

1. **Quite a number of people have times when they drink more than usual; what is the most you will drink in any one day?**
   N.B. Please note if home or pub measures. Units (1 unit = 8 grams alcohol) relating to pub measures, are shown in brackets.

TYPE OF DRINK	AMOUNT	
Beer/Lager/Cider	Pints (2) or Cans (1.5)	____ = Units/day
Strong Beer/Lager/Cider	Pints (5) or Cans (4)	
Wine	Glasses (1.5) or Bottles (9)	
Fortified Wine (Sherry, Martini)	Glasses (1) or Bottles (12)	
Spirits (Gin, Whisky, Vodka)	Singles (1) or Doubles (2) or Bottles (30)	

2. **If this is more than 8 units/day for a man, or 6 units/day for a woman, does this happen:**

Once a week or more?	YES: PAT +ve
or	
Between once a month and once a week?	YES: PAT +ve
or	
Neither (ie once a month or less)?	YES: PAT -ve (go to Question 3)

3. **Do you feel your current attendance in A&E is related to alcohol?**

YES: PAT +ve
NO: PAT -ve

ie PAT +ve if >8 units male or 6 units female more than once a month, and/or YES to Question 3.

Annex 5
Important elements of motivational interviewing

Adapted from Miller and Rollnick, 2002.[158]

Portraying empathy

- use of open ended questions and avoiding premature closure
- respect for individual differences
- reflective listening so that patients sense you are trying to *"get on their wavelength"*
- expressing interest/concern
- acceptance that ambivalence is normal.

Developing discrepancy

- patients are helped to see the gap between the drinking and its consequences and their own goals/values - the gap between *"where I see myself, and where I want to be"*
- enhancing their awareness of consequences, perhaps adding feedback about medical symptoms and test results: *"How does this fit in?" "Would you like the medical research information on this?"*
- weighing up the pros and cons of change and of not changing
- progressing the interview so that patients present their own reasons for change.

Avoiding argument *("rolling with resistance")*

- resistance, if it occurs (such as arguing, denial, interrupting, ignoring) is not dealt with head-on, but accepted as understandable, or sidestepped by shifting focus
- labelling, such as *"I think you have an alcohol problem"* is unnecessary, and can lead to counterproductive arguing.

Supporting self efficacy

- encouraging the belief that change is possible
- encouraging a collaborative approach (patients are the experts on how they think and feel, and can choose from a menu of possibilities)
- the patient is responsible for choosing and carrying out actions towards change.

Facilitating and reinforcing "self motivating statements"

- recognising that alcohol has caused adverse consequences
- expressing concern about effects of drinking
- expressing the intention to change
- being optimistic about change.

A tenet of motivational interviewing is *"People believe what they hear themselves say"*.

