

## PRESCRIPTION PROCEDURES IN MEDICATION FOR RELAPSE PREVENTION AFTER INPATIENT TREATMENT FOR ALCOHOL USE DISORDERS IN SWITZERLAND

CAROLINE BURI, FRANZ MOGGI\*, ANNA GIOVANOLI and WERNER STRIK

University Hospital of Psychiatry Bern, Switzerland

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**Abstract — Aims:** In randomized controlled trials with high internal validity, pharmacotherapy using acamprosate, naltrexone, and, to a somewhat lesser extent, disulfiram has proved effective in preventing relapse in patients with alcohol use disorders (AUD). There remains, however, a paucity of studies with sufficient external validity in which the effectiveness of pharmacotherapy in clinical practice is investigated. This study aimed to make a contribution to close this gap in research. **Methods:** In this naturalistic, prospective study, a comparison on indices of substance use, psychiatric symptoms, and treatment service utilization was carried out using samples of 92 patients who received pharmacotherapy and 323 patients who did not receive pharmacotherapy following discharge from 12 residential AUD programmes (index stay). **Results:** Patients that received pharmacotherapy were more likely to use alcohol during the index stay and at the 1-year follow-up. Moreover, this patient group more readily utilized treatment services during a 2-year period prior to and a 1-year period following index stay than patients who were not given pharmacotherapy. Nevertheless, when pharmacotherapy was prescribed before first post-treatment alcohol use, it was associated with delay of alcohol use, fewer relapses, and a reduced need for inpatient treatment. In many cases, however, medication was not prescribed until alcohol use and relapse had occurred. The length of time to first alcohol use was longer, and the cumulative abstinence rate higher, for disulfiram than for acamprosate, the latter being generally prescribed for more severely alcohol-dependent patients. **Conclusions:** There is a need for further studies to probe the reasons why medication for relapse prevention is not prescribed upon discharge from residential treatment and for less severely alcohol-dependent patients.

### INTRODUCTION

Acamprosate, naltrexone, and disulfiram constitute the only medications currently approved for pharmacotherapy in alcohol use disorders Alcohol Use Disorders (AUD). In a well-designed, methodological analysis of 361 controlled clinical trials of treatments for AUD, Miller and Wilbourne found that the efficacy of two medications (i.e. acamprosate and naltrexone) was equally high as that of psychosocial treatments, such as brief intervention, motivational enhancement, and several cognitive-behavioural interventions (CBI) (Miller and Wilbourne, 2002). Acamprosate, a modulator of glutamatergic activity, is thought to reduce withdrawal relief craving by attenuating central nervous system hyperexcitability due to lack of alcohol, which may, in turn, cause physiological and psychological distress. Naltrexone, an opioid antagonist, which weakens the positive effects of alcohol, is considered effective against reward craving. In two comprehensive reviews of pharmacotherapy for AUD (Heinz *et al.*, 2003; Mann, 2004), it was concluded that acamprosate and naltrexone both decrease relapse rates but not abstinence rates. Whereas the efficacy of acamprosate did not appear to be influenced by additional psychosocial treatment, pharmacotherapy using naltrexone obtained better results in conjunction with CBI than with supportive/12-step treatment (Berglund *et al.*, 2003; Mann, 2004). These findings have been confirmed in three recent and sound meta-analyses, which provided evidence of small effect sizes for pharmacotherapy compared to placebo ( $d = 0.06–0.28$ ) (Mann *et al.*, 2004; Berglund, 2005; Roozen *et al.*, 2005). In a randomized controlled study, Kiefer and colleagues found that the

combination of acamprosate and naltrexone had the greatest effect on relapse rates—greater than that of acamprosate alone and placebo, although not any greater than that of naltrexone alone (Kiefer *et al.*, 2003). Similarly, Feeney and colleagues reported in a matched controlled clinical study that patients treated with a combination of acamprosate, naltrexone, and CBI (combination group) tended to achieve higher abstinence rates than patients treated either with CBI alone or with CBI and acamprosate (Feeney *et al.*, 2006). In addition, the combination group reported more days to first breach of abstinence than the group treated with CBI alone. No significant differences were found between the combination group and the CBI and acamprosate group.

