WORKING GROUP ON ACUTE PURCHASING

Summary of Evidence of Effectiveness for Selective Serotonin Re-uptake Inhibitors and Tricyclic Antidepressants in the First Line Treatment of Depression

January 2000

GUIDANCE NOTE FOR PURCHASERS 00/02

Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help Health Authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by Health Authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 11 January 2000 at which this Guidance Note for Purchasers (in a draft form) was considered.

SUMMARY OF EVIDENCE OF EFFECTIVENESS FOR SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS IN THE FIRST LINE TREATMENT OF DEPRESSION

AUTHORS: Beard SM, McGarrity C, Touch S. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 2000. Guidance Note for Purchasers: 00/02.

EXPERT ADVISORS TO TRENT DEC:

Mr SM Beard, Senior Operational Research Analyst, ScHARR, The University of Sheffield.
Dr C McGarrity, Consultant in Public Health Medicine, Leicestershire Health Authority.

(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: From the many randomised controlled trials and meta-analyses published, there appears to be no difference in efficacy or adverse reaction between SSRIs and the newer TCAs. Currently, the cost of lofepramine is cheaper than most of the SSRIs, and should therefore be the drug of choice for the first line treatment. The Committee felt that it would be helpful if clear guidelines on diagnosis, treatment and management of depression in primary care were developed.

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S M Beard
C McGarrity
S Touch

Series Editor: Nick Payne

Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

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Information Resources
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 0703
Fax 0114 272 4095
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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor M Clarke (Leicester); and
Professor H Williams (Nottingham).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

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What is the expected burden of major depression?

Depression remains a significant burden on society as a whole and is one of the most common reasons for consulting a general practitioner.

Accepting previous UK estimates of annual consultation rates by patients with major depression of about 6%, around 30,000 diagnosed depressed patients per annum would be expected to be seen, in the primary care sector, for a 'typical' health authority population of 500,000.

Up to 25% of people suffering depression will not present to primary healthcare services, and of those who do only approximately 50% will be diagnosed accurately on their initial visit. Therefore, the true burden of depression within the community is likely to be much higher than that actually recognised in general practice.

What are the current levels of SSRI prescribing?

The volume of antidepressant prescribing generally has increased over the last decade, with substantial growth in the use of drugs such as selective serotonin re-uptake inhibitors (SSRI)s and heterocyclics. Overall, prescribing rates are now similar between SSRIs and tricyclic antidepressants (TCA)s with 47% of the total prescribing volume attributable to SSRIs. In cost terms, SSRIs are now estimated to account for over 85% of the total NHS antidepressant budget, currently estimated at approximately £214 million per year.

Recent analysis of UK patterns of prescribing for antidepressants in general practice reveals that TCAs remain commonly (60-70%) prescribed at dosages below the theoretical therapeutic levels, and this remains unexplained by legitimate periods of simple dosage titration. This sub-therapeutic dosaging issue is not generally seen with SSRIs, or newer TCA-related drugs.

Do SSRIs have a greater clinical efficacy than TCAs?

There exists a large body of well over 100 randomised controlled trials (RCT)s which have made direct comparisons of efficacy and clinical effectiveness between SSRIs and TCAs. However, these trials are dominated by small studies conducted within the secondary care setting over clinically short periods of time (6-12 weeks), thus, limiting their individual power and generalisability. Trials also vary in terms of the TCA type used as a comparator (i.e. older TCA, newer TCA or heterocyclic). Also the precise dosing of the comparator drug and the SSRI can vary enormously. This heterogeneity across the trial evidence base limits individual trial power and overall generalisability.

There are now several formal meta-analyses which suggest that, despite small effect advantage in favour of TCAs, there are no significant clinical differences between SSRIs and TCAs.

Are SSRIs better tolerated than TCAs?

The meta-analyses have commonly used both overall and adverse effect related drop-out rates from RCTs as proxies for treatment tolerability. On an individual RCT trial basis there remains great variation in both study design and patient group leading to similar differences in findings for drop-outs. The general conclusions are that SSRIs and related drugs are generally better tolerated than the older TCAs and that treatment withdrawals, due to adverse effects, are less common when using SSRIs than TCAs.

The overall drop-out rate for TCA-related drugs is commonly reported at levels of around 30-35% (or 14-19% when limited to drop-outs related to adverse effects only). The typical absolute difference in overall ‘all-cause’ drop-out rates appears to be approximately 4-5%, in absolute terms, in favour of SSRIs.

Current evidence suggests that observed differences between SSRIs and TCAs, in terms of overall and adverse effect related drop-out rates, only reach statistical significance when considering the older TCAs (commonly associated with poorer adverse effect profiles). This point has a big impact in terms of an appropriate choice of reference TCA drugs.

Do patients taking SSRIs have a reduced likelihood of overdose or suicide?

Although there is a strong theoretical argument that a move towards the wider use of first-line SSRIs could reduce levels of suicide and associated costs, there remains no clear evidence of any economic advantage. It is also debatable as to whether a real reduction is possible, or whether it would simply shift the balance in the methods of suicide. This is an area which requires more research, and is likely to require a modelling approach due to the very low observed event frequency.

Are SSRIs more cost-effective in treating major depression than TCAs?

The relative cost-effectiveness and economic case for the first-line use of newer SSRI drugs have been considered by a number of studies and have generated much debate. The majority of these studies have been based on either clinical decision models or on retrospective analysis of patient records. Whilst earlier economic studies tended to support an economic advantage with SSRIs, a number of later modelling studies have challenged this view. The most contentious modelling issue relates to the interpretation of drop-out data drawn from previous RCTs, meta-analyses and/or expert-panels.

There remains only one naturalistic randomised study of SSRIs and TCAs, which appears to suggest that, in a clinically realistic environment, where switching treatment is allowed, there is no clear evidence of a cost-effectiveness advantage for the general first-line use of SSRIs. Therefore, as yet, there appears to be no clear economic evidence which can support the use of first-line SSRIs for all patients.

Are SSRIs more expensive than TCAs?

The cost of SSRIs is currently around 5-6 times that of standard TCA drugs, such as amitriptyline and dothiepin. Newer TCA-related drugs, including lofepramine, although more expensive than older TCAs, also remain significantly cheaper than SSRIs (at around 25% of average SSRI costs).

However, generic versions of fluoxetine (Prozac - expected in early 2000) will almost certainly drive down the costs of all SSRIs and it would seem unlikely that such scales of increased costs of SSRIs will persist. In the light of the existing data on both cost-

effectiveness and patient drug tolerance, a lower drug cost for SSRIs is likely to lead to a much more favourable and clearer cost-effectiveness argument in favour of SSRIs.

What other new evidence on SSRIs should we expect?

An ongoing HTA randomised study is likely to provide further UK-based evidence of the role of first-line SSRIs in the treatment of depression; however, this is not expected to report until at least the year 2002.

There remain two ongoing meta-analyses, conducted as part of the Cochrane collaboration, which should provide health professionals with regular up-dated considerations of the evidence related to the first-line use of SSRIs, in terms of both efficacy and patient tolerance of treatment.

On the basis of the current evidence, the key messages for purchasers are:

- To formulate local guidelines on the diagnosis and management of depression.

- That further work is required specifically to answer the question of the cost-effectiveness of SSRIs compared with newer TCAs.

- To consider the use of the newer TCA lofepramine - unless contraindicated as a first line drug choice.

ABBREVIATIONS

CCOHTA	Canadian co-ordinating office for health technology assessment
CEA	Cost-effectiveness analysis combining cost and health benefits
CER	Cost-effectiveness Ratio
CUA	Cost utility analysis combining cost and benefits weighted for patient preference
GPRD	General Practice Research Database
HCA	Heterocyclic antidepressant
HDRS	Hamilton Depression Rating Scale
HMO	Health Maintenance Organisation
MAIO	Monoamine oxadase inhibitor
MAOI	Monoamine oxidose Inhibitors
NNT	Number needed to treat
ONS	Office of National Statistics
OPCS	Office of Population Censues and Survey
OR	Odds ratio
PPA	Prescriptions pricing authority
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RIMA	Reversible inhibitor monoamine oxadase
RR	Relative Risk
SSRI	Selective serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant

1. INTRODUCTORY REMARKS

Depression is widely recognised as a significant burden on health services and society as a whole, and can result in significant levels of suffering for both patients and families alike.[1] It is estimated that around two thirds of adults will, at some time in their lives, experience depression or worry of sufficient severity to influence their daily activities.[2] For the majority of people, episodes of depression are relatively short-lived, but a minority experience a range of severe psychological and physical symptoms.

Depression remains one of the most common reasons for consulting a general practitioner, and the majority of depressed people who receive treatment do so within a primary care setting. Despite the impact of national campaigns to heighten the general awareness of depression as a serious health issue,[3,4,5] it is widely accepted that clinical depression remains under-treated in many cases. Almost a half of all cases of major depression remain unrecognised on initial presentation to primary care health services; with patients often presenting with non-specific 'physical' symptoms related to their underlying mental illness.[2]

The discovery of antidepressants has undoubtedly shifted the balance of treatment more towards drug-based therapy. The development of less toxic and better tolerated novel drugs, such as selective serotonin re-uptake inhibitors (SSRI)s, has further accelerated the use of pharmacology in the management of depression, leading to considerable interest in their relative efficiency and effectiveness in the treatment of depressive illness. As a result, the proportion of patients prescribed SSRIs for depression has increased dramatically, bringing with it an overall increase in the drug bill for antidepressants.[6]

The SSRIs remain relatively expensive drugs, when compared to alternative tricyclic antidepressant (TCA) drug therapy, with prescribing data suggesting costs of up to 5-6 times those of conventional TCAs. Their increased use as a first-line treatment, therefore, poses a real challenge to existing and future drug budgets.[7]

There are now well over 100 recognised randomised controlled trials (RCT)s which have compared SSRI drugs with either older tricyclic antidepressants or newer TCA-related heterocyclic antidepressants (HCA)s. However, despite this considerable research effort, there appears little consensus as to which class of drug should be given as first-line treatment in depression.

The purpose of this Guidance Note is to bring together an overall picture of the current evidence, views and guidelines related to the first-line use of SSRIs.

The report considers two key research issues:

1. What is the quantity/quality of evidence regarding the significant difference in clinical efficacy/effectiveness between SSRIs and TCAs/TCA-related drugs (both in randomised studies and natural clinical settings)?

2. Is there any evidence to suggest a clear advantage between antidepressant treatments in terms of their value for money?

2. DESCRIPTION OF UNDERLYING DISEASE

The importance of improving identification, diagnosis and the appropriate treatment of people with depression has long been recognised. The Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) criteria for major depression defines that a patient must have had symptoms for a period of at least two weeks, including at least five of the following symptom types:[8]

- depressed mood
- loss of interest/pleasure
- psychomotor agitation/retardation
- feelings of worthlessness/excessive guilt
- impaired thinking/indecisiveness
- weight loss/gain
- insomnia or hypersomnia
- fatigue/loss of energy
- suicidal thoughts

The criteria specify that the first two of these symptoms (i.e. a depressed mood and loss of interest) must be present for a diagnosis of major depression. Similar criteria for diagnosis exist within the International Classification of Diseases (ICD-10) diagnosis coding.[9]

Depression often results in a long-term chronic illness, with relapses commonplace and cyclical patterns of disease the norm for many patients. The historical social stigma, that past generations have placed on mental illness, also compounds this problem with many sufferers failing to present to the health services. Previous estimates of the rate of non-presentation suggest that anywhere between 25-50% of people suffering depression will not visit their GP. It is also difficult to estimate accurately the true rates of successful diagnosis of depressed patients who present to GPs. However, it is widely believed that GPs will only diagnose correctly 40-50% of presenting cases at an initial consultation. Therefore, despite the existence of recognised and accepted common diagnostic criteria, the estimation of both incidence and prevalence for major depression remains extremely problematic; complicated further by the diverse nature of depressive illnesses themselves. It is likely, therefore, that what is seen as formally diagnosed depression represents only a fraction of the true burden of illness in the community.

