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Research Article

"Keep an Eye on me, Doc!": Outpatient Voluntary Supervised Disulfiram for the Treatment of Alcohol Use Disorders in a Community Setting

Abigail Yang[1], Stefanie Leung[1,2] and Apo Demirkol[1,3]*

[1]*Drug and Alcohol Service, South Eastern Sydney Local Health District, Australia*
[2]*Discipline of Addiction Medicine, Sydney Medical School, University of Sydney, Australia*
[3]*School of Public Health and Community Medicine, University of South Wales, Australia*

***Corresponding author**
Apo Demirkol, Drug and Alcohol Service c/o The Langton Centre, 591 South Dowling Street, Surry Hills NSW 2010 Australia, Tel: 61-2-9332-8777; Fax: 61-2-9332-8700; Email: Apo.Demirkol@sesiahs.health.nsw.gov.au

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Abstract

Background: Across the world, 3.3 million people die every year as a result of harmful use of alcohol [1]. In Australia, excessive alcohol intake is responsible for 3.2% of the total burden of disease and injury [2]. Disulfiram is one of the few pharmacotherapies approved for the treatment of alcohol dependence, and interferes with the metabolism of alcohol causing unpleasant symptoms as a deterrent effect. To date, no studies have examined the efficacy of disulfiram in an outpatient setting in Australia. The aim of this study was to describe the medium term outcomes of patients commencing disulfiram in a specialised drug and alcohol outpatient setting in Australia.

Materials and Methods: Data was extracted from outpatient clinical notes for all patients commenced on disulfiram at any location in the drug and alcohol service between 1 January and 31 December 2013. **Results:** 80 patients were included in the study. At three months following commencement of treatment, 42 patients (53%) were considered to have been successfully retained in treatment. 36 (45%) patients reported remaining completely abstinent from alcohol during their first three months of treatment. Patients that self-referred to outpatient disulfiram treatment had 75% lesser odds of succeeding in treatment compared to those that were referred by other means (i.e. via hospital, GP or forensic services).

Conclusions: This study demonstrates that patients receiving supervised disulfiram for three months in the context of this treatment model can achieve abstinence. Further work is needed to compare this with other treatment options.

ABBREVIATIONS

FDA: Food and Drug Administration; TGA: Therapeutic Goods Administration; DDC: Diethyl Dithio Carbamate; LFT: Liver Function Test; IQR: Inter quartile range; AA: Alcoholics Anonymous; SMART: Self-Management and Recovery Training; NRT: Nicotine Replacement Therapy; OR: Odds Ratio; CI: Confidence Interval; GP: General Practitioner;

INTRODUCTION

Across the world, 3.3 million people die every year as a result of harmful use of alcohol, which represents 5.9% of all deaths [1]. Alcohol is responsible for 5.1% of the total burden of disease and injury worldwide [1]. It is a major modifiable risk factor for morbidity and mortality, both in the short term through road and other accidents and violence, and in the longer term through liver disease and brain damage. In Australia, excessive alcohol intake is responsible for 3.2% of the total burden of disease and injury [2]. Data from the most recent National Drug Strategy Household Survey conducted in 2013 shows that 18.2% of the population aged 14 years or over exceeded the lifetime risk guidelines for alcohol consumption (no more than two standard drinks on any day), and 26% exceeded the single occasion risk guidelines (no more than four standard drinks on any single occasion) at least once a month [3]. The survey also showed that excessive alcohol consumption is of great concern to the community, with 34% of people nominating as the drug responsible for the most number of deaths and 43% nominating it as the drug of most serious concern to the general community [3]. It is estimated that in 2004 – 2005, the cost to Australian society of alcohol use was $15.3 billion. This included costs related to crime, loss of productivity, road accidents, and health care costs, including almost $694 million in hospital costs [4].

Disulfiram is one of the few pharmacotherapies approved by the Food and Drug Administration (FDA) in the United States,

the European Medicines Agency, and the Therapeutic Goods Administration (TGA) in Australia for the treatment of alcohol dependence. It interferes with the metabolism of alcohol by inhibiting the enzyme aldehyde dehydrogenase. This results in an accumulation of acetaldehyde, a toxic intermediary substance [5], and the onset of unpleasant symptoms including intense cutaneous flushing, sweating, palpitations, tachycardia, headache, dyspnea, hyperventilation, hypertension and vomiting [6]. These undesirable effects act to deter patients from drinking alcohol when taking it, but do not have an effect on cravings [7]. However, these effects also make ensuring good patient compliance with the medication a clinical challenge. Thus, prescription of oral disulfiram in contemporary clinical practice tends to fall short of its potential.