In contrast to the findings of these two single-site trials, the results of the COMBINE study failed to support the combined use of acamprosate and naltrexone (Anton *et al.*, 2006). This randomized controlled clinical multisite trial evaluated the efficacy of these two most promising pharmacotherapies, used both singly and in combination, and also in conjunction with psychosocial treatments, namely brief intervention with medical management (Pettinati *et al.*, 2004) and a series of the most effective CBI (Miller, 2004). Anton and colleagues report that overall medical management with naltrexone or CBI attained the best alcohol use outcome. Acamprosate showed no evidence of efficacy, either when administered alone or together with CBI. Patients receiving only CBI had worse outcomes than those in the other groups. However, effect sizes observed during treatment were small and largely disappeared over the 1-year post-treatment period.

There is somewhat less evidence for the efficacy of disulfiram alone compared to control groups (Miller and Wilbourne, 2002). Berglund's meta-analysis even revealed an effect size of zero in placebo-controlled studies, while determining a moderate effect size ( $d = 0.53$ ) for disulfiram when pharmacotherapy was paired with supervision or

\*Author to whom correspondence should be addressed at: University Hospital of Psychiatry Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland. Tel: +41 (0)31 930 9111; Fax: +41 (0)31 930 9404; E-mail: moggi@puk.unibe.ch

contingency management (Berglund, 2005). Ehrenreich and colleagues—presenting results from an intensive long-term outpatient programme for individuals suffering from chronic alcoholism—determined that the relapse rate of patients who were given disulfiram was considerably lower than that of controls (30% vs 70%) (Ehrenreich *et al.*, 1997). Furthermore, Petrakis and colleagues found no differences in alcohol use outcomes of dually diagnosed patients who had been prescribed either disulfiram or naltrexone, a finding which suggests that the medications had been of the same standard (Petrakis *et al.*, 2005). Finally, Fuller and Gordis conclude that the supervised administration of disulfiram is warranted for patients struggling to achieve abstinence (Fuller and Gordis, 2004).

The aforementioned findings are all based on methodologically sound *efficacy* studies with high *internal validity*, hence allowing the conclusion to be drawn that a significant difference in outcome between treatment and control conditions is causally linked to treatment. However, it is not a foregone conclusion that a treatment providing good results in an efficacy study will also work in clinical practice. For example, applying typical patient exclusion criteria usually results in patient samples that do not adequately reflect the cross-section of AUD patients encountered in clinical practice, something that may compromise the generalizability of the results (Humphreys and Weisner, 2000). It may, therefore, prove more expedient to conduct an *effectiveness* study with sufficient *external validity* in order to determine which treatment is most effective under field conditions (Seligman, 1995; Bühringer, 2006). Such an evaluation should ideally utilize a naturalistic, prospective, and multisite design that capitalizes on realistic treatment selection and conditions. It should furthermore enable patients to express their preferences for particular treatments, while maximising compliance with treatment and minimizing attrition and crossover to non-assigned programmes (Moos *et al.*, 1990b; Ogborne, 1995).

It is such an evaluation paradigm that underlies the Swiss Multisite Study (SMS 2000), the aim of which is to identify those characteristics of inpatient treatment programmes that are associated with favourable outcome in AUD patients at the 1-year follow-up (Moggi *et al.*, 2007). The authors expanded the focus of the SMS 2000 by examining: (i) which patient characteristics (i.e. substance use, psychiatric symptoms, and service utilization) are related to a higher likelihood of medication for relapse prevention being prescribed; (ii) whether prescribing medication is associated with outcome indices; and (iii) whether acamprosate and disulfiram are related to outcome indices in different ways.

## MATERIALS AND METHODS

### *Procedure*

The authors selected 12 standard-practice residential programmes for treating AUD patients, thereby capitalising on realistic treatment conditions and typical treatment orientations in programmes representative for the German-speaking part of Switzerland. On admission and after detoxification,

patients completed an intake information form (IIF) (Maude-Griffin *et al.*, 1992), which enabled assessment of sociodemographic characteristics, indices of substance use and its consequences, psychological and social functioning, treatment motivation, prior involvement in outpatient treatment and self-help activities, and the number of prior hospitalizations. At discharge, patients completed a discharge information form (DIF) (Maude-Griffin *et al.*, 1992), which enabled assessment of indices of substance use, as well as psychological and social functioning. The clinical diagnoses were discharge diagnoses made by doctoral-level clinical staff. These diagnoses included Axis I and Axis II disorders as well as medical conditions and were based on the guidelines of the International Classification of Diseases, 10th Revision (Dilling *et al.*, 1991). At follow-up, about 1 year after discharge from the index stay, patients completed a Follow-up Information Form (FIF) (Maude-Griffin *et al.*, 1992), which enabled assessment of content areas identical to those in the IIF. In addition, patients were asked whether they had been prescribed any medication to prevent alcohol relapse and, if yes, what medication this was and when they had started taking it.