Examples of previously published estimates of prevalence rates for major depression are shown in Table 1. Analysis of data on general practice consultations suggests an annual consultation rate of individuals with diagnosed depression of between 5-6%, with an expected 2-3 consultations per patient.[10,11] The Office of Population Censuses and Surveys

(OPCS) survey of Psychiatric Morbidity estimated that 2-3% of the adult population experienced a depressive episode during the previous week of the survey (or 9-10% if the wider diagnostic category of depressive episode or mixed anxiety and depressive disorder was adopted).[12]

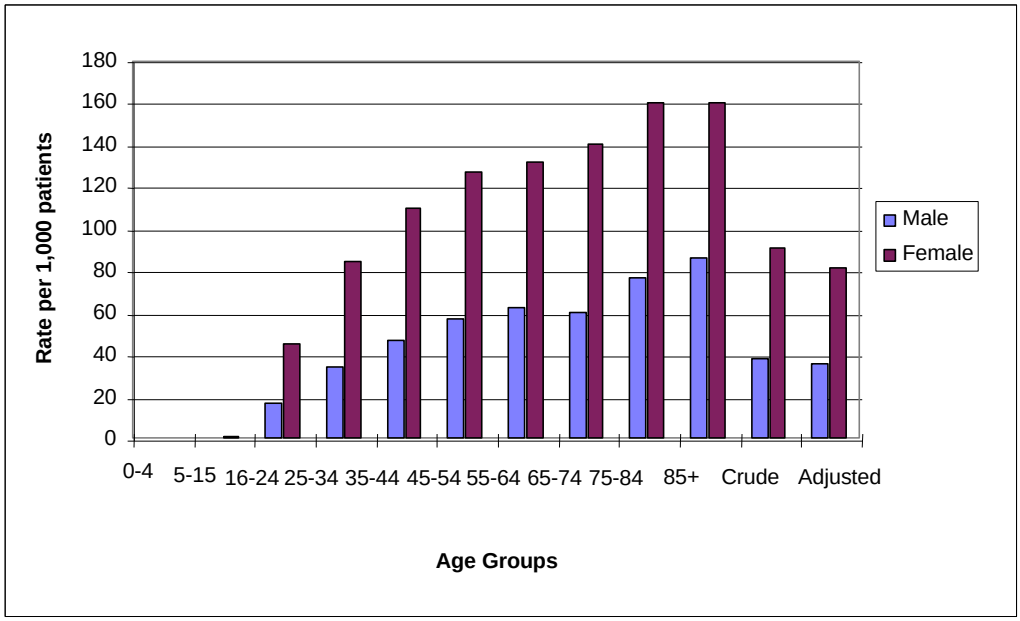
Table 1 Estimates of Prevalence of Major Depression

Source	Consultation Rate of Patients / Prevalence
Key National Survey Data	
1. Key Health Statistics from General Practice 1996[11] General Practice Research Database (GPRD) – annual figures (ICD 9 : 298,300,311 + drug prescribing 4.1-4.3 BNF)	• 59.1 per 1,000 patients • 5.9% per annum consultation rate • 8.2% female / 3.6% male
2. Morbidity Statistics in General Practice, 1991[10] Annual figures from GP electronic records (ICD 9 298,300,311 as in Key Statistics)	• 45.8 per 1,000 patients • 99.6 consultations per 1,000 patients • 4.6% per annum consultation rate
3. OPCS Surveys of Psychiatric Morbidity in Great Britain[12] *Report 1 : The prevalence of psychiatric morbidity among adults living in private households* 1 week prevalence survey	• Depressive episode: 2.1% in last week • Depressive episode + Mixed anxiety & depressive disorder: 9 - 10 % in last week
4. Health of the Nation - Key Area Handbook - Mental Health	• Depressive disorders: 2%-5% *(precise time period unclear)* • Affective psychosis 0.1%-0.5%

Accepting the Key Health Statistics from General Practice (1996) figures as a reasonably representative and reliable estimate of a national annual consultation rate for depression, (i.e. 5.9% per annum.), then the primary care sector, for a 'typical' health authority (population 500,000) might expect to see around 30,000 diagnosed depressed patients per annum.

Episodes of major depression are reported to be around twice as common amongst women as men, rising steadily with age, and are strongly associated with adverse social and economic circumstances such as unemployment, divorce or separation, inadequate housing and lower social class.[2] A national age/sex break down of the prevalence of treated depression is shown in Figure 1; it is taken from the Key Health Statistics from General Practice, 1996. The data are summed to a crude overall rate, which is further adjusted to reflect the national age/sex mix.

Figure 1 Consultation Rates (persons) for Treated Depression per 1,000 Population per Annum



3. CURRENT SERVICE PROVISION

3.1 PROFILE OF CURRENTLY PRESCRIBED ANTIDEPRESSANTS

The current treatment for major depression is very much focused on the delivery of health care services through the primary care network. As such, it is general practitioners, practice nurses and community mental health professionals who play the major role in both the identification and diagnosis of depressive illness and the delivery of clinically effective treatments.

Drug-based therapy using antidepressants (see Table 2) remains the main treatment mode for depression within the UK, with an estimated one million person-years of treatment provided annually.[7] There are five main sub-groups of antidepressant: the older 'first-generation' TCAs; newer 'second-generation' TCAs; TCA-related drugs (heterocyclics); monoamine-oxadase inhibitors (MAOIs); and SSRIs (including related drugs).[13,14]

First-generation TCAs were first introduced in 1959 and have remained, to date, the most frequently used group of antidepressant drugs. Newer TCAs and TCA-related drugs have been developed subsequently; they tend to be generally less toxic and different in their side-effect profile in comparison with the older TCAs. TCAs act by blocking re-uptake of the neurotransmitters serotonin and noradrenalin.

The SSRIs, as a drug class, are far more targeted in their mechanism of action of blocking serotonin (5-HT). With reduced adverse-effect profiles, they are generally found to be less sedative and are viewed as 'safer' in terms of their impacts on patient life-style (for example, driving and the use of machinery). SSRIs cause minimal anticholinergic or psychomotor side-effects, lack cardiotoxicity and their use does not lead to the weight gain commonly associated with TCAs. The risk of toxicity in overdose is also greatly reduced.[15]

MAOIs tend to have a number of associated dietary and drug interaction restrictions. Their use can also influence the subsequent use of other antidepressant groups (TCAs and SSRIs). As such, there is a general recommendation that a 1-2 week antidepressant-free period is observed when switching either from, or to, a MAOI-based therapy. A sub-class of these drugs is based on reversible inhibition of monoamine oxidase (RIMA)s. These drugs carry slightly less risk of interaction, but diet and drug restrictions still apply. In relative terms, the MAOI and RIMA drugs represent a very limited share of the antidepressant

market and are commonly reserved for use in drug-resistant patients or those with specific phobic forms of depression; thus, they are not considered as a potential option for first-line treatment.

Table 2 Currently Prescribed Antidepressant Drugs in the UK

Class	Drug	Market Share % (Prescription Numbers)	
		Within Class	Overall
TCAs (older)	Amitriptyline	38.5%	18.7%
"	Imipramine	5.1%	2.5%
TCAs (newer)	Dothipen	42.2%	20.5%
"	Doxepin	2.1%	1.0%
"	Desipramine	0.1%	0.0%
"	Trimipramine	3.5%	1.7%
"	Amoxapine	0.1%	0.1%
"	Clomipramine	6.4%	3.1%
"	Nortriptyline	1.9%	0.9%
"	Protriptyline	0.1%	0.1%
"	Viloxazine	0.0%	0.0%
"	Mirtazapine	0.1%	0.0%
Total Market Share		**100%**	**49%**
TCA-related (heterocyclics)	Lofepramine	67.6%	6.9%
	Maprotiline	1.6%	0.2%
"	Mianserin	6.4%	0.7%
"	Trazodone	24.5%	2.5%
Total Market Share		**100%**	**8%**
MAOIs	Phenelzine	31.1%	0.3%
"	Isocarboxazid	5.7%	0.1%
"	Tranylcypromine	32.5%	0.3%
RIMA	Moclobemide	30.7%	0.3%
Total Market Share		**100%**	**1%**
SSRIs & Related	Fluoxetine	43.2%	23.3%
"	Fluvoxamine	0.9%	0.5%
"	Paroxetine	32.6%	17.6%
"	Sertraline	12.9%	6.9%
"	Citalopram	3.8%	2.0%
"	Nefrazodone	1.4%	0.8%
"	Venlafaxine	5.2%	2.8%
Total Market Share		**100%**	**43%**

Source : Mediplus data,1996

Therefore, the real choice faced by a GP wanting to use antidepressant drugs to treat a patient with an initial episode of depression, lies between an SSRI or a TCA (either conventional or a more recent related drug). Table 2 lists the current UK prescribed antidepressant drugs and indicates the market share of each drug, both within class and across all antidepressants, based on an analysis of 1997 prescribing data for England.

Despite the fact that most antidepressants have comparative clinical efficacy when prescribed optimally, a significant number of patients do drop-out of treatment and patients can experience relapse following initial treatment success.[16] The level of drop-outs and relapses can be related, at least in part, to the tolerability of the drug (in terms of its adverse event profile) and the overall clinical efficacy of the drug.

3.2 KEY THEMES OF ANTIDEPRESSANT PRESCRIBING

The Defeat Depression Campaign has greatly influenced the management of depression within the UK in recent years.[5] This campaign was organised by the Royal Colleges of General Practitioners and Psychiatrists and formulated an overall consensus of opinion as to the best practice in treating depressed patients. The emerging themes from the study are summarised below:

- optimum therapeutic dosage;
- adequate continuation of prescribing;
- compliance with drug therapy.

Although an accurate diagnostic process is the first step in providing good coverage of health services for depression, in itself it does not ensure effective treatment. The prescribed dosages of antidepressants are often much lower than those suggested in clinical guidelines, possibly due to the reluctance of GPs to expose patients to unpleasant side-effects or inadequate reviews of therapeutic levels.

As a rule, patients remain far more likely to receive an adequate therapeutic dose of an SSRI than a TCA.[17] Donoghue et al. analysed national prescribing data using both Prescription Pricing Authority (PPA) data, and a general practice data (DIN-LINK) covering the records of over 750,000 patients.[18,19] These studies both suggest that whilst over 95% of prescribing of SSRIs is achieved at therapeutic dosage levels, this is certainly not the case with the older TCAs (estimated to be prescribed at therapeutic dosages in only 10-15% of cases). The results were close between both databases, despite the fact that only the DIN-LINK data allowed prescribing volumes to be restricted to diagnostic codes for major depression.

As a result, TCAs are often given at such low levels that adverse events are unlikely to occur, but this also restricts the therapeutic impact of the treatment. There appeared to be only a small temporal change in the levels of sub-therapeutic prescribing of TCAs, when

these data were considered for both 1993 and 1995. Overall, the proportion of all prescriptions for antidepressants at sub-therapeutic dosages decreased from 60% to 47%, but this was almost entirely due to the increased market share of SSRIs (21% to 35%) over the same period of time. The issue of actual prescribing dosage being less than used in RCTs, and hence that adopted in guidelines, will have a significant impact on the actual clinical effectiveness and hence overall cost-effectiveness of treatment.

Adequate continuation of prescribing is also of major importance. To prevent relapse, a four to six month continuation or maintenance phase is recommended after initial recovery/response to episodic treatment.[5] It is even suggested that, for patients with a history of relapse, longer-term maintenance of up to two years should be considered. Unfortunately, an estimated 40% of patients only receive medication for up to a maximum of three months irrespective of the specific type of antidepressant medication. As a result, relapse remains a serious problem and around half of patients, whose symptoms have initially resolved successfully, experience relapse within a year of discontinuing the drug treatment.

Patient compliance (or adherence) is another influential aspect of prescribing that will impact on a treatment's overall effectiveness. Adherence to treatment is a complex issue and will be related not only to the adverse effects of a treatment (or tolerability), and the clinical efficacy of the treatment, but also to socio-demographic factors.

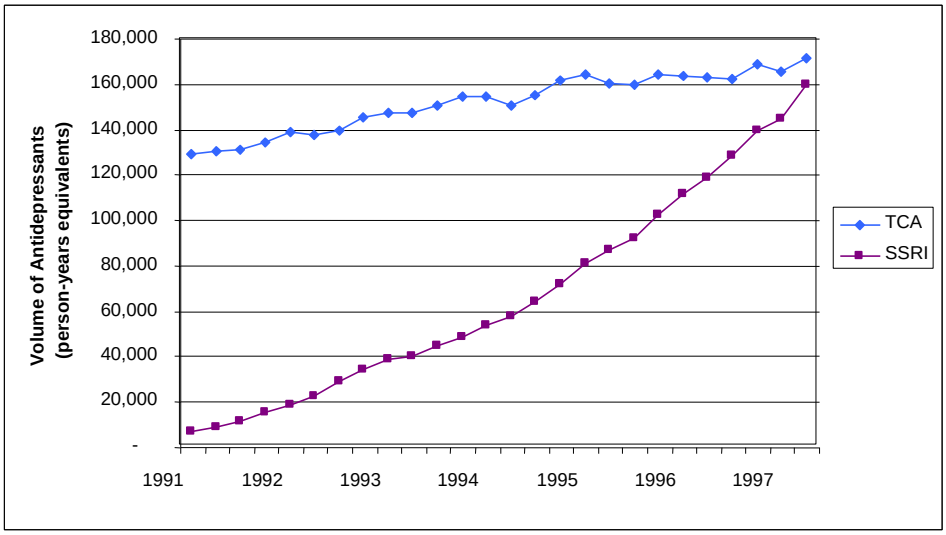
Therefore, a theoretically optimal antidepressant therapy is one which can be prescribed consistently at a therapeutic dosage, for adequate periods of time after resolution of the depressive episode, whilst maximising patient adherence through minimised adverse events.

3.3 PRESCRIBING PATTERNS FOR ANTIDEPRESSANTS

A recent study by Mason et al.[6] looked at the prescribing patterns of antidepressants in England over the period 1991 to 1997. The primary aim of this analysis was to attempt to assess the impact of previous antidepressant prescribing advice, as provided by the Effective Health Care Bulletin, which was distributed to all health authorities and GPs in England and Wales in 1993.[2] The total quantity and cost of primary care prescribing of antidepressants was derived from data obtained from the PPA, reflecting the total number of prescriptions reimbursed on a quarterly basis. Because prescriptions may not accurately describe the true volume of drugs used, in terms of patient treatment, the authors adjusted

the quantity data using the World Health Organisation's tables of defined daily doses. This provided the volume of antidepressants used, calculated in person year equivalents.

