

ORIGINAL MANUSCRIPT

Supervised Disulfiram in Relapse Prevention in Alcohol-Dependent Patients Suffering From Comorbid Borderline Personality Disorder—A Case Series

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Abstract — **Aims:** Disulfiram is widely used to prevent alcoholic relapse. However, due to the intended adverse reaction with ethanol, some believe that its use is dangerous for patients with personality disorders or psychiatric comorbidities because of their increased risk of impulsivity or suicidal behaviour. We examined the safety and efficacy in relapse prevention of a series of alcoholics with borderline personality disorder (BPD). **Methods:** Case history study of patients diagnosed with BPD, prescribed disulfiram in a dose of 1.5–2.5 g/week, supervised by a physician in up to three brief contacts per week. **Results:** Two out of eight patients remained completely abstinent during the supervised disulfiram therapy over a mean period of 9.25 months. Adherence to treatment was 18.44 ± 21.78 months. The first relapse occurred after 1.38 ± 1.41 months. The cumulated time of abstinence was 16.88 ± 20.48 months. The overall tolerability was considered to be high; dizziness and fatigue appeared in all patients at the beginning of the therapy but did not persist. No serious adverse events or ethanol–disulfiram interactions were observed. No suicidal behaviour was reported. **Conclusions:** Although case observations should be interpreted with caution, supervised disulfiram seems to deserve further investigation in patients with comorbid BPD, for whom it appears to help prevent alcoholic relapse.

INTRODUCTION

The efficacy of pharmacological and psychosocial treatments for relapse prevention in alcoholism has been supported in several reviews (Berglund *et al.*, 2003; Chick *et al.*, 2003; Mann, 2004; Mutschler *et al.*, 2008a, 2008b). Currently, three different substances are fairly widely licensed for pharmacological alcohol relapse prevention: The NMDA receptor modulator acamprostate, the μ -opioid antagonist naltrexone and the acetaldehyde dehydrogenase (ALDH-1 and -2) inhibitor disulfiram (Mann, 2004). Disulfiram is an irreversible inhibitor of ALDH-1 and ALDH-2 and increases acetaldehyde levels during alcohol drinking (Mutschler *et al.*, 2008a, 2008b; Arolfo *et al.*, 2009) and is thus used as an aversive therapeutic agent (Suh *et al.*, 2006). Besides the inhibition of ALDH-1 and ALDH-2, recently other possible central modes of actions (e.g. inhibition of the dopamine beta hydroxylase) of disulfiram are discussed (Weinshenker and Schroeder, 2007; Mutschler *et al.*, 2008a, 2008b).

There are three published randomized controlled studies that compared naltrexone and/or acamprostate with disulfiram. Supervised treatment with disulfiram appeared to be more effective in alcohol relapse prevention compared to naltrexone and acamprostate even though patients treated with those compounds (sometimes called ‘anti-craving drugs’) reported lower craving levels (de Sousa and de Sousa, 2004, 2005; Laaksonen *et al.*, 2008; Diehl *et al.*, 2010). However, disulfiram use widely varies between clinical settings partly because of doubts about efficacy and safety concerns (rare fulminant hepatitis, and the possibility of a dangerous ethanol–disulfiram reaction, caused by increased acetaldehyde levels during alcohol drinking). Disulfiram is sometimes assumed to be more dangerous in patients with personality disorders (especially patients with borderline personality disorders, BPD) since these patients tend to be impulsive, their

self-control is reduced and they self-injure and make suicidal threats/attempts more than patients with alcohol dependence without concomitant psychiatric disorders (Aberg, 1984). But there are also less logical reasons for the sparse use of disulfiram; for example, some therapists believe that alcohol dependence should be treated without recourse to medication, and commentators (e.g. Brewer, 1990) have remarked that the literature demonstrating the efficacy of supervised disulfiram is often ignored or misinterpreted, even by medical reviewers.

The fear that patients with BPD especially could suffer serious harm by drinking alcohol while taking disulfiram contributes to the common opinion that disulfiram is not suitable for the treatment of alcohol addiction in patients with this personality disorder. However, they are a group who particularly tend to have poor treatment outcomes with higher rates of relapse to alcohol and a greater likelihood for developing alcohol-related problems (Pettinati *et al.*, 1999; Stepp *et al.*, 2005; Preuss *et al.*, 2009).