To date, there have been no studies examining the efficacy of disulfiram in an outpatient setting in Australia. The aim of this study was therefore to describe the medium term outcomes of patients commencing disulfiram in a specialized drug and alcohol outpatient setting in Australia.

MATERIALS AND METHODS

The study was conducted at a large specialized community-based tertiary drug and alcohol clinic serving a population of approximately 380,000 people and the two tertiary referral teaching hospitals with which it is associated. Ethics approval was obtained from the South Eastern Sydney Local Health District Human Research Ethics Committee.

Context: An outpatient model of care

The drug and alcohol service in which this study was conducted includes but is not limited to a large specialized community-based tertiary drug and alcohol clinic, an inpatient service at one tertiary referral teaching hospital, and consultation liaison services at a second tertiary referral teaching hospital. The usual treatment plan for disulfiram treatment at the community-based clinic involves daily supervised dosing of disulfiram by nursing staff, who also conduct a brief consultation where they check on the patient's physical and psychosocial welfare. Patients are required to undergo breath analysis before dosing, and are reviewed regularly by the medical officer prescribing the disulfiram. A typical treatment plan is to transition patients from initial daily supervised dosing to weekly dispensing of takeaway doses over the course of three months, eventually to an external prescription. The community-based drug and alcohol clinic bears the cost of the disulfiram for the first three months, after which time patients must pay for an external prescription. Unlike acamprosate and naltrexone, the two other medications licensed for the treatment of alcohol use disorder, the cost of disulfiram is not subsidized by the Australian Government via its Pharmaceutical Benefits Scheme, so patients or services must bear the full cost of the medication. All patients are offered group and/or individual counseling for relapse prevention, and are also encouraged to attend self-help groups such as Alcoholics Anonymous (AA) and SMART (Self-Management And Recovery Training). Studies have demonstrated that the combination of disulfiram and medical care with counselling is more effective than disulfiram and medical care alone [8].

Data Gathering Stage 1

Data was extracted from the internal pharmacy dispensing databases of the drug and alcohol service to generate a list of patients supplied with disulfiram for the treatment of alcohol dependence, whether as in patients or outpatients, between 1 January 2013 and 31 December 2013.

Data Gathering Stage 2

Data was extracted from outpatient clinical notes for all patients identified in Stage 1. The study population was defined as all patients commenced on disulfiram at any location in the drug and alcohol service between 1 January and 31 December 2013. Patients were excluded from the study if they had commenced treatment with disulfiram prior to 1 January 2013, did not attend the community-based clinic for follow-up, or were supplied disulfiram but chose not to start treatment (Figure 1). For all eligible patients, data on demographics, substance use, medical history, adjunct treatments provided and treatment outcomes at 3 months were extracted.

Outcomes

Retention in treatment was defined as retention in drug and alcohol treatment with disulfiram either at the clinic or with a general practitioner, referral to residential rehabilitation or retention in treatment with an alternative pharmacotherapy. Treatment dropout before three months was defined as stopping disulfiram due to adverse events, refusal to continue with disulfiram treatment, or loss to follow up prior to three months. For patients lost to follow up prior to three months, the duration of treatment prior to loss to follow up was extracted. A lapse to drinking was defined as any episode of alcohol use while being prescribed disulfiram.

Statistical analysis

Data analysis was performed using SPSS 22 statistical software. Descriptive statistics (i.e. frequency, median, range and inter quartile range, IQR) were used to characterize the population and summarize the proportion of patients that received additional treatments in the 3-month period whilst on disulfiram. A multivariate binary logistic regression was performed using the enter method to ascertain the effects of age, current diagnosis of liver disease, concurrent engagement with other therapies (i.e. naltrexone, acamprosate, varenicline/nicotine replacement therapy, group sessions, individual counseling, social worker or AA/SMART), concomitant benzodiazepine and opioid use, past use of disulfiram and source of referral to the outpatient clinic on the likelihood that patients would be retained in treatment after three months on disulfiram. Continuous data variables were not used to ensure maximum power of analysis due to the small sample size.

RESULTS

92 patients were identified as having been supplied disulfiram through the hospital pharmacy between 1 January and 31 December 2013. A further 29 patients were identified as having been supplied disulfiram through the outpatient service between 1 January and 31 December 2013, for a total of 121 patients. Of these, 41 were excluded for the following reasons: refusal to

start treatment (n=1), follow-up outside of the outpatient service (n=1), or commencement of treatment prior to 1 January 2013 (n=39) (Figure 1).