Figure 2 Volume of Antidepressants used in England (shown quarterly in person-year equivalents)



Source : Mason et al. (1998/99), Health Trends, Vol 30, No 4 ,1998/9.

In the first quarter of 1991, GPs were prescribing less than 7,000 person years of SSRI treatment. At the same time, the volume of prescribed TCAs was just under 129,000 person years. However, between 1991 and 1997 the volume of SSRIs prescribed increased substantially. Prescribing rates rapidly approached the higher volume of TCAs and soon after the end of the period of monitoring prescribing levels of SSRIs overtook those of TCAs (see Figure 2). In the first quarter of 1997, GPs were prescribing in total over 330,000 patient years of antidepressant treatment (equivalent to treating 2.4% of the population), with 47% of the total prescribing volume due to SSRIs.

A similar study of GPs' perceptions of antidepressants by Martin et al. examined the number of inceptions (beginning of a course of treatment) and discontinuations of antidepressants in general practice.[20] The study collected a total of 4,000 GP weeks of recording per year, between July 1990 and June 1995. Overall, antidepressant inceptions rose by 116% between 1990 and 1995. However, over the same period, SSRI inceptions increased by an exceptional 732%.

3.4 CURRENT SERVICE COSTS

Previous estimates of the direct UK health costs of treating depression range between £222 million and £420 million a year, and include both drug and non-drug costs.[1,21] In fact, such studies have typically suggested that the cost of antidepressants accounts for only 15-20% of such cost burden of illness estimates.

However, as previously highlighted, more recent analysis shows dramatic increases in the prescribing of SSRIs over recent years, with an almost equal volume of market share between SSRIs and TCAs now clearly evident.[6] Levels of SSRI prescribing are judged to account for over 85% of the total NHS antidepressant cost, with the annual NHS drug costs for all antidepressants, as of the last quarter of data, estimated at £214 million per year. Previous guidelines have estimated annual NHS antidepressant expenditure at £160 million, therefore, it is clear that the overall costs of antidepressant prescribing are increasing rapidly year on year.[7] To date, the NHS cost of SSRIs is 5-6-times that of conventional TCAs, and remains higher than that of newer-TCAs (see Table 3).

Table 3 Average per Patient Cost of 28 Days' Treatment at WHO Defined Daily Dose

Antidepressant Sub-Group	Cost (£), March 1996
Average older TCA	£3.93
Lofepramine	£7.73
Average SSRI	£21.74
SSRI-related	£35.47
RIMA	£19.01
Average Antidepressant	£11.31

Source : North of England Guidelines

4. METHODS

The aim of this evidence-based literature search strategy was to identify existing published reviews and meta-analyses which have considered a comparison of efficacy, clinical-effectiveness or cost-effectiveness between at least one SSRI antidepressant and a recognised TCA or TCA-related alternative antidepressant. Given the prior knowledge of the existence of a number of key relevant meta-analyses, the authors did not attempt to re-identify all original randomised double-blinded controlled clinical trials of SSRIs versus either placebo or TCA/related drugs, as they felt that the published data provided a sufficient evidence-based review already.

As such, the search strategy was focused on a review of the following mainstream health related electronic databases, covering the period January 1990 - June 1999: MEDLINE; EmBASE; PsychLit.

As well as focusing on these key reference databases, the authors also reference abstracts held on the Cochrane systematic review database and the NEEDS/DARE databases held at the NHS Centre for Reviews and Dissemination, again using the same general search terms.

In conducting the search, combinations of terms were used which related to:

- serotonin-uptake-inhibitors/all subheadings;
- antidepressive-agents, trycyclic/all subheadings;
- meta-analysis;
- review-literature/all subheadings.

In order to ensure coverage of pharmacoeconomic studies of antidepressants published since the publication of the identified economic reviews, a supplementary literature search was conducted based on the electronic databases MEDLINE, Psychlit and EmBASE covering the period January 1998 to March 1999. The authors looked specifically for studies related to the search term ‘costs-and-cost-analysis/all subheadings’, in combination with the earlier search terms. They also considered, as a secondary focus to their study, literature on antidepressant-related suicide, using MEDLINE and the terms ‘suicide/all subheadings’, again in combination with the earlier search terms.

5. RESULTS

5.1 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

Overall, eight individual meta-analyses were identified,[7,13,16,22,23,24,25,26] two guidance papers[6,7] and one systematic review,[27] all of which considered the relative clinical efficacy and effectiveness of SSRIs compared to TCAs.

Altogether, six key reviews of published cost-effectiveness/economic evaluation based studies were found.[28,29,30,31,32,33] In total, the search strategy identified 20 published studies which provided a formal evaluation of cost-effectiveness for at least one SSRI, against at least one reference TCA. Studies which were restricted to comparisons across different SSRI drugs were not included as these fell outside the report brief.

5.2 EVIDENCE OF EFFECTIVENESS

The relative clinical efficacy and clinical effectiveness of SSRI and TCA antidepressants have been explored through an extensive body of randomised controlled studies conducted world-wide. These studies have been undertaken in a range of different health care settings, but were most commonly conducted within a secondary care in-patient or out-patient context. This bias towards secondary care causes problems in generalising results and conclusions to a primary care setting, where the profile of patients may be very different, often with less severe illness, and where optimal treatment is more difficult to attain.

Another general criticism of the existing RCT evidence base is that actual patient definitions and/or inclusion criteria tend to vary greatly between trials. Also, actual patient numbers remain relatively small, meaning that results of statistical significance are very difficult to obtain from individual trials alone.

The existence of this large set of poorly powered randomised studies has lead to a number of published attempts to summarise and pool such data using formal techniques of meta-analysis. The following provides a brief overview of the scope of the meta-analyses evidence base, in particular with reference to clinical efficacy and effectiveness, and highlights the key messages and interpretations of outcomes drawn from these studies. Table 4 provides a summary of the meta-analyses.

Table 4 Published Meta-Analyses - Summary of Designs

Authors	RCTs	Drop-out	Efficacy	Setting	Antidepressant Reference Drugs Included	
					SSRIs	Comparator Drug (definitions as per Hotopf et al., 1997)
Song et al., 1993[16]	63	Overall	Y	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine	Old TCAs; amitriptyline, imipramine New TCAs; dothiepin, nortriptyline, desipramine, clomipramine, doxepin *Heterocyclic;* bupropion, maprotiline, mianserin, nomifensine, trazodone
Montgomery et al.,1994[22]	42	Side-effect / Failure	N	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine	Old TCAs amitriptyline, imipramine *New TCAs;* clomipramine, dothiepin, doxepin
Montgomery et al. 1995[26]	67	Side-effect / Failure	N	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine	Old TCAs; amitriptyline, imipramine *New TCAs;* clomipramine, dothiepin, doxepin, desipramine
Anderson et al. 1995[23]	62	Overall / Side-effect / Failure	N	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine / citalopram	Old TCAs; amitriptyline, imipramine *New TCAs;* dothiepin, desipramine, clomipramine, doxepin
Hotopf et al., 1997[13]	105	Overall	N	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine	*Old TCAs;* amitriptyline, imipramine *New TCAs;* dothiepin, nortriptyline, desipramine, clomipramine, doxepin *Heterocyclic;* bupropion, mianserin, trazodone, maprotiline, amineptine, nomifensine
CCOHTA 1997[34]	104	Overall/ Side-effect / Failure	Y	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine	*Old TCAs;* amitriptyline, imipramine *New TCAs;* dothiepin, doxepin, clomipramine, , maprotiline, oxaprotiline, desipramine, nortriptyline *Heterocyclic;* mianserin, trazodone, moclobmide, bupropion, amineptime, nomifensine, lofepramine
North of England Guidelines 1999[7]	98	Overall	Y	Secondary/ Primary care	fluoxetine / sertraline / paroxetine / fluvoxamine / citalopram + nefazodone / venafaxine (related drugs)	*Old TCAs;* amitriptyline, imipramine *New TCAs;* dothiepin, doxepin clomipramine, maprotiline, desipramine, nortriptyline *Heterocyclic;* mianserin, trazadone, moclobemide, bupropion, amineptine, lofepramine,
Anderson et al., 1998[25]	25	Overall / Side-effect / Failure	Y	In-patient	fluoxetine / paroxetine / fluvoxamine / citalopram	*Old TCAs;* amitriptyline, imipramine *New TCAs;* clomipramine, maprotiline, desipramine

Table 5 Published Meta-Analyses - Summary of Outcomes

Reference	Outcomes Measured (SSRIs vs TCAs)							
	Treatment Effect (Hamilton Rating Scale)		Withdrawals due to Side-effects (Odds Ratio)	Withdrawals due to Lack of Efficacy (Odds Ratio)	Overall Withdrawal Rates (Odds Ratio)	Overall Withdrawal Rates due to Drug Type (Odds Ratio)		
	SSRIs vs. Classical TCAs	SSRIs vs. Non-SSRI			* = relative risk	Old TCA	Newer TCA	Heterocyclics
Song et al., 1993[16]	0.004† (-0.096 to 0.105)		0.805 (0.648 to 1.001)	1.022 (0.801 to 1.034)	0.95 (0.816 to 1.107)			
Montgomery et al., 1994[22]			0.68 (0.57 to 0.80)	1.18 (0.89 to 1.57)				
Montgomery et al., 1995[26]			0.70 (0.61 to 0.79)	1.09 (0.91 to 1.32)				
Anderson et al., 1995[23]			0.68 (0.58 to 0.79)	1.13 (0.90 to 1.42)	0.87 (0.75 to 1.00)			
Hotopf et al., 1997[13]					0.86 (0.78 to 0.94)	0.82 (0.72 to 0.92)	0.89 (0.74 to 1.06)	1.02 (0.78 to 1.35)
CCOHTA 1997[34]	-0.06 (-0.20 to 0.09)	-0.01 (-0.08 to 0.06)						
North of England 1999[7]					0.87* (0.80 to 0.95)			
Anderson et al., 1998[25]			0.66* (0.50 to 0.87)	1.13* (0.84 to 1.51)	0.88* (0.75 to 1.03)			

†Pooled difference of mean Hamilton scores over 20 randomised trials which provided full standard deviation clinical efficacy data.

Table 6 Summary of Meta-Analyses

Reference	Outcomes Measured		
	Withdrawals due to Side Effects (% patients) SSRIs vs. TCAs	Withdrawals due to Lack of Efficacy (% patients) SSRIs vs. TCAs	Overall Withdrawal Rates (% patients) SSRIs vs. TCAs
Song et al., 1993[16]	15.4% vs 18.8%	7.0% vs 6.8%	32.3% vs 33.2%
Montgomery et al., 1994[22]	14.9% vs 19.0%	6.0% vs 5.1 %	-
Montgomery et al., 1995[26]	13.9% vs 18.8%	7.4% vs 6.8%	-
Anderson et al., 1995[23]	14.4% vs 18.8%	7.3% vs 6.8%	30.8% vs 33.4%
Hotopf et al., 1997[13]	-	-	28% vs 31% *
CCOHTA 1997[34]			
North of England 1999[7]	-	-	27.7% vs 32.7%
Anderson et al., 1998[25] **	9.1% vs 14.2%	11.6% vs 10.0%	25.5% vs 29.0%

*calculated as per Anderson et al. 1995 methodology

** in-patients only study

Tables 5 and 6 summarise the results from the identified meta-analyses. Outcomes are reported as the standardised difference for the Hamilton Depression Rating Scale (HDRS) for depression and as an odds ratio (OR) of the drop-out rate of patients in the SSRI group relative to that in the comparator drug group. Additionally, 95% confidence intervals are provided for both measures.

Clinical Efficacy

Only four of the meta-analyses considered explicitly clinical efficacy as a specific outcome measure, using standardised methods to combine studies with different outcome rating scales.[7,16,25,34] The majority of the randomised trials have used the HDRS as a tool for measuring the severity of a patient's episodic illness.

Song et al. considered treatment effect, using elements of the HDRS, from 63 randomised double-blinded studies which had compared an SSRI to a non-SSRI antidepressant.[16] Median trial duration was six weeks, with the longest trial period observed at twelve weeks

of active treatment. The overall conclusion was that there were no significant differences between the two drug groups in terms of their clinical efficacy.

The resulting Effective Health Care Bulletin (EHCB) was strongly informed by the findings of the Song et al. study, and was distributed to all GPs in England and Wales.[2] This document was intended to provide information on the prevalence and recognition of major depression and the effectiveness of potential treatment options available to primary care teams. The document attempted to use the evidence existing at the time to influence the future prescribing of antidepressants, recognising the potential cost implications of wide-spread SSRI usage. The efficacy conclusions mirrored those expressed by Song et al., in that SSRIs were generally considered to have equal clinical effect to TCAs, although the evidence base was recognised as being dominated by studies of small patient numbers with no distinct sub-group analysis to suggest target patient groups.

The North of England Evidence-based Guideline Development Project shared common authorship with the Song et al. study (and subsequent EHCB) and was centred on a revised meta-analysis of key RCTs considering relative efficacy, overall drop-out rates, effective doses, toxicity and safety between SSRIs (including lofepramine) and TCAs. The study considered data from 98 RCTs, published before February 1997. It found a slight clinical efficacy advantage in favour of TCAs, but deemed it to be of 'uncertain practical importance'. On average, the results suggested that in 51.4% of cases a TCA-treated patient would have a lower HDRS score than one on SSRIs and SSRI-related drugs. The authors effectively concluded that efficacy was the same between the two antidepressant drug classes.

The Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA) group was able to review 104 individual RCTs comparing SSRIs with TCAs, and concluded that there was no statistically significant differences in terms of clinical efficacy (measured as an overall efficacy effect) between any groups of antidepressants.[34] This meta-analysis included trials against placebo which did confirm conclusively the efficacy of SSRIs over a ‘no-treatment’ option.

Finally, Anderson et al. published a revised meta-analysis building upon a previous study but, importantly, restricted the analysis to in-patient studies only.[25] They included trials of the heterocyclic drug, maprotiline, previously excluded from their original study. Clinical efficacy data from 25 RCTs were considered. The analysis considered a general split of the TCA

group into dual-action (i.e. those inhibiting both 5HT and noradrenalin re-uptake) and single-action (noradrenalin re-uptake only). The study concluded that only dual-action TCAs were more efficacious than SSRIs. Overall, there was a statistically significant efficacy difference, in favour of TCAs, when all TCAs were grouped together. The authors commented on the low numbers in the trials (median <40 patients) and the likelihood that the patient group had more severe depression than commonly seen in general practice.

Treatment Tolerability

The majority of the meta-analysis studies focused on the relative patient acceptability of SSRIs, assessed through analyses of discontinuation, or drop-out rates, as a proxy for patient adherence / treatment tolerability.

Song et al. compared overall drop-out rates for SSRIs and TCAs finding no significant differences. They concluded that SSRIs, as a first-line therapy, would be expected to be less cost-effective than non-SSRI antidepressants.[16] Importantly, the study included data from 12 trials which used newer TCA-related drugs (or heterocyclics), including trazodone, maprotiline, mianserin, bupropion and nomifesine. This inclusion has been criticised by some for introducing potential bias against SSRIs, as newer TCA-related drugs tend to have a better adverse-event/tolerability profile than seen with older TCAs.

Montgomery et al. published two meta-analyses, in 1994 and 1995.[22,26] The second meta-analysis, extending the original time-period and scope of the first, included evidence from 67 RCTs, of which 10 had placebo arms. Analysis of drop-out rates were based on 3,474 SSRI-treated patients and 3,378 TCA-treated patients. However, the analysis was restricted to trial data which used older first-generation TCAs as comparator drugs. This decision was justified by the argument that the newer generation drugs (heterocyclics), although having better side-effect profiles, were not 'true' TCAs and that their inclusion into the study would introduce bias against SSRIs. The analysis of Song et al. was strongly criticised by Montgomery et al. for the inclusion of such heterocyclic comparator drugs.

The analyses reported a small, but significantly lower, discontinuation rate, due to adverse effects, for SSRIs than for TCAs (13.9% versus 18.7%; for SSRIs and TCAs respectively – from the second Montgomery study). The equivalent odds ratio was quoted as 0.7 (95% CI; 0.61 – 0.79). However, withdrawals due to lack of efficacy were comparable between the two groups (7.4% versus 6.8% for SSRIs and TCAs respectively), as were those related to

treatment failure/lack of efficacy. This study was criticised for not having analysed overall 'all-cause' drop-out rates.

Anderson et al. considered differences in drop-out rates due to side-effects and lack of efficacy as well as in overall 'all-cause' drop-out rates.[23] As with Montgomery et al., RCTs were restricted to those with comparator arms based on older first generation TCAs only, justified on the basis that such drugs were 'not true TCAs and that they did not represent a true alternative treatment option'. Thus, specific trials using heterocyclic TCA-related drugs, originally included in the analysis of Song et al., were excluded (14 in total).

The main findings were again similar to those of Montgomery et al., in that TCAs were clearly less well tolerated than SSRIs. The difference between TCAs and SSRIs was more noticeable for drop-out due to adverse effects (OR 0.68, 95% CI 0.58 to 0.79) than for overall drop-out (OR 0.87, 95% CI 0.75 to 1.00). However, the differences in overall drop-out rates were relatively small in absolute terms (30.8% vs 33.4% for SSRIs and TCAs); this equates to three avoided drop-outs for every 100 cases treated, or a number needed to treat (NNT) of around thirty patients. In contrast, there was no significant difference between withdrawals due to treatment failure, again confirming the original findings of Montgomery et al. The study has been criticised by some for its exclusion of heterocyclic comparison trials, and, in particular, for its statement that these drugs (in particular lofepramine and trazodone) are 'of minor importance clinically in terms of numbers of prescriptions' and are 'nearly as expensive as SSRIs'.

Hotopf et al. produced a further meta-analysis of 105 RCTs.[13] The study set out to investigate whether advantages in drop-out rates in favour of SSRIs remained present when SSRIs were compared to three sub-groups of TCAs, namely: older TCAs; newer TCAs; or heterocyclics (Table 2 has been grouped by this categorisation). The analysis concentrated on an assessment of the overall drop-out rate in the belief that this represented a 'more accurate reflection of treatment acceptance'.

Overall, there was a total discontinuation rate of 31%, with a relative risk (RR) for SSRIs of 0.9 (i.e. an absolute 3% reduction in drop-out rate). Of the three sub groups, it was only against the older TCAs that SSRIs showed any significant advantage in terms of overall drop-out rate (OR 0.82, 95% CI; 0.72–0.92). Due to the large number of such trials making comparisons with older TCAs, this advantage was also reflected in the overall drop-out rates when all studies were pooled (OR: 0.86, 95% CI; 0.78–0.94). Hotopf rightly commented on

the low number of studies comparing SSRIs with heterocyclic drugs. This led to very wide confidence intervals and suggested a need for further randomised trial evidence in respect of these drugs. In conclusion, the authors argued that it was only in relation to older TCAs that SSRIs could be considered to have improved significantly the drop-out rate and, hence, effectiveness. The most important point raised was that combining the results of all TCA groups together masks great differences between the individual drugs themselves.

The North of England Guidelines (1997) reported that overall drop-out rates were 4-5% lower (in absolute values) with SSRIs, than with TCAs (27.7% vs 32.7% respectively).[7] This equated to a relative risk of 0.87 (95% CI: 0.80-0.95). However, they rightly point out that this result, as with all the other meta-analyses, is measured over relatively short time spans, averaging six-weeks. The authors considered overall drop-out rates separately against the two most commonly referenced TCAs (i.e. amitriptyline and imipramine) - the relative risks for SSRIs were 0.87 (95% CI: 0.77-0.99) and 0.91 (95% CI: 0.77-0.99) respectively. An interesting observation was that differences in drop-out rates in favour of SSRIs increased over time, when results were considered in chronological order. This possibly reflects the wider inclusion of previously TCA-challenged patients, improvements in reporting or general differences in patient management. However, there is no solid evidence to draw any firmer conclusions from this observation. The authors also went on to analyse trials that compared TCAs to lofepramine (a newer TCA-related drug associated with a much lower rate of adverse events). There were no significant differences in either efficacy or drop-out rate from other antidepressants included in 17 RCTs.

The CCOHTA study measured differences in overall drop-out rates and again found no significant differences.[34] As with the meta-analysis of Song et al. the group included comparisons with both older and newer TCAs and related drugs including: amitriptyline, imipramine, clomipramine, mianserin, traxodone and moclobemide. Overall, 46 trials were identified which compared SSRIs with classical TCAs and 117 trials which compared SSRIs with other TCAs and related drugs.

In their consideration of drop-out data for diagnosed depressed in-patients, Anderson et al. found discontinuation due to adverse effect was significantly lower with SSRIs than TCAs (9.1% vs 14.2%); with an OR of 0.66 (95% CI: 0.5-0.87).[25] However, this significance was not repeated when the overall drop-out rate was considered, although there was a trend towards SSRIs (25.5% vs 29%).

Toxicity and Suicide

The published Office for National Statistics (ONS) mortality statistics for 1997 revealed 400 antidepressant-related deaths in England and Wales (220 male/180 female).[35] Of these 168 (42%) were clearly suicide attempts and 67 (17%) were the result of accidental poisonings. The remaining 41% had no known purpose designated. Overall, clear suicide/self-harm related deaths totalled 3,424 for the same period, implying that roughly 5% of suicides (168/3,424) are antidepressant related. Hotopf et al. previously identified a UK suicide rate of 8 per 10,000, of which 7% were associated with an overdose of antidepressants.[27]

In a recent review of antidepressant-related suicide, Jick et al. reviewed the medical records of a population of approximately four million across England and Wales over the period January 1988 to February 1993, through the general practice VAMP database (roughly representing a 7% national sample).[36] Using recorded diagnosis codes and prescribing data the authors analyse suicide rates, mode of suicide and person-years at risk for individual antidepressants. The results revealed that 143 people were identified as having died through suicide and 172,598 people received at least one antidepressant prescription. Overall, the rate of suicide was 8.5 per 10,000 years risk, with notably higher rates for males (relative risk 2.8). Dothiepin was used as the reference point (given its common use) and relative risks were calculated for individual antidepressants. Although overall suicide rates appeared higher for those taking newer medications, such as fluoxetine (relative risk 2.1) and mainserin (relative risk 1.8), rates of suicide through overdose were noticeably much higher for classical TCAs. One explanation for this is that, in the absence of randomisation, those having greater assessed risks of suicidal tendencies are likely to be prescribed less toxic drugs, therefore, biasing the results. Patients on less toxic drugs had significantly higher rates of previous antidepressant usage. Overall the study found that 14% of the recorded suicides were associated with antidepressant overdose.

This mirrored previous findings from a Swedish study of antidepressant-related suicide.[37] This study considered data for a much larger number of suicide cases (n=3400) and found that less than 16% had detectable levels of antidepressant present. Of these, only a third had levels interpreted as contributing to death through toxicity (approximately 5-6%).

Taken together, such findings appear to suggest that moving all antidepressant prescribing towards the less toxic TCAs and SSRIs could potentially avoid somewhere between 5-10% of all suicides. However, caution needs to be taken in drawing such conclusions, as the link

between depression and suicide remains a complex issue. It is clear from the Jick et al. Study[36] that suicidal patients prescribed non-toxic medication can, and do, seek alternative methods of suicide. However, it is also true that expanding the use of less-toxic drugs would potentially avoid accidental overdose in low suicide risk patients who are currently on TCA medication. Roughly 50% of such antidepressant-related deaths remain accidental.

The North of England guidelines reviewed data on poisonings and fatalities and levels of antidepressant prescribing for the UK, covering the period 1993-95.[7] These data suggested an overall mortality rate due to overdose on antidepressants of roughly 30 in 100,000 years risk. Restricting this analysis to TCAs (non-lofepramine), this rate rose to 170 in 100,000 years risk. Comparative rates for lofepramine (1.7 in 100,000) and SSRIs (1 in 100,000), confirm that the risk of suicide through antidepressant toxicity is much reduced in the less toxic drugs.

Freemantle et al. considered the relative risks of suicide through antidepressant overdose and concluded that, on a cost per life saved basis, the costs of moving towards the routine use of first-line low-toxic SSRI drugs were high (average £50,000 per life year saved) and that other approaches to suicide avoidance should be evaluated.[38] However, Freemantle assumed the same clinical effectiveness and tolerance for the two drug groups. If, due to sub-therapeutic dosage and poor compliance, TCAs are less effective, then the incremental cost per life year values for SSRIs is likely to be lower. There has also been criticism of the fact that the overall suicide rate was not used, again from the viewpoint that alternative methods can be sought out by determined suicidal patients.

As well as considering the potentially achievable benefits of life years saved, through wider usage of drugs with a low toxicity, and the associated costs, it is important also to consider the influence of this strategy on para-suicides, which can present a significant cost burden to the NHS.

The potential cost of health care support in cases of attempted suicide from antidepressant overdose has been considered by a US study by Revicki et al.[39] The study reviewed records on 136 patients who presented to emergency health services with overdoses of antidepressant (121 TCA related and 15 fluoxetine). Although 84% of TCA overdose patients had some degree of stay in intensive care, none of the fluoxetine patients required such care. TCA patients also had much longer mean lengths of stay (3.6 days versus 0.73 days respectively). Mean medical costs were significantly lower for the fluoxetine patients (US $1,269 versus US$5,764).

D'Mello et al.[40] also considered the same issue in a retrospective US review of 24 cases of antidepressant-related overdoses. This study also found significantly shorter lengths of stay for SSRI patients (3 days versus 7 days) and significantly lower health care costs (US $5,379 versus US$22,923), although the precise build-up of these costs was not stated.

5.2.1 Summary of Key Efficacy and Effectiveness Issues

The following summarises the main themes of the current evidence base related to SSRI use as a first-line treatment for major depression.

Drug Efficacy - The general consensus is that there appears to be no significant difference between any of the antidepressant groups in terms of efficacy. Irrespective of the viewpoint taken, none of the meta-analyses appears to reveal any meaningful difference in overall effect size, whether measured using the Clinical Global Impression score or HDRS. TCAs, if anything, appear to be slightly more efficacious than SSRIs, but the difference is argued as having little clinical importance and fails to reach a statistical significance. As expected, the only significant differences for SSRIs were when compared to placebo.