In Switzerland, only acamprosate and disulfiram are approved, while naltrexone may be prescribed off-label. The present study was approved by the Ethics Committee of the Canton of Bern (Proposal No. 109/99).

### *Patients*

All patients presenting substance use disorders (SUD) who started an index stay in any of the 12 programmes were asked to participate in the evaluation. A total of 805 out of 1088 patients (74.0%) agreed to participate. Of these, 587 (72.9%) suffered from an AUD exclusively and were not diagnosed with a SUD. Of this sample, 415 (70.7%) completed the forms on admission, at discharge, and at the 1-year follow-up. All the other patients dropped out of the respective programme before detoxification, were unable to participate on medical or language grounds, or, alternatively, refused to participate.

Patients who responded to all three measurements were compared with non-responding patients on indices of demographic characteristics, substance use, and psychiatric symptoms and diagnoses. Respondents were slightly older than non-respondents (46.3 vs 44.7 years;  $t = -2.38$ ,  $df = 585$ ,  $P < 0.05$ ) and were more likely to be female (34.0% vs 24.4%;  $\chi^2 = 4.74$ ,  $df = 1$ ,  $P < 0.05$ ), married (39.8% vs 26.5%;  $\chi^2 = 8.48$ ,  $df = 1$ ,  $P < 0.01$ ), and employed (58.7% vs 47.0%;  $\chi^2 = 8.48$ ,  $df = 1$ ,  $P < 0.05$ ). No differences were found with respect to other indices.

Of the responding patients, 90.5% lived in their own home or in a flat; mean length of education was 12.2 years ( $SD = 2.90$ ). Ninety two patients (22.2%) reported having taken medication during the 1-year follow-up period, 313 patients (75.4%) had not been prescribed any pharmacotherapy, and 10 (2.4%) did not give an answer. Disulfiram had been prescribed to 65 patients (70.7%), acamprosate to 16 (17.4%), naltrexone to 2 (2.2%), and 9 (9.9%) failed to specify what medication they had received. 40.7% had been diagnosed with co-occurring mental disorders, i.e. 56.2% suffered from a personality disorder, 34.9% from depression, 11.8%

from an anxiety disorder, and 1.2% from a psychotic disorder (co-occurrence of multiple psychiatric disorders was also possible).

### Assessments

Assessment instruments from the IIF, DIF, and FIF, which did not exist in German, were translated from English by a native German-speaking PhD-level psychologist, and subsequently back-translated by a native English-speaking PhD-level psychologist. In those instances of discrepancies arising between the original and back-translated English versions, the items concerned were revised and adapted accordingly.

*Alcohol and drug use.* A total of 15 items were used to assess the patients' alcohol and drug use during the preceding month. These items were adapted from the *Health and Daily Living Form* (HDL) (Moos *et al.*, 1990a) and from the *Treatment Outcome Prospective Study* (TOPS) (Hubbard *et al.*, 1989). Patients were asked about how often and in what amounts they consumed beer, wine, and spirits, and also about the frequency of illicit drug use. The *severity of alcohol dependence* was assessed by means of 9 items drawn from the Alcohol Dependence Scale ( $\alpha = 0.92$ ) and modified to correspond with DSM criteria for alcohol dependence (Maude-Griffin *et al.*, 1992). Item responses ranged from 'never' (0) to 'almost every day' (4), on a scale from 0–36. *Substance use consequences* ( $\alpha = 0.80$ ) were assessed using 15 items, addressing, among other things, job, family, or health issues (Maude-Griffin *et al.*, 1992). Item responses ranged from 'never' (0) to 'often' (4), on a scale from 0–60. *Alcohol craving* was assessed with 1 item from the German version of the Situational Confidence Scale (Annis and Davis, 1988; Schindler *et al.*, 1997).

