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Efficacy of sodium oxybate plus disulfiram for the maintenance of alcohol abstinence in treatment-resistant patients with alcohol use disorder: a multicentre retrospective study

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Abstract

Introduction. Disulfiram (DF), acamprosate, naltrexone, baclofen and sodium oxybate (SO) are currently the medications approved for the treatment of alcohol use disorder (AUD). In this context, combined pharmacological interventions and sex differences are an interesting area in the treatment of non-responder AUD patients.

Aim. To evaluate the efficacy of SO in combination with DF in maintaining alcohol abstinence in patients with AUD who failed to achieve abstinence either with SO or DF alone.

Methods and results. 126 detoxified AUD patients, previously treated with only SO or DF, were retrospectively enrolled from 2018 to 2022. At the end of treatment, a higher number of females than males (74.1% *vs* 66.3%: p=0.03) maintained continuous abstinence from alcohol, and all the females responded completely or partially to the treatment.

Conclusions. This study shows that the combination of SO and DF may be considered a further pharmacological opportunity for AUD patients (particularly in females) who do not respond to mono-therapy.

Key words

- alcohol use disorder
- combined pharmacological treatment
- disulfiram
- sodium oxybate
- sex differences

INTRODUCTION

Alcohol consumption is responsible for approximately 5.9% of all deaths (3.3 million) accounting for 5.1% of the global disease burden [1]. In addition, alcohol consumption can lead to roughly 200 different diseases (including fourteen types of cancer) and can be addictive with the risk of triggering alcohol use disorder (AUD) [1]. AUD has a worldwide prevalence of 20-30% or 10-15% in men and women, respectively [1]. Although AUD is an important public health concern, it remains severely undertreated with only 7% of adults with AUD in the US [2] and less than 10% in Europe [3] receiving pharmacotherapy and/or psychotherapy.

Currently, disulfiram (DF), acamprosate, and naltrexone are medications approved by both the FDA and EMA, and nalmefene approved solely by the EMA

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for the treatment of AUD. In addition, baclofen is approved by the French agency for the treatment of AUD, and sodium oxybate (SO) is approved by the Italian agency for the treatment of alcohol withdrawal syndrome. In this context, combined pharmacological interventions are of interest for treating non-responder AUD patients [4]. A recent systematic review has shown that so far, no drug combinations have significantly better beneficial effects than individual medications. However, targeting combined pharmacological interventions to address specific symptoms of AUD may prove more successful [5].

DF was the first medication approved by the FDA for the treatment of AUD, back in 1951. It acts as a deterrent, i.e., an aldehyde dehydrogenase inhibitor blocking the metabolism of alcohol and increasing acetaldehyde concentration. Acetaldehyde, a toxic metabolite of ethanol, produces an alcohol-induced aversive response, characterized by nausea, vomiting, sweating, flushing, and heart palpitations [6, 7]. The administration of disulfiram under supervision by a referred family member to ensure adherence, is associated with significantly better success rates compared to non-supervised treatment [6, 7].

SO, or the sodium salt of gamma-hydroxybutyrate, is approved in Italy for the treatment of alcohol withdrawal syndrome and, until 2022 for the maintenance of alcohol abstinence in AUD patients [6, 7]. SO acts on the GABA system both directly as a $GABA_B$ agonist and indirectly through SO-derived GABA [6, 7]. It has an alcohol-mimicking effect. A Cochrane meta-analysis found that SO was effective compared to placebo in the treatment of alcohol withdrawal syndrome and in preventing relapses in previously detoxified participants [8].

Many studies using combined medications for the treatment of AUD have been published without investigating in-depth gender differences [5], and only one study using DF in combination with SO for the treatment of AUD has been carried out. In this study, 52 treatment-resistant AUD patients irrespective of achieving total alcohol abstinence, remained in treatment for a statistically significant longer time when SO was co-administered with DF than with SO alone [9].

Thus, our study aims to evaluate the efficacy of SO plus DF in maintaining alcohol abstinence in patients with AUD who failed to achieve abstinence with either SO or DF alone.