Drug Tolerability - There is clear variation in the reported drop-out rates for SSRIs and TCAs taken from individual trials. The conclusion from the published meta-analyses is that SSRIs and related drugs are generally better tolerated than the older TCAs. Treatment withdrawals due to side-effects are less common when using SSRIs than TCAs. The typical absolute difference in overall drop-out rate appears to be 4-5% in favour of SSRIs, with overall drop-out rate for TCA-related drugs at around 30-35% (or 14-19% if taken as drop-out related to adverse effects). What remains uncertain is the true difference between TCAs and SSRIs in terms of longer-term patient adherence.

Adverse Effects Profile - SSRIs are generally associated with more frequent cases of nausea, anorexia, diarrhoea, anxiety, agitation, insomnia, nervousness compared to TCAs, which, in turn, are associated with more frequent cases of dry mouth, constipation, blurred vision, dizziness and weight gain.[34] SSRIs have fewer sedative, cardiovascular, anticholinergic or psychomotor adverse effects and do not lead to weight gain, but do have more gastro-intestinal side-effects.[34] SSRIs have a much reduced adverse effect profile over traditional TCA drugs, as do the newer TCAs/heterocyclics.

Relapse and Recurrence Rates - It has been suggested that there are benefits of improved recurrence/relapse rates towards SSRIs.[41] However, there is currently little evidence of the relative risk of relapse between SSRIs and TCAs, and relapse is always possible for those patients suffering from depression. More longer-term studies are required.

Safety and Toxicity - SSRIs and lofepramine appear less toxic in overdose than older TCAs, as can be seen from the analysis of the North of England guidelines. Earlier studies suggest that overall suicide rates between patients do not vary according to antidepressant medication, implying that suicidal tendencies are more complex than simply having the means to hand. Another aspect of the risk of TCA-related overdose is that the presence of drugs in the home presents a means of suicide to people other than the patients themselves. Therefore, a wider assessment of family situations may be necessary in the process of considering appropriate medications for patients with depression. Further research is needed to judge the true suicide impacts of widespread SSRI usage in terms of avoided healthcare costs, life years saved and, importantly, the costs of attempted suicide.

General Points

These efficacy and effectiveness results come largely from well designed controlled trials conducted within an environment designed to optimise levels of therapeutic dosage and levels of patient adherence. Also, and very importantly, the studies are predominantly secondary care based. Therefore, it is likely that the disadvantages of TCAs, especially used in primary care, are to some extent masked. However, despite these potential biases, significant differences in rates of adverse effects have been found between SSRIs and TCAs.

An obvious general criticism of the randomised trial evidence base is that the low patient numbers mean that statistical significance is only observed for large differences in treatment effects, and that the very short time periods involved (maximum 12 weeks) are likely to misrepresent the situation further. Long-term rates of drop-out and other potential differences remain unknown.

Although the published meta-analyses have all adopted what appear to be sound and recognised statistical methodologies in the process of the pooling of data, there are differences in analytical approach which have led to different interpretations of the RCT

evidence base. In particular, there are two key areas upon which mental health researchers have differing views.

1) Choice of Comparator Drugs

Firstly, there is clear disagreement as to what justifies a sound and clinically relevant choice of comparator antidepressant drugs. Whilst some argue that the inclusion of newer heterocyclic drugs is not appropriate, and that comparisons should be made with the most commonly prescribed drugs (e.g. amitryptiline, imipramine, dothipen and clomipramine) rather than the 'best' alternative treatment,[22,23] others clearly dispute this point of view.[7,16,27] The counter-argument for including heterocyclic drugs is that they are now prescribed at significant volumes within the NHS. It is also stressed that the tolerance advantages of SSRIs may well hold true for newer TCAs, such as lofepramine, at much lower costs.

An analysis of Prescription Pricing Authority data for antidepressants tends to support this point of view, in that both trazodone and lofepramine are prescribed in significant volumes, indicating that heterocyclics are being widely used in clinical practice (see Table 2). It is also clear that the cost of these drugs is significantly lower than the branded versions of the SSRIs (although this may alter when patents for SSRIs begin to elapse).

The combined findings of all the meta-analyses suggest that it is inappropriate to consider all TCA and TCA-related drugs as having equivalent clinical effectiveness. Of all the published meta-analyses, Hotopf et al. 1997[13] and the CCOHTA report[34] provide what appears to be the clearest considerations of both comparative efficacy and drop-outs related to different sub-groups of antidepressants (including comparisons of SSRIs with older TCAs, newer TCAs and heterocyclics). Such sub-group analysis of drop-out rates supports the existence of at least three sub-classes of these TCA antidepressant drugs, when both tolerability profiles and treatment costs are taken into account (see Appendix).

2) Choice of Drop-out Measure

There is also wide debate over which precise measure of drop-out rate provides the most reliable and informative measure of tolerability or effectiveness. It is argued strongly that reasons for discontinuation are far more complex than a response to adverse effects alone, and that overall drop-out rates are far more important in considering treatment effectiveness. As such, the majority of meta-analysis studies have used on overall all-cause drop-out rate as a proxy for tolerability of treatment.[13]

Further debate on drop-out rate is related to the interpretation of study outcomes in the form of either relative, or absolute, difference. Some researchers stress the low absolute differences in overall drop-out rate, as suggested by the meta-analysis at around 4-5%.[42,43] This is argued to have little consequence when considering the cost-effectiveness of treatment as studies have shown that patients failing on TCAs can switch successfully to SSRIs with very similar long-term continuation rates, as with patients on first-line SSRI treatment.[44] However, an equally vocal group of researchers takes the opposite view on this issue, believing that even a small difference can be a clinical advantage to patients.[45]

5.3 ECONOMIC ANALYSIS

5.3.1 Background

With NHS costs of SSRIs currently standing at around 5-6 times those of typical TCAs, there is an obvious interest in not only the relative clinical effectiveness of SSRIs and TCAs, but also their overall economic effectiveness (typically judged in terms of a cost per patient treated, cost per recovery or cost per Quality Adjusted Life Year). The real issue is whether the current higher drug costs for SSRIs are worth paying given the potential benefits. These benefits are said to be a reduction in adverse effects/toxicity, improved compliance, and reduced risks of suicidal overdose. In direct response to these concerns there has been a number of studies, published over the last decade, aimed at evaluating the relative cost-effectiveness of different classes of antidepressant drugs.

The essential research questions remain:

1. Can the higher costs of SSRIs be offset by the potential reduction in other treatment-related costs?

2. Can SSRIs provide marginal patient benefits value in terms of improved quality of life or acceptable levels of cost per additional recovery?

The evaluation of the pharmacoeconomics of drug treatments for depression is fraught with difficulties and, at present, can at best provide only an indication as to the relative cost-effectiveness of interventions. Many of the key issues in addressing such research questions have been discussed previously and highlighted in the published literature. A

recent series of papers by Henry et al. discusses many of the problems faced in using formal RCT studies to evaluate both the clinical and cost-effectiveness of antidepressants:[46,47]

- Chronic recurrent nature of disease
- Lack of adequate clinical reality of RCTs
- Tendency for compliance to be optimal in RCT
- Exclusion of more complicated patients
- Inadequate consideration of long-term cost impacts
- Inadequate costing of adverse events
- Graduation of severity
- Optimal dosing of TCAs
- Limited to study setting

Many of these criticisms of using RCTs to evaluate economic effectiveness are general points and concerns, rather than being specific to the area of depression.

The purpose of the remainder of this section is to provide an overview of the quantity and quality of the existing health economic evidence for SSRIs and to reflect on the likely study design which would provide the standard of evidence that would illuminate the outstanding issues.

5.3.2 Methodology & Approach

One of the most thorough reviews of the current state of evidence-base regarding the cost-effectiveness of antidepressants comes from a publication by Woods & Baker, 1999.[31]

More recently, there have been five additional published reviews of the cost-effectiveness of SSRIs versus TCAs. Wilde et al. focused exclusively on the relative effectiveness of fluoxetine (Prozac™) against standard TCAs.[30] Further studies consider the case for SSRIs vs. TCAs within the context of a wider overview of pharmacoeconomics of antidepressant therapy.[28,29,32,33]

Given the considerable volume of previous work, and the apparently thorough methodologies adopted in their search strategies, the chapter has been based on a combined summary of the findings of all of these peer-reviewed studies.

5.3.3 Forms of Economic Assessments Identified

Full cost-benefit analyses, where both the costs of treatment and treatment benefits are expressed in purely monetary terms, using techniques such as willingness to pay, are notoriously difficult to formulate. This is reflected in the types of economic evaluations identified, which were predominantly cost-effectiveness studies.

More influential than the exact type of economic assessment is the analytical methodology adopted in evaluating the evidence of health benefits and costs. Overall, the approaches adopted by the identified studies included in this review can be categorised into three types.

- Prospective randomised studies;
- Retrospective reviews of case-data / administrative data-bases;
- Clinical decision modelling / simulation analysis.

The vast majority of studies (13 out of 20) identified used a modelling approach, with a number of other studies (6 out of 20) retrospectively reviewing the outcomes and treatment costs of patients using historical database records (see Tables 7 and 8). Importantly, only one randomised study was identified which provided evidence on the cost-effectiveness of SSRIs versus TCAs.

5.3.4 Key Prospective Trial Design Studies

Simon et al. published the first, and to-date only, randomised study of antidepressants, comparing the first-line use of SSRIs (fluoxetine) against two control arms both based on TCAs (imipramine and desipramine).[44] This study was based within a US cohort including major depression patients (n=536) who were treated within the context of a primary care system. The costing element of the study was based on a health care provider prospective and as such targeted direct costs only, ignoring potential indirect costs such as family care, employment costs and patient costs.

The six-month duration study attempted to provide a more real-world clinical setting than may have been possible with the strict constraints of a formal RCT. As such, the study was blinded only to clinical assessors and not patients or primary clinicians. Patient recruitment was also designed to ensure a more representative sample, although suicidal tendencies and recent use of antidepressants were employed as exclusion criteria. Switching between

Table 7 Retrospective Cost-effectiveness Studies

Reference / Setting / Size / Dates	SSRI Therapy	TCA Reference	Study Design and Data Sources	Principal Outcomes	Results
Sclar et al. (1994)[48] US N=701 1/1/89-10/31/93	Fluoxetine	Amitriptyline Nortriptyline Desipramine	HMO patients staying on initial antidepressant for 12 month period. Treatment switching excluded.	Depression related 12 month healthcare expenditure	Fluoxetine < TCA
Skaer et al. (1995)[49] US N=823 1/1/89-6/30/94	Sertraline	Amitriptyline Nortriptyline Desipramine	HMO single episode depressed patients staying on initial antidepressant for 12 month period Treatment switching excluded.	As for Sclar et al., 1994	Sertraline < TCA
Forder et al. (1996)[50] UK N=398 dates not stated	Sertraline	All TCAs	General practice patients selected from clinical trial & matched control individuals Intention-to-treat analysis.	Direct and partial indirect 12 month cost per successfully treated patient and per patient. (Included accommodation and living costs).	Sertraline < TCA
Smith & Sherrill. (1996)[51] US N=152 1994	SSRIs	TCAs	HMO, ICD-9 major depression, received antidepressant > 3 month, excluded if switched drug.	Depression related 12 month healthcare expenditure.	SSRIs = TCAs
Simon et al. (1998)[42] US N=5,169 1/1/92-30/6/94	Fluoxetine	Desipramine Imipramine	HMO based. Depressed patients initially prescribed antidepressant with a minimum of 6 months follow-up data available Intention-to-treat analysis.	Depression related 6 month healthcare expenditures.	SSRI =TCA
Sclar et al. (1998)[14] US 1/7/88-31/12/91	Fluoxetine	Amitriptyline Nortriptyline	HMO, ICD-9 major depression .	Depression related healthcare expenditures.	Fluoxetine <= TCA

< indicates a lower cost-effectiveness ratio (CER), and hence better cost-effectiveness.

= indicates equivalent cost-effectiveness.