Annex 6

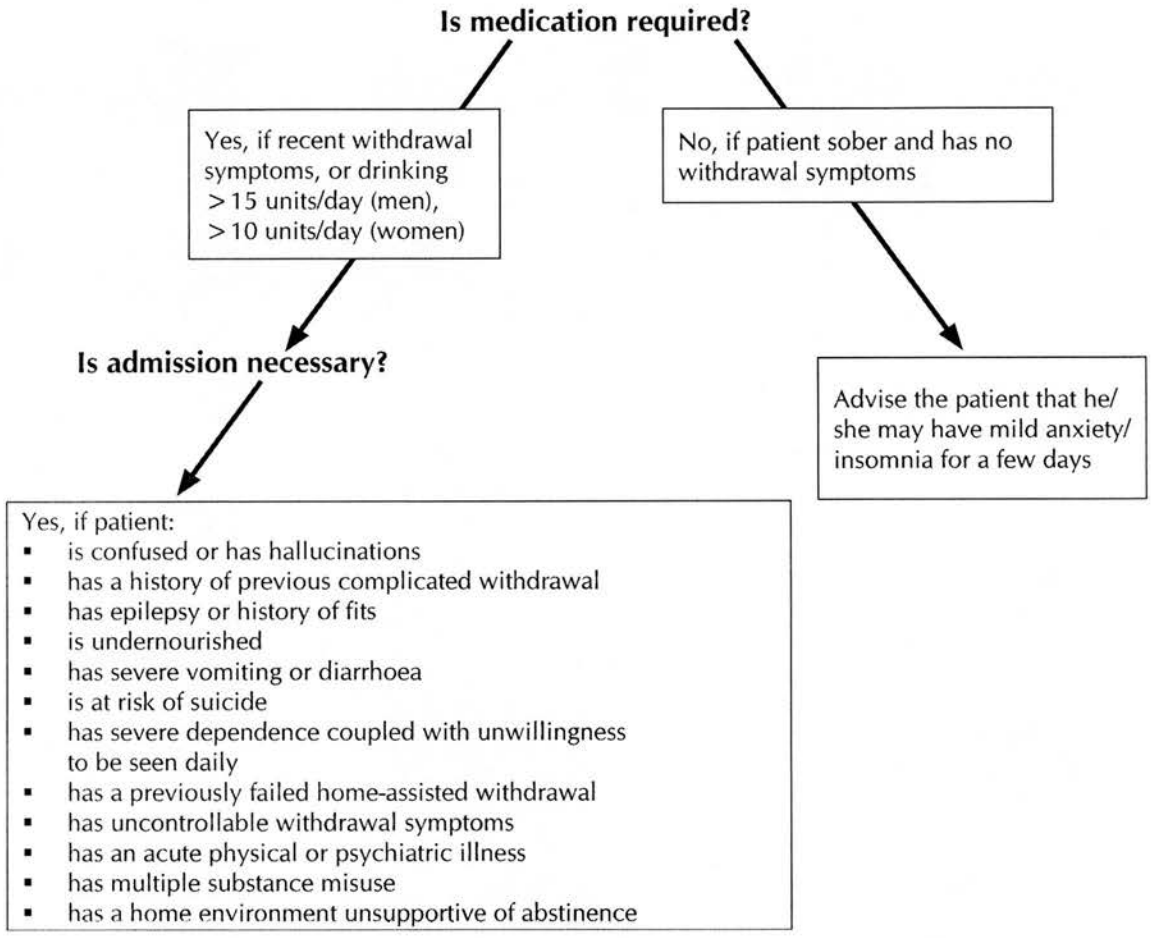
Advice to patients on withdrawing from alcohol at home

1. If you have been chemically dependent on alcohol, stopping drinking causes you to get tense, edgy, perhaps shaky or sweaty, and unable to sleep. There can be vomiting or diarrhoea. This "rebound" of the nervous system can be severe. Medication controls the symptoms while the body adjusts to being without alcohol. This usually takes three to seven days from the time of your last alcoholic drink. If you don't take medication, the symptoms would be worst in the first 48 hours, and then gradually disappear. This is why, if you do take medication, the dose starts high and then reduces. If you have been prescribed 10 mg tablets of chlordiazepoxide, use the table below to remind you when to take the right number of tablets.
2. **YOU HAVE AGREED NOT TO DRINK ALCOHOL.** You may get thirsty. Drink fruit juices and water but do not overdo it. You do not have to "flush" alcohol out of the body. More than three litres of fluid could be too much. Don't drink more than three cups of coffee or five cups of tea. These contain caffeine which disturbs sleep and causes nervousness.
3. **AIM TO AVOID STRESS.** The important task is not to give in to the urge to take alcohol. Help yourself relax by going for a walk, listening to music, or taking a bath.
4. **SLEEP.** You may find that even with the capsules, or as they are reduced, your sleep is disturbed. You need not worry about this - lack of sleep does not seriously harm you, starting to drink again does. Your sleep pattern will return to normal in a month or so. It is better not to take sleeping pills so that your natural sleep rhythm returns. Try going to bed later. Take a bedtime snack or milky drink.
5. **The capsules may make you drowsy so you must not drive or operate machinery. If you get drowsy, miss out a dose.**
6. **MEALS.** Even when you are not hungry, try to eat small amounts regularly. Your appetite will return.