*Treatment motivation* was measured by means of the sum scores as derived from the Determination and Action stages as rated on the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (Miller and Tonigan, 1996). Each of these stages was assessed by 4 items, to which responses ranged from 'strongly disagree' (0) to 'strongly agree' (4), on a scale from 0–32. Cronbach's alpha was 0.73.

*Psychiatric symptoms* were assessed by means of selected items from the Brief Symptom Inventory (BSI) (Derogatis, 1993; German version: Franke 2000). Item responses ranged from 'not at all' (0) to 'extremely' (4). *Emotional distress* was measured by a combination of depression ( $\alpha = 0.88$ ) and anxiety ( $\alpha = 0.84$ ; range = 0–24). *Psychotic symptoms* were measured by a combination of paranoid ideation ( $\alpha = 0.70$ ; range = 0–20) and psychoticism ( $\alpha = 0.72$ ; range = 0–20).

*Prior and post treatments* were measured by quantifying any *in- or outpatient treatment* for SUD or other psychiatric disorders during a 2-year period before and a 1-year period following index stay (coded as 1 = 1 or more, 0 = none), as well as the number of outpatient sessions attended by patients.

To assess patient substance use and functioning, focus was placed on the following *outcome measures*: (a) *abstinence from alcohol and drugs*, as reflected by reports of no alcohol and/or drug consumption (coded as 1 = abstinent, 0 = not abstinent); (b) *time to first alcohol use*, as defined by the number of days to first alcohol use after index

stay; (c) *relapse*, as reflected by reports of relapse as perceived by patients; (d) *gram alcohol per regular drinking day*; (e) *substance use consequences*; (f) *severity of alcohol dependence*; (g) *craving*; (h) *treatment motivation*; (i) *emotional distress*; (j) *psychotic symptoms*; and (k) *in- or outpatient treatment* as a result of substance use or other psychiatric disorders during the 1-year follow-up period.

### Statistical procedures

$\chi^2$  for categorical data and *t*-tests for continuous data were computed to compare the two groups of patients with/without post-treatment medication on indices of alcohol use and its consequences, craving, treatment motivation, psychiatric symptoms, and service utilization. Kaplan-Meier survival analyses were performed to determine whether the two patient groups differed in terms of time to first alcohol use and relapse, and whether there were any differences between patients taking acamprosate and those taking disulfiram. Effect sizes (ES) were estimated by calculating  $d^*$  for categorical data (Hasselblad and Hedges, 1995) and  $d$  for continuous data (Cohen, 1988).

## RESULTS

Patients taking post-treatment medication tended to be somewhat younger and more likely to have had outpatient treatment for psychiatric disorders during the 2 years prior to index stay than patients not taking post-treatment medication. The former patient group showed a slightly greater propensity to use alcohol during index stay, as well as a significantly higher probability to have had SUD inpatient treatment during the 2 years prior to index stay (Table 1). In addition, patients ( $N = 48$ ) medicated after their first alcohol use reported consuming more grams of alcohol per regular drinking day prior to index stay than patients ( $N = 29$ ) medicated before their first alcohol use (206.3 g vs 139.7 g,  $t = 2.96$ ,  $df = 70.28$ ,  $P < 0.01$ ,  $ES = 0.65$ ). Patients taking acamprosate ( $N = 16$ ) scored higher on the severity of alcohol dependence scale than patients taking disulfiram ( $N = 61$ ; 23.9 vs 18.5,  $t = 2.14$ ,  $df = 25.29$ ,  $P < 0.01$ ,  $ES = 0.59$ ). No significant differences were found either with respect to other demographic and treatment characteristics or on alcohol use and psychiatric symptoms indices.

Patients taking post-treatment medication were more likely to have used alcohol and to have suffered relapses during follow-up than patients without post-treatment medication. The former patient group also consumed slightly larger quantities of alcohol per regular drinking day, reported a somewhat larger number of alcohol dependence symptoms, and tended to suffer more heavily from emotional distress. Moreover, they more clearly tended to take advantage of SUD in- and outpatient treatment, and of outpatient treatment for psychiatric disorders during the 1-year period following index stay (Table 2).

It is self-evident that all patients medicated after their first alcohol use had drunk, but only 55.2% of patients medicated before a potential relapse reported some subsequent alcohol use ( $\chi^2 = 25.89$ ,  $df = 1$ ,  $P < 0.001$ ;  $ES = 1.42$ ).