Table 8 Simulation-based Cost-effectiveness Studies

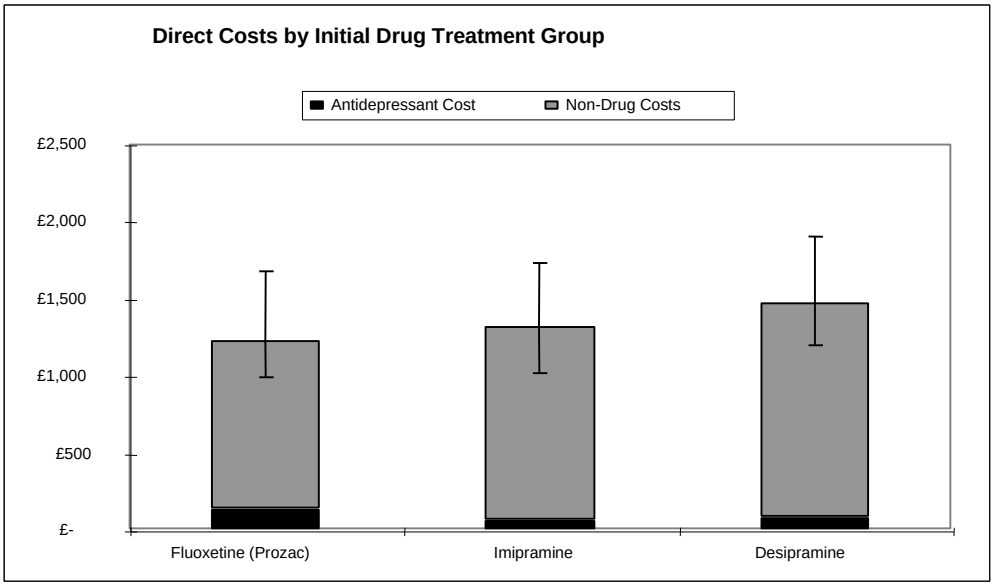
Author / Year	Setting	SSRI Therapy	TCA Reference	Method	Form	Time Horizon	Source Data	Outcome	Results	Conclusion
Jonsson/ Bebbington UK 1994[21]	Primary care	Paroxetine	Imipramine	Decision Tree	CEA	12 mths	Clinical trial data (6wk) 717 pts Expert panel/ focus group Meta analysis Cost database Direct costs (UK)	Cost per successful treatment Cost per treated patient	No difference in cost Lower cost per successful patient for Paroxetine (£824 vs £1,024)	SSRI < TCA
Stewart UK 1994[52]	Primary care	Paroxetine Sertraline	Amitriptyline Imipramine	Decision Tree	CEA	12 mths	RCTs Direct costs (UK)	Cost per successful treatment	£491.25 Imipramine(I) £539.00 Amitriptyline(a) £581.46 Sertraline(s) £547.65 Paroxetine(p)	i < a < p < s
McFarland 1994[53]	Primary care	Paroxetine	Imipramine	Decision Tree	CEA	12 mths	Primary care data base	Cost per patient	No differences	SSRI <= TCA
Hatziandrou et al., 1994[54]	Young female	Sertraline	Dothiepin	Markov State Model	CUA	24 mths	Life-time costs 2 cohorts of 35 year old women Expert panel	Cost per QALY	Cost : £3407 vs £1648 QALY : 14.9 vs 14.1 Marginal cost/QALY = £2172	Sertraline more costly, but looks cost effective
Lapierre et al. 1995[55]	Primary care	Paroxetine	Imipramine	Decision Tree	CEA	12 mths	Clinical trial data (6wk) 717 pts Expert panel/ focus group	Direct cost per patient	Lower for Paroxetine $Can1679 Paroxetine $Can1793 Imipramine	SSRI < TCA
Einarson et al., 1995 [56]	A: In-patient B: Out-patient	Ventafaxine (v) SSRIs (s)	TCAs (t) HCAs (h)	Clinical Decision Analysis	CEA	6 mths	Meta analysis Expert panel Direct costs (Can)	Direct cost per symptom-free day	HCAs most cost effective in out-patients Ventafaxine most cost-effective in out-patients	A: v < h < t < s B: h < v < s < t
Bentkover, 1995[57]	Primary care / secondary care	Paroxetine	Imipramine	Decision Tree	CEA	12 mths	Clinical trial data (6wk) 717 pts Expert panel/ focus group Cost database	Direct cost per patient	Lower for Paroxetine $US2348 Paroxetine $US2448 Imipramine	SSRI < TCA
Hylan et al. 1996[58]	Primary care	Fluoxetine	Imipramine	Decision Tree	CEA	6 mths		Direct + indirect cost per successful treatment		F < I
Nuijten et al., 1995 [59]	Unspecified	Citalopram	Doxepin Amitriptyline Trimipramine	Markov state	CEA	12 mths	Literature review US guidelines Expert opinion Direct costs & working dats (Germany)	Direct cost per patient. Time free of depression	Lower direct cost for Citalopram (DM 3764 vs DM 4577) More time in illness free state (8.2 mths vs 7.8 mths)	C < TCA

Author / Year	Setting	SSRI Therapy	TCA Reference	Method	Form	Time Horizon	Source Data	Outcome	Results	Conclusion
Revicki et al. 1995[60]	Young female	Nefrazodone Fluoxetine	Imipramine	Clinical Decision Analysis	CUA	Life-time with 9 mths	Life-time costs 3 cohorts of 30 year old women expert panel	Costs per patient Cost per QALY	Lower cost per patient: $Can 50664 Nefrazodone $Can 52111 Imipramine $Can 50678 Fluoxetine Higher QALY figures: 13.90 QALY Nefrazodone 13.18 QALY Imipramine 13.79 QALY Fluoxetine $Can 2009 Cost per QALY for Nefrazodone over TCA $Can 2349 Cost per QALY for Fluoxetine over TCA	N < f < i
Montgomery et al. 1996[61]	Primary care	Nefazodone	Imipramine	Clinical Decision Analysis	CEA	12 mths	Used a single RCT Direct Costs (UK)	Cost per successful treatment	Lower cost for nefazodone £242 nefazodone £323 imipramine	N < I
Einarson et al. 1997[62]	Out-patient	Ventafaxine (SSRIs) Paroxetine Sertraline Fluoxetine Sertraline	Amitriptyline Imipramine Nortriptyline Desipramine	Decision Tree	CEA	6 mths	Meta analysis Expert panel Direct costs (Can)	Cost per patient Cost per success	Ventafaxine and SSRIs have higher costs per patient and success than TCAs Cost per patient : £4770 / £5072 / £6199 respectively Cost per success : £6044 / £6633 / £9035 respectively	V<SSRI<TCA
Revicki et al. 1997[63]	Young female	Nefrazodone Fluoxetine	Imipramine Imipramine step (i.e. followed by nefrazodone on failure)	Markov State Model	CUA	Life-time	Life-time costs 4 cohorts of 30 year old women expert panel	Costs per patient Cost per QALY	Nefrazodone has highest life-time cost but more QALYs $US 16,669 Nefrazodone $US 15,348 Imipramine $US 16,061 Imipramine step $US 16,998 Fluoxetine 14.58 QALY Nefrazodone 14.32 QALY Imipramine 14.40 QALY Imipramine step 14.58 QALY Fluoxetine $US 2555 Cost per QALY for nefrazodone over Imipramine step	I<is<n<f

treatments was also freely allowed, with patients shown to be unsuited to TCAs (through a trial-of-treatment) being moved on to the SSRI (fluoxetine) arm. The overall design was intended to allow existing clinical practice to be reflected in order to assess effectiveness rather than efficacy.

Although the mean cost of treatment was much higher (up to twice) in the SSRI (fluoxetine) arm, the overall treatment costs for the six-months of the study were not significantly different. The only significant cost differences between the treatment groups were the actual drug costs themselves (see Figure 3). The costs for all treatment groups were dominated by out-patient costs, which included not only drug costs, but also primary care visits, mental health team visits and other pharmacy costs. Figure 3 shows the treatment costs for each of the three treatment arms, with the cost of antidepressants shown separately. The drug costs included costs after switching. The 95% confidence intervals have also been included, as published.

Figure 3 Treatment Costs

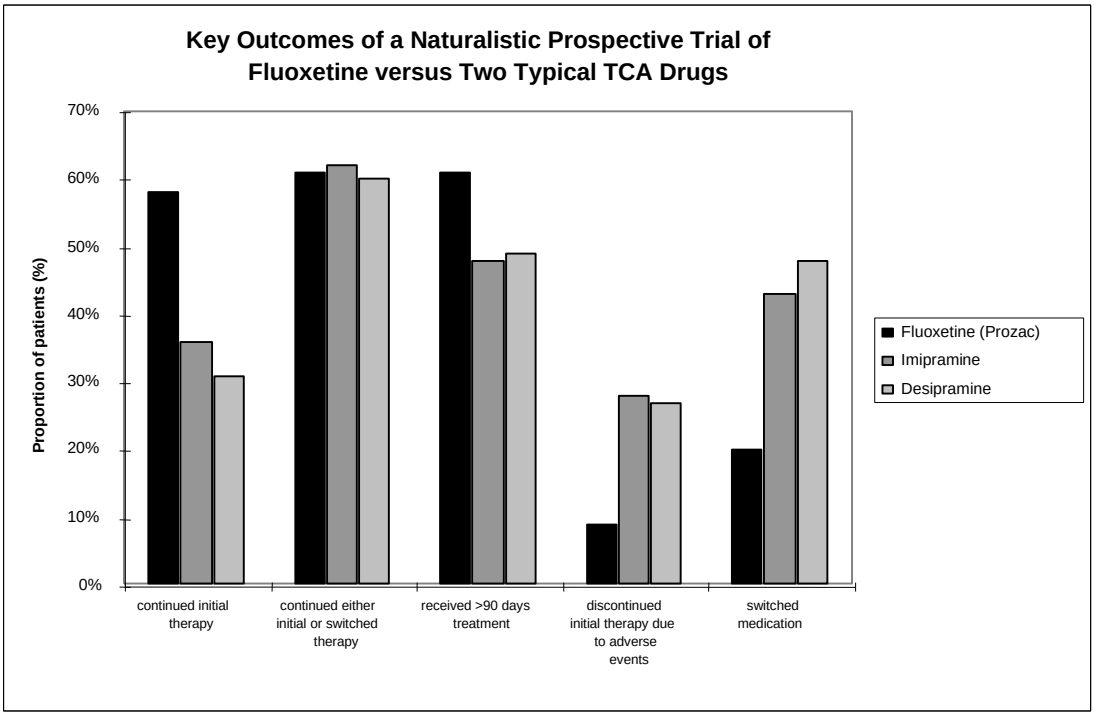


Discontinuation rates for the SSRI (fluoxetine) arm were found to be 10-20% less than the TCA arms (see Figure 4). However the data also show that patients who discontinued TCAs and switched to SSRIs had very similar continuation rates, suggesting that problems with patient adherence were short-lived, with no longer-term impact on subsequent switches in therapy. Interestingly, 51% of all treatment switches occurred within one month of initial treatment, indicating a relatively quick evaluation of treatment effectiveness. However, this may be due to the very close follow-up of patients. Overall, the SSRI arm experienced fewer

adverse reactions, in particular dizziness, constipation and dry mouth. The study found no significant difference between any of the three treatment groups in terms of quality of life or symptom-scores at the study end-point.

Overall, the authors concluded that from a cost-effectiveness point of view there was no clear evidence of improved effectiveness for the first-line use of SSRIs in a naturalistic setting and that, in the light of this, the option should be left open to individual clinicians. The main caveat of the study must be the relatively short time period (6-months) which would have excluded the possibility of differences in long-term costs. Also, there is likely to remain a tendency for patients on TCAs to have improved adherence, optimal dosage and to have early switches in the treatment offered.

Figure 4 Trial Outcomes



5.3.5 Key Retrospective Studies

The review identified six key retrospective studies which have assessed the cost-effectiveness of SSRIs as a first-line treatment in comparison with a TCA reference treatment.[14,42,48-51] The analysis of retrospective case-series data can provide a useful method of ensuring a more clinically realistic view of the effectiveness and cost-effectiveness of the treatment options. The advantages of such studies are that they are

quick, relatively inexpensive to perform and allow the realities of clinical practice to be included implicitly in their outcomes.

A series of retrospective studies, by Sclar et al. and Skaer et al.[14,48,49] have reviewed the records of depressed patients using computer archives. These studies included patients who had received treatment for 6-12 month periods on either TCA or SSRI antidepressants. They excluded patients who switched treatment and, hence, were likely to have biased the cost data in favour of TCAs. The first of these studies compared TCAs with the SSRI fluoxetine. A second study from the same group effectively repeated this analysis using the SSRI setraline. Irrespective of the SSRI group used, these studies have consistently showed that, despite higher drug acquisition costs, SSRIs had overall health costs no greater than those of TCAs, when considered over a reasonable length of time approaching 12 months. Overall, these studies have received criticism levelled at the relatively young patient group, the lack of an intention to treat analysis (excluded TCA switching patients) and the lack of control for baseline depression severity.[64]

Forder et al. provided the only UK perspective, retrospectively comparing patient costs and outcomes after initial treatment based on sertraline against a similar patient group under TCA alternatives.[50] The most common TCA was dothiepin (110 of 196 patients). However, the group contained a profile of all TCA alternatives including lofepramine (19 of 196 patients). Following up patient records over a 12 month period after the commencement of initial treatment, there was no observed switching to SSRIs in the TCA group (although switching was observed within the TCA group in 8% of cases). However, 30 patients (16%) did switch from SSRI to TCAs. One of the key concerns with this study would be the much shorter average treatment time for sertraline (168 days) compared with TCAs (278 days), thus reducing SSRI treatment costs disproportionately. This difference may reflect a faster response of patients to the drug and be a justified completion of therapy. However, the paper suggests that SSRI patients were more likely to remain depressed following a cessation of treatment, suggesting that initial treatment should have lasted longer. The study found around 25% of TCA patients were receiving sub-therapeutic dosages that could not be explained by a justified titration phase at the end of treatment, or on switching therapy. This confirmed the findings of the prescription analysis by Donoghue and Tylee regarding TCA dosages in primary care settings.[18] Overall, the study suggested that 12-month treatment costs for patients treated initially with sertraline are significantly lower than those of TCA treated patients. However, the inclusion of accommodation and personal consumption costs clearly inflate this difference. When restricted to 12-month direct health

costs only, the costs per 'very much improved' patient were £1,882 for SSRIs and £2,490 for TCAs respectively.