A total of 80 patients met the eligibility criteria for inclusion in the study. Their ages ranged from 24 to 67 years, with a median age of 44 (IQR 11). 50 patients (63%) were male. The median number of drinking days per week was seven (range 2 – 7, IQR 0), and the median daily amount of alcohol consumed was 180g (range 40 to 550g, IQR 15).

In terms of previous experiences with pharmacotherapy, 29 (36%) of the patients had tried disulfiram previously. 18 (23%) had tried acamprosate, and 13 (16%) had tried naltrexone. Only five patients (6.3%) had tried treatment with all of those forms of pharmacotherapy in the past.

Table 1 describes any additional treatments that patients in the study population accepted in addition to disulfiram treatment, at any point and for any duration during the three months of treatment with disulfiram. 63 patients received some form of additional treatment and 9 received only disulfiram. No information was available for eight patients.

At three months following commencement of treatment, 42 patients (53%) were considered to have been successfully retained in treatment: 26 patients (33%) were receiving on-going disulfiram treatment dispensed by the outpatient center, 10 (13%) were successfully referred to a general practitioner (GP) for follow-up, four (5%) entered residential rehabilitation, and two (3%) switched to another pharmacotherapy. In addition, another two patients were transferred to another drug and alcohol service.

Of those patients who were not treated successfully, one patient stopped disulfiram due to the adverse effect of lethargy. 13 (16%) had refused to continue treatment. 22(28%) were lost to follow-up, in whom median treatment time was 1.5months (range 0.25 to 3, IQR 2).36 (45%) patients reported remaining completely abstinent from alcohol during their first three months of treatment. 18 (23%) reported one lapse to drinking, four (5%) reported two lapses, and one patient reported three lapses. Information about lapse to drinking was not available for 21 (26%) patients.

The binary logistic regression model was statistically significant, χ^2 (7) = 12.813, p <0.05, and the model explained 26.4% (Nagelkerke R^2) of the variance in treatment outcome and correctly classified 71.2% of cases. Patients that self-referred to outpatient disulfiram treatment had 75% lesser odds of succeeding in treatment compared to those that were referred by other means (i.e. via hospital, GP or forensic services) (Table 2). Moreover there was a trend towards increasing age being associated with decreased odds of achieving successful treatment outcomes with disulfiram. Previous treatment with disulfiram, concurrent engagement with other therapies and concomitant drug use were not found to add significantly to the model.

DISCUSSION

Despite the deterrent effect of the disulfiram-ethanol reaction,

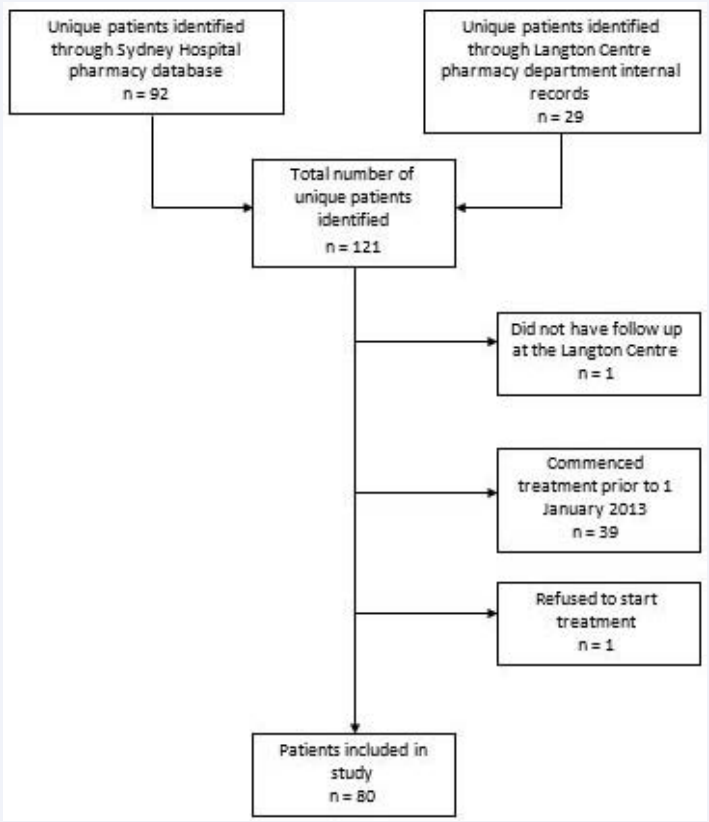

Figure 1 Identification of patients for study inclusion.