Table 1. Comparison, at time of index stay, between patients with/without subsequent pharmacotherapy: patients' demographic characteristics, treatment service utilization, substance use, and psychiatric symptoms

Patient characteristics at index stay	Medication <sup>a</sup>		No medication		Test		ES	
	%/M	SD	%/M	SD	t	$\chi^2$	d	d*
<i>Demographics</i>								
Age	45.0	8.84	47.0	9.42	1.80 <sup>†</sup>	—	0.22	—
Female (%)	24.1	—	75.9	—	—	0.12	—	0.06
Male (%)	22.0	—	78.0	—	—	—	—	—
Married (% yes)	41.3	—	39.0	—	—	0.08	—	0.05
Employed (% yes)	64.1	—	57.1	—	—	1.19	—	0.16
<i>Alcohol use</i>								
Alcohol in g per regular drinking day	177.3	111.80	163.5	105.15	1.08	—	0.13	—
Severity of alcohol dependence	20.1	10.14	18.9	10.41	1.01	—	0.12	—
Craving for alcohol	3.4	1.29	3.6	1.23	1.17	—	0.16	—
Treatment motivation	38.7	5.39	38.7	5.48	0.07	—	0.00	—
Alcohol use during index stay (% yes)	32.6	—	21.4	—	—	4.33*	—	0.32
<i>Psychiatric symptoms</i>								
Emotional distress	14.2	8.53	14.0	9.87	0.15	—	0.02	—
Psychotic symptoms	9.9	6.47	9.5	6.91	0.15	—	0.06	—
<i>Treatment (2 years prior to index stay)</i>								
Inpatient SUD (% yes)	55.4	—	35.5	—	—	11.00***	—	0.45
Outpatient SUD (% yes)	48.9	—	39.0	—	—	2.50	—	0.22
Inpatient psychiatric disorders (% yes)	13.0	—	9.9	—	—	0.45	—	0.17
Outpatient psychiatric disorders (% yes)	32.6	—	22.0	—	—	3.74 <sup>†</sup>	—	0.30

Notes: <sup>a</sup>Due to missing data, *N* varies from 91–92 in the medication group and from 309–313 in the no medication group; SUD, Substance Use Disorders; Test = Statistical test; ES, Effect size; M/%, Mean/Percent; SD, Standard deviation; *t*, *t*-test;  $\chi^2$ , Chi-square test; *d*, Cohen's *d*; *d*\*, Hasselblad & Hedges' *d*\*.

<sup>†</sup> *P* < 0.10;

\* *P* < 0.05;

\*\*\* *P* < 0.001.

Table 2. Comparison, at time of 1-year follow-up, between patients with/without prior pharmacotherapy: outcomes and treatment service utilization

Outcomes and treatment	Medication <sup>a</sup>		No medication		Test		ES	
	%/M	SD	%/M	SD	t	$\chi^2$	d	d*
<i>Alcohol use outcomes</i>								
Alcohol use (% yes)	84.8	—	60.1	—	—	18.19***	—	0.72
Time to first alcohol use in days <sup>b</sup>	72.0	77.21	78.8	80.64	0.63	—	0.09	—
Alcohol relapse (% yes)	67.4	—	29.8	—	—	39.90***	—	0.87
Alcohol in g per regular drinking day	66.7	92.37	44.9	73.45	1.98*	—	0.26	—
Alcohol use consequences	7.8	8.00	6.5	7.66	1.41	—	0.18	—
Severity of alcohol dependence	6.8	9.60	4.6	7.62	1.99*	—	0.25	—
Craving for alcohol	3.4	1.34	3.6	1.46	1.15	—	0.14	—
Treatment motivation	36.8	5.88	32.5	7.52	4.86***	—	0.64	—
<i>Psychiatric outcomes</i>								
Emotional distress	8.1	6.73	6.5	7.00	1.86 <sup>†</sup>	—	0.24	—
Psychotic symptoms	6.2	5.71	5.4	5.29	1.33	—	0.15	—
<i>Treatment during follow-up</i>								
Inpatient SUD (% yes)	41.1	—	9.6	—	—	47.65***	—	1.04
Outpatient SUD (% yes)	70.8	—	38.5	—	—	27.72***	—	0.75
Inpatient psychiatric disorders (% yes)	6.7	—	3.3	—	—	1.27	—	0.41
Outpatient psychiatric disorders (% yes)	32.2	—	18.4	—	—	7.11**	—	0.41

Notes: <sup>a</sup>Due to missing data, *N* varies from 83–92 in the medication group and from 301–313 in the no medication group.