The most recent of the studies identified was that of Simon et al.[41] This study compared initial treatment with fluoxetine with TCAs (desipramine and imipramine). Again the patient group had a relatively low median age (40-50 years). Patients on the SSRI were observed to be older and to have more severe chronic illness scores and higher pre-treatment costs. The analysis of costs was conducted on an intention to treat basis (including treatment switching) and found that, in the six month period following the initial prescription, health service costs were higher for fluoxetine (US$2,401) than either of the two TCAs (US$2,003 and US$1,929 respectively). Excluding the actual drug costs of antidepressants, the cost figures were (US$2,179, US$1,907 and US$1,861 respectively). However, when these 'non-antidepressant' costs were subjected to an adjustment for age/sex/illness severity this relationship changed with fluoxetine having a numerically lower, but effectively equivalent, cost for the six-month period (US$1,963, US$2,069 and US$2,015 respectively). Over the period average antidepressant drug costs were US$222 for fluoxetine patients compared with US$60-100 for TCA treated patients.

5.3.6 Key Modelling Studies

The most commonly adopted methodology was the use of decision analysis and simulation modelling techniques to consider alternative treatment options (SSRIs versus TCAs) over medium to long-term periods of time (six months plus).

As with all such health economic modelling approaches there are, by definition, assumptions taken in respect of the underlying logical structure, treatment pathways adopted, and the parameters used to populate the model. In most studies the majority of the model data (related to treatment success, drop-out rates and resource utilisation) have been taken from the key published meta-analyses (as previously detailed in chapter 2), specific RCTs and the views of clinical expert panels.

To date, one of the most quoted modelling studies is that of Jonsson and Bebbington (the JB Study) which compared paroxetine (SSRI) with imipramine (TCA).[21] Overall, the study found a cost-effectiveness advantage in favour of the SSRI as a first–line treatment, when considering the cost per successfully treated patient. However, this study has received criticism in terms of both the length of treatment adopted (12 weeks) and the assumed lack

of efficacy of subsequent second-line treatment switches. The relatively high drop-out rates in all groups, taken directly from a single RCT, were also criticised as being far greater than those suggested by other studies, although sensitivity analysis still maintained a cost-effective argument in favour of SSRIs even at levels of drop-out rate of around 4%.[64]

In a similar modelling exercise, Bentkover et al. used a simulation decision tree model to compare the treatment costs of patients with major depression using paroxetine or imipramine.[57] The study derived much of its data on treatment efficacy and drop-out rates from the same single RCT of 717 patients, over a six week active treatment phase.[64] The treatments for the patients who remained in the Dunbar trial were shown to have equivalent efficacy results. Dunbar et al.[64] reported an overall drop-out rate at 42.5% for SSRIs versus 53.5% for TCAs and drop-out rates due to adverse effects of 23% and 36% respectively. Importantly, these rates are far in excess of those suggested by any of the published meta-analysis. The study used identical 10% rates of relapse during maintenance treatment, despite claiming some evidence of differences in favour of SSRIs. Rates of relapse following treatment completion were taken at 25%. Baseline results suggest virtually identical overall treatment costs per patient at US$2,348 (SSRIs) and US$2,448 (TCAs). The key differences in resource usage were those noted in costs of hospitalisations. No statement on cost-effectiveness was made explicitly. This trial had very similar outcomes and design to an earlier trial by Lapierre et al.[55] (having Bentkover as a co-author).

A later revision of the JB Study by Woods et al. used the same basic model structure but, after revising assumptions on drop-out rates and treatment efficacy, found that TCAs became more favourable in terms of their cost-effectiveness ratios.[65] This study assumed that initial treatment lasted for 20 weeks, with treatment after relapse assumed to run over a 52 week period. One general criticism of this study, and of most other modelling approaches, comes from the fact that short-term clinical trial data were used to underpin the model and were extrapolated out to suggest 12-month outcomes. This has potential flaws as drop-out rates can vary over time and will not necessarily remain constant. Assumed relative differences in drop-out rates of 20% in favour of SSRIs were much higher than those suggested in other studies.

McFarland et al. considered the same drug comparison (paroxetine vs imipramine) over a one year period using a decision tree model over a 12 month period.[53] The study took the prospective of a US primary care Health Maintenance Organisation (HMO). The study found little difference in total treatment costs per patient.

Stewart et al. considered the treatment of depression within a primary care context using a typical decision-tree model structure. The model considered treatment with TCAs (imipramine, amitriptyline) and SSRIs (sertraline, paroxetine).[52] A successfully treated patient was given an initial 12 weeks treatment with 26 weeks follow-on maintenance treatment. The maximum treatment period was one year, representing patients who switched therapy up to a maximum of three times due to either treatment failure, relapse or adverse effect related drop-out. Using drop-out rates for adverse effects calculated from placebo-controlled studies only (19% SSRI, 27% TCA from Montgomery et al.)[3] and efficacy rates from individual drug trials (55% amitriptyline, 65.1% imipramine, 70% sertraline, 70.8% paroxetine), the study suggested costs per successfully treated patient of £491.25 (imipramine), £539.00 (amitriptyline), £581.46 (paroxetine) and £547.65 (sertraline). From these data the authors concluded that there was no indication of a clear cost-advantage towards SSRIs over TCAs.

However, as part of the sensitivity analysis, the authors also considered total drop-out rates from Song et al., giving alternative cost per success results (£575.91, £632.02, £660.36, £584.02 respectively).[16] This is an important comparison as Montgomery et al. is recognised as being more favourable towards SSRIs, due to its selection of reference TCAs.[3] Despite this potential bias back towards TCAs, the sensitivity results seem to suggest an almost equal cost per successfully treated patient between TCAs and SSRIs. The study can be criticised for a lack of robustness due to its use of efficacy data taken from an individual trial, rather than from a meta-analysis.

Unfortunately, it also appears that the actual rates used (32.3% SSRI and 33.2% TCA) in this sensitivity analysis related to total drop-out (including efficacy). Rates excluding elements related to efficacy should have been 25.3% and 26.4% respectively. This difference will have led to, at least some of, the higher cost data observed.

Stewart et al. revisited their original study, factoring in both cost inflation (observed as positive in non-drug resource areas but negative for antidepressants) and potential sub-therapeutic dosaging.[66] Cost inflation alone reduced the cost gap further, although SSRIs still remained the more expensive treatment option (£796.97 versus £776.91). However, these costs were much higher than those in the previous study. The cost per extra recovery is quoted at £2,518 (compared with £4,417 from the previous paper). Interestingly, the revised analysis also considered efficacy data taken directly from the meta-analyses of

Song et al.[16] and Montgomery et al.[61] Both suggest a much smaller difference in efficacy drop-outs. The effect of this was to increase dramatically the cost per extra recovery. Factoring in adjustments for proportions of patients treated at sub-therapeutic dosaging, and using a placebo response (69% efficacy rate from Montgomery et al.[22]) all cost differences reduced to minimal levels.[18]

Montgomery et al. conducted an economic analysis of nefrazodone against imipramine using the original model structure as presented by Jonsson and Bebbington,[21] up-dating both costs and treatment patterns. Rates of adverse effects, drop-out and relapse were taken from a randomised trial of nefrazodone (BMS). The study considered 12-month treatment costs following an initial treatment period of 12 weeks, and allowed the chance of further relapse and re-treatment. The study found lower costs per treated patient in favour of nefrazodone (£218 versus £242). This advantage was also reflected in measures of cost per successfully treated patient (£242 versus £323). Treatment failure was estimated to cost £669 per patient and accounted for between 31-56% of total treatment costs. Data on drop-out rates were suggested at 9% and 20% respectively. Drop-out due to relapse (or failure rate) was assumed at 9% for each treatment (the JB Model had previously assumed 25%). Overall treatment success rates can be inferred from the study at rates of 82.8% and 72.8% respectively (or overall drop-out at 17.2% and 27.2 % respectively).

Einarson et al. report on a cost-effectiveness analysis conducted directly alongside the findings of the CCOHTA meta-analysis (previously detailed).[56] This study considered a range of SSRIs and TCAs and resulted in a decision tree model representing treatment over six months. The results confirmed that SSRIs had a total treatment cost advantage over TCAs (Can$5,072 versus Can$6,199) and that venlafaxine (Can$4,770) had cost advantages over both.

Four of the studies have actually used a cost-utility approach attempting to place values on health states in the form of quality adjusted life years (QALY)s.

Hatziandrou et al. used a Markov model which simulated the movement of patients between levels of illness severity over a one year time span.[54] The transition probabilities for the model were derived from an expert panel/focus group approach adopting modified Delphi techniques. Using a standard gamble approach they placed utility values on heath states which ranged from 0.785 to 0.95. Overall, the average life-time costs of treatment were £3,407 for SSRI treatment compared with £1,648 for episodic treatment with the dothiepin

(TCA). The corresponding QALY data were 14.9 and 14.1 respectively, representing a marginal utility gain of 0.8 QALYs. The study resulted in a cost per QALY of £2,172 for sertraline over dothiepin.

Revicki et al. conducted a cost-utility analysis (CUA) of nefazodone, fluoxetine and imipramine.[60] Using a combined decision tree and Markov model approach the study considered the life-time direct treatment costs of all three patient groups.[60,67] Using similar techniques to Hatziandrou et al., periods spent in different health states were valued on a utility scale of 0 to 1, by direct cross-sectional interviewing of 70 patients. Costs and benefits were both discounted at 5% per annum. Patients (assumed female aged 30 years) were treated for a nine month period for a maximum of three episodes before long-term treatment was provided. From published literature, the model estimated rates of new episodes following recovery from the initial episode, predicting that 50% of patients have a new episode after one year. These rates were adapted to reflect low and high rates of recurrence for differing compliance groups (fully, partial and non-compliant). Around 10% of all patients were assumed to remain treatment-resistant irrespective of initial antidepressant treatment. Overall, the life-time costs (1993 Can$) were estimated at Can$50,664 nefazodone, Can$50,678 fluoxetine and Can$52,111 imipramine. There were also utility advantages in favour of both nefazodone and fluoxetine over imipramine of 13.90 QALYs, 13.79 QALYs and 13.18 QALYs respectively.

Revicki et al. repeated a similar later analysis of nefazodone including reference to a policy of first-line TCA, with a later switch to SSRI fluoxetine on treatment failure.[63] Again, nefazodone was shown not to be cost saving, but it was incrementally more cost effective when considered as a cost per QALY (US$2,555 per QALY gain).

5.3.7 Conclusions

The relative economic arguments of the first-line use of newer SSRI drugs has been studied previously by a number of recognised lead authors and has generated much debate. Whilst earlier economic studies tended to support an economic advantage of SSRIs, a number of later studies have challenged this view. Many of the contentious points relate to the interpretation of data drawn from previous meta-analyses and expert-panels. It is clear that models which attempt to include the effects of a sub-therapeutic dose (still commonly seen with TCAs) produce much lower costs per successfully treated patient.

As yet, there appears to be no clear economic evidence of a difference between SSRIs and TCAs which can support fully the use of SSRIs as the first-line treatment for all patients.

6. OTHER ISSUES

6.1 PATENT ISSUES

Whilst SSRIs exist as purely branded products, the price differential between classical TCAs and SSRIs, typically a £20-25 difference in monthly prescribing costs, will continue to play a major role in influencing treatment choice.

However, it is important to acknowledge that the first of the SSRIs fluoxetine (Prozac™) came off patent in early 2000, at about the same time as the publication of this report. This will obviously lead to the creation of generic versions of the drug. The precise number of such generic drugs, and speed of up-take, will depend on the interest of the relevant generic drug companies, however, it would be fair to expect such interest to be high in this case. The cost of generic fluoxetine is certain to be a lot less than the current list price of Prozac (roughly £19.38 per 28 day treatment - eBNF).[68] The manufacturers of Prozac have indicated that they will still be actively marketing the drug as a branded product, along with additional services. What also remains unclear is exactly how this process will affect the remaining branded SSRIs, which will only begin to come off patent a number of years later.

6.2 ONGOING RESEARCH

Meta-analysis/ Systematic Review

As part of the Cochrane systematic reviews database there is a published protocol for an ongoing meta-analysis which is expected to begin to report in early 2000.[69] This provides an extension of earlier published reviews.[13,61] Early feedback from the later of these reviews indicates very similar findings to the original report. (1999, Hotopf M. personal communication).

Randomised Studies

There is an ongoing randomised controlled study designed specifically to consider the cost-effectiveness of SSRIs related to TCAs as a first-line treatment for major depression. This study is being conducted through the University of Southampton, Mental Health Group (Thompson C. personal communication) and is a response to an HTA primary research call.

This HTA study, called the AHEAD study (Assessing the Health Economics of Antidepressants), is a pragmatic RCT in representative general practice patients of three types of antidepressant treatment:

1. SSRIs: fluoxetine, paroxetine or sertraline (GP decides which is most appropriate for the patient);
2. Tricyclics: imipramine, amitriptyline or dothiepin (GP decides again);
3. Lofepramine (No choices).

Endpoints are to be assessed over one year, with monthly assessments using: self-ratings of depression; EuroQuoL and SF 36; use of services questionnaire. Costs will be calculated within an NHS frame, but data will also be collected on employment, and accidents (non-costed). A fourth arm to the study of patients allows for a refusal of randomisation, but accepted follow-up. This will be used to check on the representativeness of the outcome in the randomised group.

7. CONCLUSIONS

The main issue addressed by this review is the comparative effectiveness of SSRIs with other antidepressants, which principally means the older and newer TCAs.