METHODS

We retrospectively enrolled 126 detoxified AUD patients consecutively admitted over a period of 24 months to four outpatient clinics: two in the north (Lugo and Ravenna), one in the center (Pisa) and one in the south (Soverato) of Italy. AUD was defined according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria [10]. All patients failed to achieve abstinence either with SO (101 patients) or DF (25 patients) alone, so they were treated with oral doses of SO (50-100 mg/kg of body weight, *tid*), and DF (250 mg daily) in combination for 12 weeks. SO and DF were administered by a referred family member. Each subject underwent weekly outpatient visits for 12 weeks, recording the degree of abstinence from alcohol and the amount of any daily alcohol intake (expressed as standard US drinks; one standard US drink =12 g of absolute alcohol) [1]. Based on the treatment response, patients were divided into three groups: total responders (complete alcohol abstinence), partial responders (reduction of at least 30% of alcohol intake), and non-responders (incomplete abstinence or reduction of <30% of alcohol intake). These parameters were assessed on the basis of participant self-evaluation, the interview with a family member and alcohol concentration in the blood and saliva (Assay for the Qualitative Detection of Alcohol in Saliva; Alcohol OnSite, Varian Inc., USA). Laboratory parameters of alcohol abuse – aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltraspeptidase (GGT), and mean red blood cell volume (MCV) – were assessed (*Figure 1*) at the beginning of treatment and at the end of the third month. A more accurate investigation of the quantity of the abused SO or the possible association of DF and alcohol was carried out with the assistance of patients and their family members, to whom the SO and DF had been entrusted. In addition to weekly counselling sessions and pharmacological therapy, self-help groups, such as alcoholics anonymous (AA) and social services, were recommended.

The study was carried out in accordance with the ethical standards of the 1975 Declaration of Helsinki, as revised in 2013.

Statistical analysis

The sociodemographic and medical characteristics of the sample were expressed as mean and standard deviations (SD) or median and interquartile range (IQR) for quantitative variables (based on their normal or non-normal distribution), and as absolute and relative frequencies for categorical variables. The characteristics and treatment outcomes of the participants were compared for men and women using the Student t-test, the Mann-Whitney U-test, and the Chi-square test, as appropriate. Intra-individual changes in biochemical parameters from the beginning of treatment to the 3-month assessment were evaluated using the non-parametric Wilcoxon test for paired samples. All analyses were performed using R statistical software. P-values less than 0.05 were considered statistically significant.

RESULTS

The sample included 126 patients (99 males and 27 females) with AUD, whose clinical and demographic characteristics are shown in *Table 1*. Males and females did not differ in terms of age and education, while the former were more likely to have a longer alcohol addiction, a higher alcohol intake, more use of illegal drugs, less psychiatric co-morbidity, and higher Cloninger type II alcoholism (*Table 1*).

At the end of treatment, significant differences in the response rate were observed between males and females (p=0.03) (*Table 2*). In particular, continuous abstinence from alcohol was maintained by 85 patients (68%), with a higher frequency in females than males (74.1% *vs* 66.3%) and the same trend was observed in the 22