<sup>b</sup> Only those patients who reported any alcohol use (*N* = 75 in the medication group and *N* = 181 in the no medication group); SUD, Substance Use Disorders; Test = Statistical test; ES, Effect size; M/%, Mean/Percent; SD, Standard deviation; *t*, *t*-test;  $\chi^2$ , Chi-square test; *d*, Cohen's *d*; *d*\*, Hasselblad & Hedges' *d*\*.

<sup>†</sup> *P* < 0.10;

\* *P* < 0.05;

\*\* *P* < 0.01;

\*\*\* *P* < 0.001.

While 78.7% of patients medicated after their first alcohol use reported at least one alcohol relapse, the relapse rate was a modest 37.9% for patients medicated before a potential relapse ( $\chi^2 = 12.83$ ,  $df = 1$ ,  $P < 0.001$ ,  $ES = 0.99$ ). Moreover, 46.8% of patients medicated after their first alcohol use had SUD inpatient treatment at least once, whereas such treatment was given to only 20.7% of patients medicated before a potential relapse ( $\chi^2 = 5.26$ ,  $df = 1$ ,  $P < 0.05$ ,  $ES = 0.13$ ). Another finding was that, on average, patients taking acamprosate started drinking 51 days after index stay, while this time span was 137 days for patients taking disulfiram ( $t = 3.03$ ,  $df = 33.28$ ,  $P < 0.01$ ,  $ES = 0.77$ ). No other differences between patient groups were found at the 1-year follow-up.

The cumulative probability of abstinence during the 1-year follow-up period—in terms of the number of days to first alcohol use—was considerably higher for patients without medication than for patients with medication (Fig. 1(a); log rank = 21.54,  $df = 1$ ,  $P < 0.001$ ). No significant difference was found, however, between the cumulative probability of abstinence among patients who had received medication before their first alcohol use, and among patients who had not (Fig. 1(b); log rank = 0.64,  $df = 1$ ,  $P > 0.05$ ). In contrast, there were significant differences found between patients without medication and patients medicated before their first alcohol use, on the one hand, and patients who received medication after their first alcohol use, on the other (Fig. 1(b); log rank = 32.27,  $df = 1$ ,  $P < 0.001$  and log rank = 32.27,  $df = 1$ ,  $P < 0.001$ , respectively). Also, the cumulative probability of abstinence was higher for patients taking disulfiram than for patients taking acamprosate (Fig. 1(c); log rank = 11.78,  $df = 1$ ,  $P < 0.001$ ).

DISCUSSION

The aims of the present naturalistic, prospective, multisite study were to examine: (i) which patient characteristics are associated with pharmacotherapy for relapse prevention; (ii) whether prescribing medication is associated with outcome indices; and (iii) whether acamprosate and disulfiram are related to outcome indices in different ways.

*Pharmacotherapy condition, patient characteristics on admission and during index stay*

Compared to patients without pharmacotherapy, about 20% more patients with pharmacotherapy had SUD inpatient treatment in the 2-year period before the index stay, and about 11% more patients with pharmacotherapy used alcohol during the index stay, which suggests that these patients suffered from more severe alcohol dependence. However, the two groups did not differ with respect to other AUD or psychiatric disorder indices, frequency of other service utilization, or demographic variables. In addition, patients medicated after their first relapse generally consumed larger quantities of alcohol before index stay than patients medicated before their first alcohol use. It would appear that medication is more readily prescribed to patients who do not benefit from residential AUD treatment, despite their having repeatedly utilized