In clinical terms, the SSRIs appear to be as effective in improving major depression as the TCAs. They do not demand the same dose titration typical of the older TCAs and there are no issues of non-therapeutic dose formulation. They have a side-effects profile that is different from the older TCAs, although there is still a significant drop-out rate from side-effects with SSRIs. The reductions in levels of sedation for SSRIs, and certain TCAs, is likely to play a significant role in the selection of antidepressants for certain patients. In particular, parents of young infants need to have full awareness at night, users of machinery need to be able to concentrate fully and drivers also need to ensure that medication will not influence their reaction times. None of the cost-effectiveness studies identified have attempted to consider specifically the costs and benefits of TCAs and SSRIs in such sub-groups of patients.

Although safer than the older TCAs in overdose, evidence is lacking on whether this represents a real advantage in reducing the risk of suicide in the depressed patient. There are concerns that the availability of TCAs in the home provides an increased risk of overdose or poisoning in not only the patient, but also in other family members. Current research tends to suggest that suicidal patients will find other means, and studies tend to show SSRIs already being used in more severe cases.

Whilst there may be benefits for SSRIs when compared with the older TCAs, there is no such evidence of benefit compared with the newer TCA (lofepramine) although fewer studies have been conducted using this comparison.

It is of general concern that the answers to the research questions posed are not available, given that it has now been 10 years since the introduction of SSRIs and there is now an annual NHS antidepressant expenditure of approximately £200 millon. This is largely because there is no mechanism, with the launch of new drugs, to set up studies to answer questions of improved benefit over existing agents. The costs and implications of setting up RCTs must be set against the considerable costs of not doing them and the opportunity costs therein. The HTA study previously detailed may go some way to addressing this issue.

Central to the above discussions has been an assumption that all antidepressant prescribing is for properly diagnosed major depression. It is in this area that the evidence for benefit exists and the cost-effectiveness arguments are considered.

The symptoms present with depression can occur in response to a variety of other situations. There is no high level evidence for the use of antidepressants in non-major (minor) depression. Whilst the tenets of the Defeat Depression Campaign are supported, appropriate diagnosis is key to the management of depression. Diagnosing as major depression when only a minor depressive episode is present and then ensuring optimal therapeutic dosing and a full six months of drug therapy may be unnecessary expenditure and represent an important opportunity cost. Therefore, guidelines for the diagnosis of depression are advocated.

Studies which looked at allowing switches of therapy between active arms, have shown switches to occur early with a subsequent high level of compliance. There is, therefore, an important argument for starting with the cheaper TCAs, and lofepramine in particular, as first line in the absence of significant contraindications, with a change to an SSRI if there are significant side-effects. The North of England guidelines advocate this approach.

The key messages for purchasers are:

- To formulate guidelines on the diagnosis and management of depression.

- That further work is required specifically to answer the question of the cost-effectiveness of SSRIs over the newer TCAs.

- To consider the use of the newer TCA, lofepramine, in particular unless contraindicated as first line drug choice.

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CONFLICTS OF INTEREST

None of the authors of this document has any financial interests in the drugs or products being evaluated here.

EXPIRY DATE

This report will have an expiry date of December 2001 at which point the impact of generic SSRIs on the overall cost profile of antidepressants will be much clearer. In the light of the relative similarity between drugs, in terms of clinical effectiveness, any shift in monthly prescription cost difference will be an important issue.

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APPENDIX

The following table details the individual RCT data included in the meta-analysis published by Hotopf et al. 1997.[13] The trials are classified by their reference antidepressant into three distinct groups, namely older TCAs, newer TCAs and Heterocyclics. The table demonstrates significant variations in drop-out both between these wide classifications and within classifications.

Author	Year	TCAs and Related Drugs	SSRI	n randomised		drop-outs			
				TCA	SSRI	TCA	SSRI	Odds ratio	95%CI
Older Tricyclics									
Altamura	1989	amitripyline	fluxetine	14	14	4	2	0.47	0.08-2.71
Amore	1989	amitripyline	fluvoxamine	15	15	5	0	0.06	0.003-1.20
Bascara	1989	amitripyline	paroxetine	23	27	3	2	0.57	0.10-3.19
Battegay	1985	amitripyline	paroxetine	10	11	8	3	0.12	0.02-0.79
Beasley	1993	amitripyline	fluxetine	71	65	24	8	0.29	0.12-0.68
Bersani	1994	amitripyline	sertraline	34	34	4	3	0.75	0.17-3.30
Bignamini & Rapisardi	1992	amitripyline	paroxetine	153	156	20	31	1.64	0.89-3.01
Byrne	1989	amitripyline	paroxetine	35	35	9	12	1.49	0.54-4.09
Chouinard	1985	amitripyline	fluoxetine	28	23	6	2	0.4	0.08-1.93
Cohn	1990	amitripyline	sertraline	64	121	41	79	1.06	0.56-1.99
Fawcett	1989	amitripyline	fluoxetine	19	19	10	7	0.54	0.15-1.91
Feighner	1985	amitripyline	fluoxetine	22	22	12	6	0.33	0.10-1.12
Gasperini	1992	amitripyline	fluvoxamine	26	30	1	2	1.49	0.18-12.09
Harris	1991	amitripyline	fluvoxamine	34	35	8	11	1.47	0.52-4.17
Hutchinson	1992	amitripyline	paroxetine	32	56	11	12	0.53	0.20-1.37
Judd	1993	amitripyline	fluoxetine	28	30	5	7	1.37	0.40-4.73
Keegan	1991	amitripyline	fluoxetine	22	20	3	2	0.75	0.13-4.29
Kuhs & Rudolf	1989	amitripyline	paroxetine	20	20	3	6	2.22	0.51-9.70
Laursen	1985	amitripyline	paroxetine	23	21	9	5	0.51	0.14-1.81
Masco & Sheetz	1985	amitripyline	fluxetine	21	20	5	1	0.2	0.03-1.37
Moller	1993	amitripyline	paroxetine	110	112	48	37	0.64	0.37-1.10
Remick	1994	amitripyline	fluvoxamine	17	16	6	3	0.46	0.10-2.10
Reimherr	1990	amitripyline	sertraline	149	149	63	61	0.94	0.59-1.49
Amin	1984	imipramine	fluvoxamine	113	115	64	52	1.1	0.76-1.58
Arminen	1994	imipramine	paroxetine	32	25	15	13	1.22	0.44-3.41
Beasley	1993	imipramine	fluxetine	62	56	38	33	0.91	0.55-1.51
Bramanti	1988	imipramine	fluvoxamine	30	30	1	2	1.72	0.21-13.89
Bremner	1984	imipramine	fluoxetine	20	20	3	4	1.37	0.29-6.46
Bressa	1989	imipramine	fluoxetine	15	15	1	2	1.79	0.21-15.46
Cohn & Wilcox	1985	imipramine	fluoxetine	54	54	34	19	0.33	0.15-0.72
Cohn	1989	imipramine	fluoxetine	30	30	16	13	0.68	0.25-1.85
Dominguez	1985	imipramine	fluvoxamine	30	31	11	17	2.04	0.74-5.59

Author	Year	TCAs and Related Drugs	SSRI	n randomised		drop-outs			
				TCA	SSRI	TCA	SSRI	Odds ratio	95%CI
Feighner	1989	imipramine	fluoxetine	57	61	28	31	1.06	0.52-2.17
Feighner	1989	imipramine	fluvoxamine	36	31	11	10	1.09	0.40-3.01
Feighner	1993	imipramine	paroxetine	237	240	127	102	0.64	0.53-0.77
Fontaine	1991	imipramine	paroxetine	50	54	23	28	1.27	0.59-2.72
Gonella	1990	imipramine	fluvoxamine	10	10	0	1	3.33	0.12-92.00
Guelfi	1983	imipramine	fluvoxamine	77	74	18	19	1.14	0.55-2.37
Itil	1983	imipramine	fluvoxamine	25	22	12	12	1.28	0.42-3.94
Lapierre	1987	imipramine	fluvoxamine	21	22	12	7	0.37	0.11-1.24
Levine	1987	imipramine	fluoxetine	30	30	2	8	4.35	0.96-19.78
Lydiard	1989	imipramine	fluvoxamine	18	18	4	1	0.21	0.03-1.51
March	1990	imipramine	fluvoxamine	18	18	3	5	1.81	0.39-83.32
Nielsen	1991	imipramine	paroxetine	15	16	9	7	0.54	0.14-2.15
Nielsen	1993	imipramine	fluoxetine	30	29	8	8	1.04	0.34-3.19
Norton	1984	imipramine	fluvoxamine	59		30	33	1.1	0.54-2.23
Ohrberg	1992	imipramine	paroxetine	77		19	13	0.66	0.30-1.44
Shrivastava	1992	imipramine	paroxetine	38		7	15	0.21	0.07-0.60
Stark & Hardison	1985	imipramine	fluoxetine	186		87	87	1.01	0.67-1.52
Stratta	1991	imipramine	fluoxetine	14		5	0	0.06	0.003-1.22
Newer Tricyclics									
Danish University Group	1990	clomipramine	paroxetine	58		19	12	0.5	0.22-1.14
De Wilde & Doogan	1982	clomipramine	fluvoxamine	15		0	0		
De Wilde	1983	clomipramine	fluvoxamine	21		0	0		
De Wilde	1983	clomipramine	fluvoxamine	15		0	0		
Dick & Ferrero	1983	clomipramine	fluvoxamine	15		3	4	1.19	0.24-5.86
Guilibert	1989	clomipramine	paroxetine	39		12	9	0.66	0.25-1.77
Klok	1981	clomipramine	fluvoxamine	18		3	5	1.81	0.39-8.32
Link & Dunbar	1992	clomipramine	paroxetine	154		28	26	0.91	0.52-1.59
Link & Dunbar	1992	clomipramine	paroxetine	56		26	27	0.94	0.46-1.94
Link & Dunbar	1992	clomipramine	paroxetine	43		9	14	1.85	0.71-4.82
Moon	1993	clomipramine	sertra	55		10	2	0.22	0.05-0.92
Noguera	1991	clomipramine	fluoxetine	60		16	13	0.77	0.34-1.76
Robert	1989	clomipramine	fluoxetine	72		24	16	0.59	0.28-1.23
Bowden	1993	desipramine	fluoxetine	30		8	5	0.62	0.18-2.1
Nathan	1990	desipramine	fluvoxamine	20		2	0	0.21	0.01-4.69
Remick	1993	desipramine	fluoxetine	20		5	2	0.29	0.06-1.47
Roth	1990	desipramine	fluvoxamine	30		9	6	0.6	0.19-1.90
Corne & Hall	1990	dothiepin	vluox	53		7	14	2.56	0.96-6.85
Mullin	1994	dothiepin	fluvoxamine	36		12	11	0.85	0.32-2.24
Rahman	1991	dothiepin	fluvoxamine	26		5	7	1.49	0.42-5.25
South Wales Group	1988	dothiepin	fluoxetine	28		7	15	2.7	0.91-7.97
Thompson	1991	dothiepin	paroxetine	93		9	6	0.7	0.25-1.99
Dunner	1992	doxepin	paroxetine	135		39	45	1.22	0.73-2.04

Author	Year	TCAs and Related Drugs	SSRI	n randomised		drop-outs			
				TCA	SSRI	TCA	SSRI	Odds ratio	95%CI
Feighner & Cohn	1985	doxepin	fluvoxamine	79		48	37	0.59	0.31-1.11
Remick	1989	doxepin	fluoxetine	37		10	13	1.39	0.53-3.67
Tammimen & Lehtinen	1989	doxepin	fluoxetine	25		4	5	1.22	0.31-4.86
Gabre	1991	nortripyline	fluoxetine	102		45	39	0.79	0.45-1.36
Heterocyclic antidepressants									
Dalery	1992	amineptine	fluoxetine	87		14	14	1.08	0.49-2.40
Ferreri	1989	amineptine	fluoxetine	32		7	4	0.56	0.15-2.03
Feighner	1991	bupropion	fluoxetine	60		16	18	1.18	0.54-2.59
De Jonge	1991	maprotiline	fluoxetine	34		3	5	2.13	0.50-9.01
De Jonge	1991	maprotiline	fluvox	24		6	4	0.63	0.16-2.43
Poelinger & Haber	1989	maprotiline	fluoxetine	69		8	12	1.47	0.57-3.76
Besancon	1993	mianserin	fluoxetine	33		9	13	1.79	0.64-4.97
Dormon	1992	mianserin	paroxetine	28		3	5	1.64	0.38-6.99
Mertens & Pintens	1988	mianserin	paroxetine	31		3	3	0.85	0.18-4.06
Moon & Jesinger	1991	mianserin	fluvoxamine	31		7	6	0.83	0.25-2.72
Muijen	1988	mianserin	fluoxetine	27		13	12	0.93	0.32-2.67
Perez & Ashford	1990	mianserin	vluvoxamine	30		8	8	1	0.33-3.05
Phanjoo	1991	mianserin	fluvoxamine	25		10	9	0.85	0.28-2.60
Teneri & Kohler	1989	nomifensine	fluoxetine	20		1	5	4.55	0.66-31.18
Debus	1988	trazodone	fluoxetine	21		101	8	0.64	0.19-2.10
Falk	1989	trazodone	fluoxetine	13		9	3	0.14	0.03-0.72
Perry	1989	trazodone	fluoxetine	19		4	4	0.88	0.20-3.85

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