Table 1: Treatments received in addition to disulfiram by study population.

	n	%
Group counselling	21	26
Individual counselling	38	48
Self help group e.g. AA/SMART	15	19
Residential rehabilitation	6	8
Concurrent acamprosate	8	10
Concurrent naltrexone	15	19
NRT/varenicline	1	1
Referral to welfare officer	6	8
No other treatment (received disulfiram only)	9	11
Unknown	8	10

Abbreviations: AA: Alcoholics Anonymous; SMART: Self-Management and Recovery Training; NRT: Nicotine Replacement Therapy

Table 2: Patient related demographic and treatment variables.

Predictor	p value	OR	95% CI (Lower – Upper)
Age	0.068	0.947	(0.894 – 1.004)
History of liver disease	0.859	0.851	(0.143 – 5.064)
Concurrent other therapy	0.452	1.945	(0.344 – 10.993)
Concomitant benzodiazepine and opioid use	0.540	0.432	(0.030 – 6.308)
Self-referred to outpatient treatment	0.028*	0.248	(0.071 – 0.861)
Past disulfiram use	0.988	1.009	(0.303 – 3.365)

Abbreviations: OR: Odds Ratio; CI: Confidence Interval

several studies conducted overseas have shown disulfiram to be safe and efficacious compared to other FDA approved pharmacotherapy's such as acamprosate and naltrexone [9,10]. To date, disulfiram has not been studied in an Australian setting, so this study is the first to do so. The rate of abstinence in this study appears to be comparable to others [11]. It is important to note, however, that this study was conducted in a specialized outpatient drug and alcohol clinic. Studies have demonstrated that disulfiram is more effective when dosing is supervised [12-14] and a number of modes of supervised dosing have been proposed in the literature including spousal, other significant support person, clinic-based and incentive-based [15,16]. This may mean that rates of abstinence are lower if disulfiram is prescribed in a primary health setting or in an outpatient setting with less supervision and psychosocial support than that provided at the service used in this study.

During the study period there was a shortage of disulfiram in Australia, due to the manufacturer's difficulty in obtaining one chemical component. The first shortage, in February – March 2013, had only a small impact on the service, but a longer, four-month shortage commencing in July resulted in existing patients receiving reduced doses (100mg daily instead of 200mg daily, or 200mg three times weekly instead of 200mg daily) (M. Clement, personal communication, September 26, 2014), and it is possible that this may have had a slight adverse effect on the rate of treatment success.

Studies in the literature have had variable success determining predictors of outcome, with one study concluding that demographic variables, previous inpatient treatment, attendance at AA or after care groups and outpatient appointments were not significant predictors of outcome [17]. In contrast, other studies have demonstrated that current partnership, used as a proxy measure of social support [18] and longer duration of alcohol dependence (19) are predictive factors of successful treatment outcome. In this study, limited power precluded analysis of several factors such as gender, length of current drinking pattern and history of previous drug and alcohol treatment. Current partnership was not considered in this study due to limited documentation, as it was not possible to verify whether partners were involved in or even aware of a patient's treatment. In addition, as a supervised dosing model of care was used this was less likely in this study to be important. This study was able however to demonstrate that source of referral is a factor associated with successful treatment outcome. That is, self-referral was associated with poorer treatment outcomes than referral by other means. Studies have demonstrated the effectiveness of brief interventions performed in both hospital emergency [20] and general practice settings [21]. It is possible that those patients in this study referred to the service by other clinicians may have moved from a pre-contemplative to contemplative stage of change as a result of exploring their alcohol use with that clinician prior to referral, contributing to this finding.

The study has several limitations. It utilized a retrospective design and many subjects were excluded as they had commenced treatment with disulfiram before the beginning of the period under study. It was not possible to use a multicenter design, as there were no other services utilizing a similar setup, so it was only possible to conduct a study at a single center, however large this setting may be with a limited sample size. Medical officers may have been more reticent about prescribing disulfiram to new patients due to the shortage of supplies during the study period. This study lays the groundwork for a prospective study which could compare the treatment outcomes of patients treated with disulfiram, acamprosate, naltrexone and/or counseling in an outpatient setting to determine if it is as safe, efficacious and cost effective.

CONCLUSION

This study demonstrates that patients receiving supervised disulfiram for three months in the context of this treatment model can achieve abstinence. Further work is needed to compare this with other treatment options.

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