Borderline personality disorder and alcohol dependence commonly overlap in both inpatient and outpatient settings. In a European clinical–epidemiological study, 5.1% of the alcohol-dependent patients were diagnosed with BPD (Echeburúa *et al.*, 2007). Trull *et al.* (2000) found alcohol use disorders (abuse or dependence) in 48.8% of patients suffering from borderline personality disorder. Currently, there are few effective and specific therapeutic strategies available for these comorbidly affected patients (Dimeff and Linehan, 2008), and evidence for any effective pharmacotherapy for BPD is somewhat limited (Lieb *et al.*, 2010).

Because disulfiram still appears to be rarely used in patients with borderline personality disorder and co-occurring alcohol dependence, we set out to examine the safety and efficacy of supervised disulfiram in alcoholics suffering from comorbid BPD and seen at our service.

Table 1. Patients characteristics: sociodemographic data and characteristics and history of the addiction

Patient	Age (years)	Gender	Registered unemployed	Living in partnership	Alcohol dependent (years)	Severity of alcohol dependence (ICD-10 criteria)	Previous inpatient detoxification (n)	Longest period of abstinence without disulfiram	Recent ethanol consumption (g/day)
A	41	Male	No	Yes	23	6/6	28	Few weeks	500
B	39	Female	Yes	No	14	5/6	11	Few weeks	150
C	51	Female	No	Yes	29	6/6	15	Few weeks	400
D	45	Female	Yes	No	25	6/6	8	Few months	240
E	47	Female	Yes	No	12	6/6	26	Few days	400
F	44	Female	Yes	No	8	4/6	3	Few months	150
G	51	Male	Yes	No	33	6/6	22	11 months	350
H	44	Female	Yes	No	20	6/6	9	Few weeks	500
Mean	45.25				20.50	5.63	15.25		336.25
SD	4.30				8.67	0.74	9.13		141.72

METHODS

Subjects and therapy

This retrospective data collection refers to our routine outpatient treatment over a period of nearly 6 years (from December 2003 to September 2009). We located eight patients (two male, six female) attending our clinic who fulfilled diagnostic criteria for alcohol dependence and BPD according to International Classification of Disease (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. For patient details, see Tables 1 and 2.

After 3 weeks of detoxification and combined psychotherapeutic treatment in our inpatient department, treatment was continued in our outpatient 'antabuse-programme'. Disulfiram was uptitrated within the last week of the 3-week inpatient treat-

ment in all patients if written informed consent was provided. In the outpatient phase, disulfiram was given 3 days per week in tablet form, with a total dose between 1.5 and 2.5 g/week.

In the outpatient programme, disulfiram intake was supervised by a physician, establishing a therapeutic ritual with high-frequency, short-term individual contacts, with take-away medication for holidays. During this therapeutic ritual, the therapist praised the patients for taking disulfiram and maintaining abstinence, thereby providing continuous reinforcement of an alcohol-free lifestyle. Regular breathalyser tests for alcohol and random urine tests for drug abuse were conducted. Development and training of alternative coping skills was encouraged; there was no specific treatment element for borderline personality disorder. In case of emergency, patients and their relatives had the possibility to contact the clinic by day or night on any day of the week.

Table 2. Patients' characteristics and current clinical data

Patient	Alcohol induced somatic sequelae	Psychiatric comorbidity (axis I)	Psychiatric comorbidity (axis II)	Dialectic behavioural therapy in the past	Psychiatric medication
A	Peptic ulcer Fatty liver	Depression (F33) Cannabis abuse (F12.1) Benzodiazepine abuse (F13.1) TD (F17.2)	BPD (borderline type) (F60.31)	Yes, as an outpatient	Oxcarbazepine 450 mg/day
B	Insulin-dependent diabetes mellitus by chronic pancreatitis	Bulimia (F50.2) Depression (F33) Benzodiazepine dependence (F13.2)	BPD (borderline type) (F60.31)	Multiple as an outpatient and inpatient	Citalopram 40 mg/day Lamotrigine 125 mg/day
C	Polyneuropathy	Depression (F33) Sedative or benzodiazepine dependence (F13.2) TD (F17.2)	BPD (borderline type) (F60.31)	Yes, as an outpatient and inpatient	Olanzapine 5 mg/day
D	Pancreatitis Dupuytren's contracture Gastritis	Benzodiazepine dependence (F13.2)	BPD (borderline type) (F60.31)	No	Quetiapine 150 mg/day
E	Fatty liver	Depression (F33) TD (F17.2)	BPD (impulsive type) (F60.30)	No	Quetiapine 50 mg/day Citalopram 20 mg/day Trimipramine 50 mg/day Valproate 800 mg/day Citalopram 20 mg/day
F	None	Depression (F33) TD (F17.2)	BPD (borderline type) (F60.31)	No	Citalopram 20 mg/day
G	Fatty liver Polyneuropathy	TD (F17.2) Abuse of cannabis, cocaine, mescaline and benzodiazepines (F19.1)	BPD (borderline type) (F60.31)	No	Mirtazapine 45mg/day Quetiapine 300 mg/day Escitalopram 10 mg/day
H	Fatty liver Peptic ulcer	Depression (F33) Posttraumatic stress disorder (F42.1)	BPD (borderline type) (F60.31)	No	Mirtazapine 45 mg/day Pregabalin 300 mg/day Quetiapine 300 mg/day Escitalopram 20 mg/day

BPD, borderline personality disorder; TD, tobacco dependence.