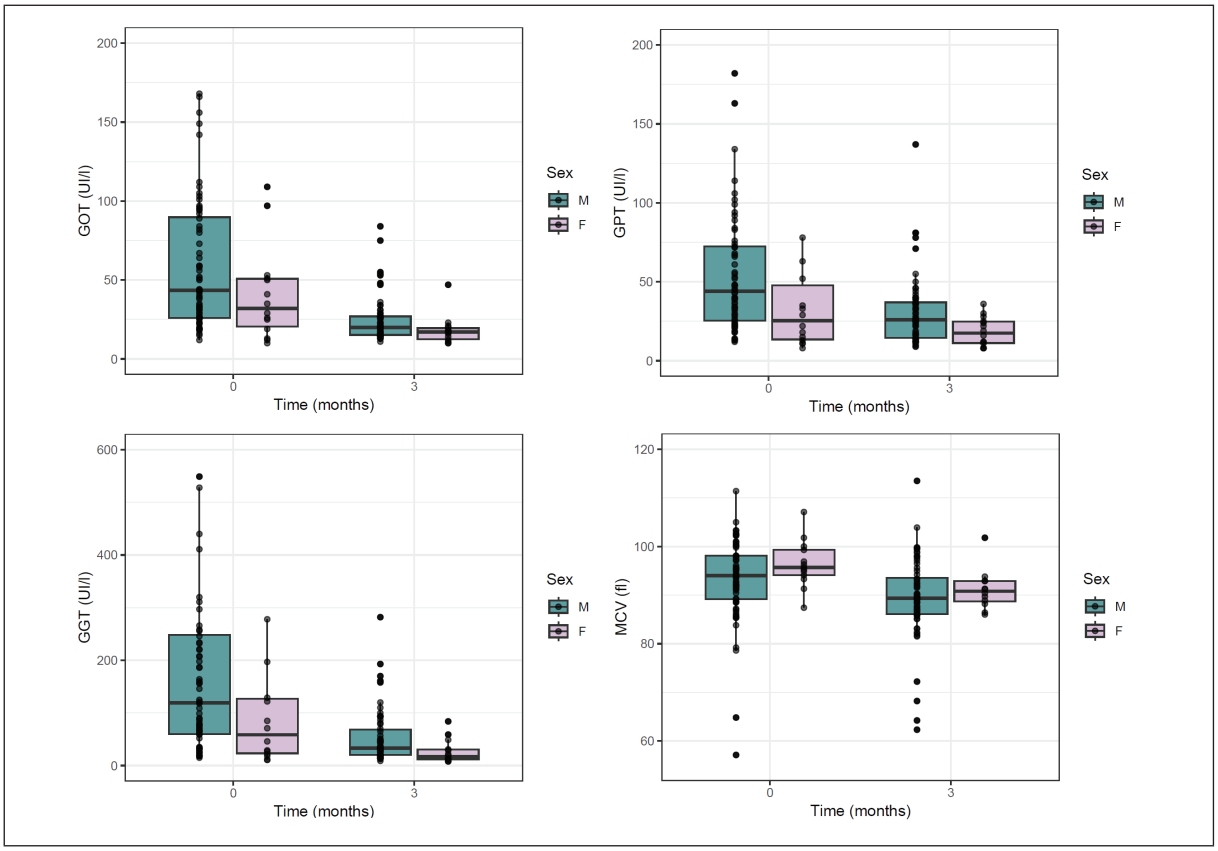

Figure 1
Difference between the beginning (T0) and end of treatment (T1) for the laboratory markers of alcohol misuse. A statistically significant difference between T0 and T1 was found for all the parameters and for both males and females (males: p<0.001 for GOT, GPT, GGT, and MCV; females: p=0.005 for GOT, p=0.02 for GPT, p=0.002 for GGT, and p=0.02 for MCV).
GOT: glutamic-oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GGT: γ-glutamyltraspeptidase; MCV: mean cellular volume.

Table 1
Characteristics of the total sample and by sex

	Overall (n=126)	M (n=99)	F (n=27)	p-value
Age: mean (%)	45.56 (9.57)	46.12 (9.72)	43.48 (8.87)	0.205
Education: subjects (%)				0.304
primary school	83 (68.0)	66 (68.0)	17 (68.0)	
secondary school	35 (28.7)	29 (29.9)	6 (24.0)	
degree	4 (3.3)	2 (2.1)	2 (8.0)	
Units of alcohol: mean (SD)	10.97 (5.69)	11.84 (5.37)	7.78 (5.81)	0.001
Time of alcohol intake: mean of years (SD)	14.94 (8.52)	16.01 (8.47)	11.00 (7.62)	0.006
Use of illicit drugs: subjects (%)	35 (28.0)	32 (32.7)	3 (11.1)	0.049
Previous use of illicit drugs subjects (%)	15 (41.7)	14 (43.8)	1 (25.0)	0.858
Illicit drugs: subjects (%)				0.001
heroin	10 (27.8)	9 (27.3)	1 (33.3)	
cocaine	13 (36.1)	13 (39.4)	0 (0.0)	
cannabis	10 (27.8)	10 (30.3)	0 (0.0)	
others	3 (8.3)	1 (3.0)	2 (66.7)	
Organic comorbidity: subjects (%)	36 (29.3)	28 (29.2)	8 (29.6)	1
Psychiatric comorbidity: subjects (%)	55 (45.1)	38 (39.6)	17 (65.4)	0.034
Cloninger type II of alcoholism: subjects (%)	60 (50.8)	55 (58.5)	5 (20.8)	0.002

M: male; F: female; n: number.