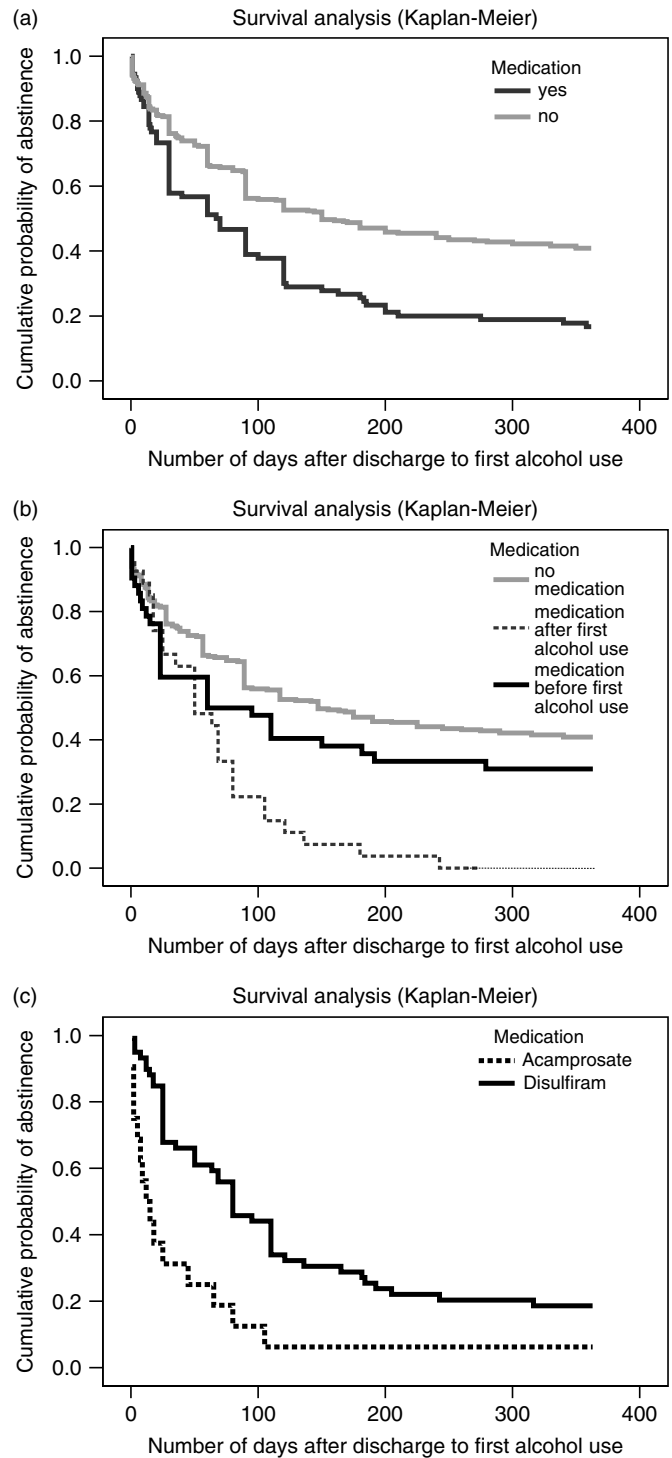


Fig. 1. Comparison of (a) pharmacotherapy versus no pharmacotherapy; (b) no pharmacotherapy versus pharmacotherapy before/after first alcohol use; and (c) disulfiram versus acamprosate. Note: Tests of significance are reported in the text.

SUD inpatient services. It may be the case that clinicians do not regard pharmacotherapy as a treatment option unless intensive psychosocial interventions have proved unsuccessful. The severity of AUD and psychiatric symptoms alike, as

well as craving and treatment motivation, all appear to be of lesser relevance for prescription than the failure of inpatient treatment.

Patients exhibiting symptoms of more severe alcohol dependence on admission were more frequently prescribed acamprosate than disulfiram. Clinicians may have based their decision in favour of acamprosate on safety grounds, arguing that heavily dependent patients would use alcohol in spite of taking disulfiram. In as much as the clinicians concerned were not queried on their reasons for prescribing a particular medication to alcohol-dependent patients, this point remains unclear. Pertinent research would shed light on clinicians' decision-making processes and serve to improve these as necessary.