Initially, we intended to observe the patients for 12 months; however, half of them continued to attend regularly beyond the 12 months ($n = 4$; 50%). Therefore, we decided to report the full-length observation time.

Because of safety concerns, we omit the administration of a 'test drink' following dosing with disulfiram. If patients reported excessive sedation, we reduced the dosage or gave disulfiram in the evening for the first days. The intended dosage of disulfiram was 1.5 g/week because this dose seems to be sufficient to cause a disulfiram-alcohol reaction without increasing the risk of toxicity in most patients (Ehrenreich and Krampe, 1999; Fuller and Gordis, 2004).

Data acquisition was performed using electronic charts that contained standardized clinical measurements including sociodemographic data, addictive behaviour and history as well as laboratory data. Our routine clinical assessment of patients' addictive behaviour was by structured interview. Data were generated at the beginning and at the end of the 3-week inpatient treatment as well as within the course of the outpatient aftercare. Abstinence was assessed at every visit by alcohol breathalyser, physicians' rating as well as patients' self-report. Additionally, we randomly performed blood analysis for serum levels of gamma-glutamyltransferase and other liver enzymes to detect drug-related hepatitis.

Outcome measures

The outcome measures refer to the outpatient treatment period. The primary outcome measure was time until the first relapse. 'Relapse' was defined as any alcohol consumption. Blood, urine or breath samples tested positive for alcohol as well as self-reports of alcohol use were classified as relapse. We deliberately did not differ between so-called 'mini-lapses', 'lapses' and 'relapses' since their verification mostly is insufficient in an outpatient setting. Discontinuation of the therapy without notice of removal was also deemed 'relapse'. Secondary outcome measures were attendance to the outpatient treatment, accumulated time of abstinence, and safety and tolerability of the treatment.

RESULTS

Baseline characteristics of the study group

The mean duration of alcohol dependence was 20.50 ± 8.67 years, the mean severity of alcohol dependence in terms of fulfilled ICD-10 criteria (0–6) of alcohol addiction was 5.63 ± 0.74 and the mean amount of alcohol consumption previous to inpatient treatment was 336.25 ± 141.72 g alcohol per day. In summary, these characteristics indicate a clinical study sample with a severe degree and history of alcohol dependence. For more details, see Table 1.

The presence of one or more alcohol-related somatic diseases in addition to alcohol dependence was found in seven patients (88%). Axis I psychiatric comorbidity was present in all patients (100%), pointing out the burden of the study sample. The diagnosis of BPD was made by external psychiatrists and confirmed by us. A dialectic behaviour therapy preceding the supervised disulfiram therapy had been undertaken in three patients (37.5%).

With regard to axis I psychiatric comorbidity, patients mostly suffered from depression and/or additional substance

abuse. Tobacco dependence was found in 75% of the study subjects. For more details, see Table 2.

The severity of addiction, sequelae of addiction and psychiatric comorbidity in our sample was higher than findings in some other clinical studies in the alcoholism field (Anton *et al.*, 2006).

Safety and adverse events

There were no serious adverse events recorded in the electronic patient record. No patient made a suicide threat during the recorded treatment phase or reported self-harming. However, we cannot exclude unreported self-harming. Tiredness during the day was the most prominent adverse event reported in all eight cases at the beginning of the therapy with disulfiram and completely disappeared in all patients within the first 6 weeks of the treatment. Two patients complained of headache and three patients reported gastrointestinal adverse events; one male patient reported sexual dysfunction.

Five of eight patients experienced mild alcohol-disulfiram reaction after drinking alcohol; specific inpatient or other therapy was not necessary in any case. The overall tolerability and safety of disulfiram was considered to be good.

Alcohol drinking outcomes

Two patients remained completely abstinent under the supervised disulfiram therapy over the treatment period examined (4.5 and 14 months). Patients were highly compliant with the treatment. Mean adherence to treatment was between 18.44 ± 21.78 months. The time elapsed before the first alcohol relapse was on average 1.38 ± 1.41 months. The cumulative alcohol abstinence achieved within the outpatient treatment was 16.88 ± 20.48 months. The patients suffered from 2.75 ± 2.96 relapses during the observation period.