Table 2
Treatment outcomes of the total sample and by sex

	Overall (n=126)	M (n=99)	F (n=27)	p-value
Side effects (%)				0.055
no	87 (70.2)	73 (75.3)	14 (51.9)	
yes, tolerable	35 (28.2)	23 (23.7)	12 (44.4)	
yes, drop-out	2 (1.6)	1 (1.0)	1 (3.7)	
Type of side effects				
nausea	4 (3.2)	3 (3.0)	1 (3.7)	1
abdominal pain	6 (4.8)	2 (2.0)	4 (14.8)	0.024
dizziness	15 (11.9)	10 (10.1)	5 (18.5)	0.389
paresthesia	5 (4.0)	2 (2.0)	3 (11.1)	0.112
sonnolence	5 (4.0)	5 (5.1)	0 (0.0)	0.525
sexual alterations	5 (4.0)	5 (5.1)	0 (0.0)	0.525
craving for sodium oxybate	4 (3.2)	3 (3.0)	1 (3.7)	1
Outcome (%)				0.039
total responders	85 (68.0)	65 (66.3)	20 (74.1)	
partial responders	22 (17.6)	15 (15.3)	7 (25.9)	
not responders	18 (14.4)	18 (18.4)	0 (0.0)	

M: male; F: female; n: number.

patients (17.6%) who reduced their alcohol intake by more than 30% (25.9% of females *vs* 15.3% of males) (*Table 2*). Overall, all 27 females included in the study had a complete or partial response to the treatment (20 achieved abstinence and 7 reduced alcohol intake).

At the end of treatment, all laboratory markers of alcohol misuse both for males and females were significantly reduced (*Figure 1*). The incidence of side effects was higher in females than males, although the difference was not statistically significant (p=0.055, *Table 2*). Indeed, women had a higher frequency of tolerated adverse effects (44.4% *vs* 23.7%) or leading to drop-out (3.7% *vs* 1%) than men, especially concerning abdominal pain (14.8% *vs* 2%, p=0.024). The two patients who dropped out for side effects reported paresthesia.

At the end of treatment, four individuals (3.2%) – 3 males (3.0%) and one female (3.7%) – developed craving for SO. One (male) eluded the control of his family member to whom SO was entrusted and voluntarily abused SO, increasing the dose two- to three-fold. However, SO-abuse was an isolated episode following the thorough explanation of the toxic consequences of SO-abuse provided during weekly counselling sessions. No patient developed withdrawal symptoms at SO discontinuation. The patient who abused SO manifested sedation and sleepiness. No additional sedative effects due to alcohol/SO interaction were observed in patients failing to maintain abstinence. In addition, of the 22 patients (17.6%) who did achieve total abstinence, 8 used alcohol in association with DF with tolerable flushing and nausea not leading to quit the treatment, while the other 14 patients, to avoid the side effects induced by the association of alcohol with DF, used alcohol without taking DF. Finally, the 18 non-responder males, due to the possibly serious side effects they would likely have undergone with the continuous use of alcohol in association with DF [11] were encouraged to discontinue treatment, offering other pharmacological options (acamprosate, naltrexone or baclofen) [11].

DISCUSSION

This study demonstrates the efficacy of SO and DF in maintaining complete alcohol abstinence in almost 70% of patients resistant to monotherapy. In particular, 100% of females responded positively with 74.1% achieving complete alcohol abstinence, and 25.9% reduced alcohol intake by more than 30%; only males were non-responders. Psychiatric comorbidity and Cloninger I type of alcoholism was more frequent in females than males, while males had higher alcohol consumption, longer alcohol use, and more use of illegal drugs than females.

The high percentage of complete abstinence in the group as a whole is a promising result, confirmed by the significant reduction of all laboratory markers of alcohol misuse both in males and females. However, data for total abstinence are not comparable with previous experience with SO and DF [9] since the main aim of the previous study was continued treatment, irrespective of achieving complete alcohol abstinence. In addition, concerning combined therapy studies, this is the first to evaluate possible sex difference. Of note, the number of females recruited by studies involving the pharmacological treatment of AUD is usually very low [12]. Furthermore, the high rate of abstinence is likely due to the different action of the two drugs. Indeed, SO with its alcohol-mimicking effect, acts as a replacement therapy for subjects who did not achieve abstinence with DF alone, while DF, considered an aversive drug, acts as a deterrent in patients who did not achieve abstinence

with SO alone. These two types of mechanism cover the major symptoms of patients affected by AUD: the discomfort induced by the discontinuation of alcohol intake and the fear of a slip or relapse.

Considering the observed sex differences in our sample, in accordance with the current literature, we found a higher percentage of females with psychiatric comorbidities, and a higher frequency of males with Cloninger type II alcoholism [13-15]. The classification of Cloninger belongs to an old but still useful differentiation of AUD typologies. Cloninger type I affects both men and women, requires genetic as well as environmental predisposition, commences late in life after years of heavy drinking, can take on either a mild or severe form, and has a characteristic personality trait (harm avoidance). Cloninger type II, in contrast, affects mainly the sons of male alcoholics, often beginning during adolescence or early adulthood, and is characterized by moderate or severe intensity, with a different characteristic personality trait (novelty seeking) [15, 16].