Number of chlordiazepoxide (10 mg) tablets to take and when to take them when withdrawing from alcohol as an outpatient

	First thing	12 noon	6 pm	Bedtime
Day 1	-	3	3	3
Day 2	2	2	2	3
Day 3	2	1	1	2
Day 4	1	1	-	2
Day 5	-	1	-	1

Annex 7
Assisting withdrawal from alcohol



Annex 8
The NHS Quality Improvement Scotland recommendations on the prevention of relapse in alcohol dependence[115]

Psychosocial interventions

- Behavioural Self Control Training (BSCT), Motivational Enhancement Therapy (MET), Marital/ Family Therapy and Coping/Social Skills Training are clinically and cost effective psychosocial interventions and are recommended treatment options for the prevention of relapse in alcohol dependence.
- Brief Interventions are not recommended, as trials in alcohol dependent people have failed to show any benefit. However, this guideline recommends Brief Interventions for hazardous drinkers (a less severely affected group than those who are considered to be alcohol dependent).
- Other psychosocial interventions are not recommended as their clinical effectiveness is unproven.

Pharmacological interventions

- Acamprosate and supervised oral disulfiram are treatment options recommended as adjuncts to psychosocial interventions. Naltrexone does not have a Marketing Authorisation for the treatment of alcohol dependence in the UK and is not recommended for routine use in NHSScotland.

Delivery of services

- Alcohol services should aim to reduce the delay between detoxification and interventions for the prevention of relapse. This would be facilitated by joint working between specialist mental health services, primary care, social work addiction services and non-statutory agencies, as recommended by the Joint Futures Group.
- Acamprosate or supervised oral disulfiram should usually be initiated by a specialist service. The specialist service will: ensure that the patient meets the criteria for suitability; ensure the assessment of the motivation and ability of the patient to use the medication correctly; monitor efficacy; and ensure that adjunctive psychosocial treatment is organised. Usage should be in accordance with the Summary of Product Characteristics and reviewed regularly during the first 12 weeks after initiation of treatment, at which stage transfer of prescribing to the general practitioner may be appropriate, even though specialist care may continue (shared care).
- Introduction to AA and non-statutory agencies such as local Councils on Alcohol (Alcohol Focus Scotland) should be part of the overall strategy of specialist NHS services for the prevention of relapse. As with other psychosocial treatments, attendance is most likely to be beneficial if it is an informed voluntary decision.
- People who are alcohol dependent should be informed about treatment choices. Their needs, preferences and social circumstances should be considered. As a result, the choice of interventions should be a shared decision between the health professional and the patient.
- NHS specialist services should contact people who drop out of treatment programmes and offer them another appointment.

Communication with patients

- Health professionals should provide patient information, including leaflets, which should be used to support discussion between health professionals and patients about the most appropriate treatment option.
- Written information about the range of available services should be readily accessible to people with alcohol problems, their families, carers and to health professionals, especially GPs. Alternative formats such as cartoons or audiovisual material should be used to support discussions with people who have low reading skills or poor concentration. Alcohol Action Teams could coordinate information requirements.
- A regularly updated comprehensive directory of alcohol services and accommodation should be developed for the benefit of NHSScotland staff, patients and their families, friends and carers.

Abbreviations

AA	Alcoholics Anonymous
A&E	Accident and Emergency
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol concentration
BNF	British National Formulary
CAGE	Attempts to **C**ut back on drinking, being **A**nnoyed at criticisms about drinking, feeling **G**uilty about drinking, and using alcohol as an **E**ye-opener
CDT	Carbohydrate deficient transferrin
CRAFT	Community reinforcement and family training
FAST	Fast Alcohol Screening Test
GGT	Serum gamma glutamyl transferase
GP	General practitioner
ICD-10	International Classification of Diseases version 10
MCV	Mean red blood cell volume
NNT	Number needed to treat
PAT	Paddington Alcohol Test
RCT	Randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SSRI	Selective serotonin reuptake inhibitor
T-ACE	**T**olerance, **A**nnoyed by someone criticising your drinking, felt need to **C**ut down, **E**ye-opener
TWEAK	**T**olerance to effects of alcohol, **W**orry about drinking, **E**ye -opener, **A**mnesia, felt the need to **K** cut down your drinking
W-K	Wernicke-Korsakov

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