#### *Pharmacotherapy, treatment service utilization, and outcomes at 1-year follow-up*

Overall, compared to patients without pharmacotherapy, 25% more patients receiving pharmacotherapy had at least once used alcohol, 37% more of these patients had at least 1 alcohol relapse, and 30% more of these patients had at least one SUD residential treatment. Specifically at the 1-year follow-up, patients receiving medication also reported slightly greater alcohol use per regular drinking day and more severe alcohol dependence symptoms, as well as less time to their first alcohol use during the follow-up period, all of which suggests that pharmacotherapy is associated with worse AUD outcome indices. However, if the comparison focuses on patients without medication and patients who were prescribed medication before their first alcohol use, no significant difference between the two patient groups with respect to the course of alcohol use is found. Indeed, the latter group reported fewer relapses and presented a reduced need for SUD inpatient treatment than patients medicated after their first alcohol use. Thus, worse AUD outcome indices were only associated with patients who did not receive medication until after their first alcohol use. Appropriately timed prescribing practices would therefore appear to prevent or delay alcohol use in patients who had repeatedly received inpatient treatment to no avail, pharmacotherapy having thereby an effect similar to that of successful inpatient treatment. Further research is needed to examine the reasons why clinicians do often not prescribe medication upon discharge from residential treatment and for less severely alcohol-dependent patients.

At the 1-year follow-up, compared to patients without pharmacotherapy, 30% more patients with pharmacotherapy reported SUD outpatient treatment and 14% more outpatient treatment for other psychiatric disorders than by patients without pharmacotherapy. They were also somewhat more motivated for treatment. These findings are in line with AUD treatment guidelines, according to which medication for relapse prevention should only be prescribed to patients who are motivated to take their medication regularly under supervision during outpatient treatment (Mann, 2004).

No differences between the two groups with respect to emotional distress or psychotic symptoms were found, and, consequently, referrals for further psychiatric inpatient treatment were unnecessary. Psychiatric symptoms do not appear

to be associated with medication for relapse prevention, neither on admission to index stay nor at the 1-year follow-up.

#### *Acamprosate, disulfiram, and alcohol use outcome*

Disulfiram is associated with a longer time to first alcohol use and a higher cumulative abstinence rate than acamprosate. This concurs with a meta-analysis conducted by Berglund that revealed the effectiveness of supervised administration of disulfiram (Berglund, 2005). If patients are struggling to achieve abstinence, disulfiram is still warranted, provided that the patients are supervised and side-effects are monitored. On admission, however, more severely alcohol-dependent patients are generally prescribed acamprosate rather than disulfiram; disulfiram administration is more closely supervised than acamprosate. These two factors may also contribute to the finding that patients receiving acamprosate did less well than patients receiving disulfiram.

#### *Limitations*

Two caveats should be noted. First, the authors' evaluation utilized a prospective, naturalistic design that capitalized on representative treatment conditions and typical treatment orientations in a selection of Swiss programmes. Naturalistic designs mirror actual conditions of treatment selection and treatment processes, thereby augmenting the external validity of the evaluation (Moos *et al.*, 1990b; Seligman, 1995). However, data are derived from self-reports rather than from reports from collaterals or biochemical markers of alcohol use. Del Boca and Darkes note that self-report measures, which are relatively inexpensive, non-invasive, and acceptable to respondents, have yielded reasonable levels of reliability and validity (Del Boca and Darkes, 2003). Reliability and validity are further enhanced if patients are assessed by research staff that are not directly associated with the treatment programme, as was the case in the present study.

Second, assuming that prescription rules are followed, it is not known on which grounds clinicians base their decisions to prescribe medication to alcohol-dependent patients. One such criterion may be individual patients' continued struggle to achieve abstinence despite several SUD residential treatments. Further research into clinicians' decision-making processes is required in order to identify the implicit criteria applied in prescribing pharmacotherapy. This is of considerable relevance because appropriately timed prescription of medication was associated with longer periods of abstinence in the present naturalistic study, and is furthermore related to better SUD outcomes in a number of randomized controlled studies (Miller and Wilbourne, 2002; Berglund, 2005; Anton *et al.*, 2006).

In summary, medication for relapse prevention is more likely to be prescribed for more severely alcohol-dependent patients. While pharmacotherapy can prevent or delay alcohol use under field conditions, it is often prescribed only after first alcohol use or after relapses have occurred. Time of abstinence proved longer, and the abstinence rate higher, for disulfiram administered under supervision (i.e. in the

course of outpatient treatment) than for acamprosate. Further studies need to examine the reasons why pharmacotherapy is not prescribed by clinicians upon patients' discharge from residential treatment and for less severely alcohol-dependent patients.

### CONFLICT OF INTEREST

There is no conflict of interest with respect to the authors' involvement in the publication.

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