Another interesting finding is that the side effect that led to two cases of drop-out was paresthesia. This is likely related to DF, one of the most frequent side effects documented during treatment with this drug [6, 7, 11]. In addition, serious side effects have not been recorded during the use of DF in combination with alcohol, likely due to abandoning the drug the day the patient decided to drink alcohol; however, in order to avoid stronger and life-threatening side effects, DF was discontinued in the 18 males who continued daily alcohol consumption in combination with DF. Indeed, because DF blocks the effect on the aldehyde dehydrogenase enzyme, the use of alcohol during treatment with DF induces an increase in acetaldehyde concentration with important side effects (acetaldehyde syndrome) characterized by facial flushing, nausea, vomiting, and further severe effects such as hypotension, arrhythmias, and respiratory depression [6, 7, 11].

Another important issue is craving and the potential for the abuse of SO [6, 7]. These effects may limit SO use, although, at therapeutic doses, they appear to be relatively rare in clinical trials [6, 17, 18]. Indeed, craving and the abuse of SO are more frequent in patients with psychiatric comorbidities or poly-drug use [17, 18]. In our study, although 28% and 45% of subjects respectively were diagnosed with poly-substance abuse and psychiatric comorbidity, craving and abuse were very low, respectively at 3.2% and 0.7%; the patient who abused SO was diagnosed with borderline personality disorder, confirming the risk of abuse in this kind of patient [16].

A further concern is the prescription of SO. All our data are for patients treated for relapse prevention before 2018. In 2018 the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) modified the clinical prescription of SO leaving only the indication for the treatment of alcohol withdrawal syndrome, removing the indication for maintaining abstinence. Despite this, important data regarding the use of SO for maintaining and for relapse prevention have been published in recent years. Specifically, a meta-regression analysis has shown that in studies with alcohol-dependent patients, a high-severity population and lengthier treatment were associated with larger SO effects [19]. Moreover, the results of a phase IIb double-blind, randomized, placebo-controlled trial for the maintenance of abstinence demonstrated a significant and clinically relevant sustained effect of SO on cumulative abstinence duration (+32.4 days, p=0.014) compared to a placebo during the 6-month treatment period [20], and *post-hoc* analysis showed that treatment with SO was associated with a significant improvement in severe AUD patients [21]. The significance of these results may contribute to scientific discussion regarding the possible review of the clinical indications for SO.

This study has some limitations. First, this is a retrospective study based on medical records; therefore, we could only use data collected during routine practice. The second limitation is the lack of a control group, which would have given the study greater impact, confirming or disproving the efficacy of the combined therapy compared to the use of a single medication. However, all patients were previously unsuccessfully treated with one or other of the drugs, singly, so it seems likely that combined therapy is more efficient in achieving alcohol abstinence or the reduction of alcohol intake. Third, carbohydrate-deficient transferrin was not collected. This marker is considered the most sensitive and specific marker of alcohol misuse [22]. Still, it is important to underline that, in our study, all markers of alcohol misuse fell significantly, confirming complete abstinence or the reduction of alcohol intake in total and partial responders.

CONCLUSIONS

In conclusion, this study suggests that SO and DF may be considered a pharmacological option for the treatment of AUD patients (particularly females) who are non-responders to monotherapy. As previously demonstrated [5], combined pharmacological therapy for the treatment of AUD may be directed to targeted symptoms or populations when monotherapy fails. This is highly significant since patients who failed to achieve abstinence or to reduce alcohol intake with one medication may be discouraged and abandon treatment; the addition of another drug may help patients to stay in treatment [9, 23], and may increase complete abstinence from alcohol or drastically reduce alcohol intake. Thus, controlled clinical trials to evaluate the efficacy of targeted combined pharmacological therapy are now warranted.

Authors' contributions

The Authors confirm their contribution to the paper as follows: study conception and design: FC, TV; papers collection: FC, TV, AGIM, FM, GC, LL, AC, FM, GC, GT, ES, SV, RDG; analysis and interpretation of results: FC, CT. All Authors reviewed the results and approved the final version of the manuscript. All Authors approved the final manuscript.

Conflict of interest statement

The Authors declare no conflict of interest.

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