DISCUSSION

Our disulfiram treatment approach within a routine clinical programme of alcohol dependence found that patients with BPD had a relatively low rate of drinking days (cumulated duration of abstinence 16.88 months), in contrast to studies in which the presence of at least one axis II disorder predicted a poor drinking outcome (Kranzler *et al.*, 1996; Wolwer *et al.*, 2001; Krampe *et al.*, 2006b; Hilwerling *et al.*, 2007).

Comparing our data with that reported by Diehl *et al.* (2010) from the same clinic, but across a broad spectrum of patients, the medians of cumulated time of abstinence are similar (10.50, confidence interval (CI) 1.00–63.50 vs 9.75, CI 5.50–12.50) despite our BDP patients exhibiting a more severe phenotype of alcohol dependence and suffering from more comorbid psychiatric disease. Moreover, compliance and safety of disulfiram treatment was satisfactory in our study. These results are in line with data published recently by Ralevski *et al.* who demonstrated that the diagnosis of personality disorder did not essentially adversely affect alcohol outcomes (Ralevski *et al.*, 2007). Patients with comorbid borderline personality disorder did not have poorer response to medication *per se* than patients without diagnosis of a personality disorder (Ralevski *et al.*, 2007). However, the follow-up period in that placebo controlled trial was only 12 weeks (Ralevski *et al.*, 2007) compared to a mean duration of ther-

apy of 18.44 months in our study. Despite this much longer observation period, we did not find a high rate of adverse events. In particular, disulfiram hepatotoxicity was not observed since this most toxic and nickel-sensitivity-associated adverse effect is more common in women (Enghusen *et al.*, 1992; Chick, 1999), and our BPD patients were mainly female. Furthermore, no cases of severe alcohol disulfiram reaction occurred in our study, although this may reflect the relatively low doses of disulfiram used (standard treatment dose in our study 1.5–2.5 g/week). The low rates of adverse events have probably contributed to the good compliance and adherence to the treatment in our study. We recognize that a key feature for the good outcome of our eight patients might be the combination of disulfiram with personal contact with a physician three times per week, which is a means to facilitate structured, frequent therapeutic contacts that enhance self-esteem and permits a relatively long-term stable therapeutic relationship. This may address a key symptom of borderline disorders, namely distress at the breaking off of relationships. Irrespective of the psychotherapeutic effects, high-frequency contact between patient and professional is indispensable for an up-to-date and safe treatment in every disulfiram-treated patient (Krampe *et al.*, 2006a).

Krampe *et al.* have investigated treatment outcome of supervised disulfiram therapy and found a positive association between worse treatment outcome and the number of past therapies as well as comorbid axis II disorder (Krampe *et al.*, 2006a).

Diehl *et al.* (2010) found that patients with a long history of alcoholism addiction showed a longer time to the first relapse when treated with supervised disulfiram than patients treated with acamprosate. As long as there are no other specific and effective pharmacological relapse prevention therapies available, supervised disulfiram seems to improve alcohol drinking outcomes in patients suffering from comorbid borderline personality disorder, especially in patients with high compliance (Neto *et al.*, 2007). Nevertheless, we believe that patients with acute major depression, acute suicidal tendency and self-inflicted injuries should not be offered disulfiram. On the other hand, we recognize that depression, suicidal tendency and self-inflicted injuries are often caused by alcohol intoxication in patients with borderline personality disorders, and in our small study no patient threatened or actually self-harmed.

The validity of uncontrolled case observations is limited. However, they are useful for first assumptions about a drug's efficacy and tolerability. In our study, we demonstrated effectiveness in alcohol drinking outcomes, good tolerability and safety in patients with comorbid borderline personality disorder and alcohol dependence. In addition to pharmacotherapy, it is also important to keep in mind that a combination of psychosocial treatments, dialectic behaviour therapies, group therapies and contingency management therapies are especially efficient and necessary for a successful therapy of these severely affected patients.

Limitations of the study

This case series does not provide a control group. Therefore, it cannot be stated that disulfiram treatment is superior to standard treatment. The number of cases is low; therefore, we cannot exclude that in other patients more or other adverse

effects occur. Furthermore, our patients were treated with a variety of other psychotropic medications that may have influenced the outcome. As expected, our sample consisted of predominately females; thus, the results cannot be readily extrapolated to men.

Nevertheless, the special strength of this case series is the performance in a 'natural' outpatient setting with standard support of the general health system.

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