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Sodium oxybate and acamprosate association for maintenance of alcohol abstinence: a case series

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Abstract

Background. Disulfiram, acamprosate (ACM), naltrexone, and nalmefene are medications currently approved for the treatment of Alcohol Use Disorder (AUD). Baclofen and sodium oxybate (SO) have been approved for the treatment of AUD and alcohol withdrawal syndrome in France and Italy, respectively. However, concerning the effectiveness of combined therapies for AUD, data from the current literature are contrasting.

Aims. To investigate the outcomes of combined therapy of SO and ACM for the maintenance of alcohol abstinence.

Methods. A sample of 48 AUD patients consecutively enrolled and treated with SO (50-100 mg/kg of body weight, t.i.d.) plus ACM (666 mg three times daily; with dosage reduced in patients with body weight <60 kg) was observed for 12 weeks.

Results. At the 3-month visit, continuous abstinence from alcohol was maintained by 34 patients (70.8%). Fifteen patients (31.3%) reported side effects like nausea, dizziness, and abdominal pain, with no significant differences between abstinent and not abstinent patients.

Conclusion. SO plus ACM may be an effective and safe pharmacological combination for maintaining alcohol abstinence in AUD patients. Future *ad hoc* clinical trials are needed to test this therapeutic association for AUD treatment.

Key words

- alcohol use disorder
- combined pharmacological treatment
- acamprosate
- sodium oxybate

INTRODUCTION

Alcohol consumption is responsible for 5.9% of all deaths (3.3 million), accounting for 5.1% of the global disease burden [1]. Alcohol Use Disorder (AUD) has a European and US adult population prevalence of 7-10% [1]. Currently, disulfiram, acamprosate (ACM), and naltrexone are medications approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), while nalmefene has been approved only by EMA for the treatment of AUD [2]. In addition, baclofen has been authorized by the French agency for the treatment of AUD [2, 3], and sodium oxybate (SO) has been approved by the Italian agency for the treatment of alcohol withdrawal syndrome [4]. The actual efficacy of these combined pharmacological therapies raised debate among experts as these drugs yielded contrasting results [5].

SO, or the sodium salt of gamma-hydroxybutyrate, acts directly on the gamma-aminobutyric acid (GABA) system as a $GABA_B$ agonist and indirectly through SO-derived GABA [4, 6, 7], and exhibits an alcohol-mimicking effect. Compared to placebo, SO was effective in the treatment of alcohol withdrawal syndrome and in preventing relapses in previously detoxified participants [8].

ACM shows a neuroprotective effect, which can be explained through the antagonistic activity on the

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N-methyl-D-aspartate (NMDA) glutamate receptor, and subsequent reduction of the excessive intracellular calcium flow [9]. This mechanism improves dysphoria, often identifiable in patients affected by AUD, and indirectly reduces alcohol craving and consumption [10].

So far, the few published studies involving SO in combination with other drugs showed positive results in the maintenance of alcohol abstinence and the prevention of relapse [11-14]. Similarly, limited evidence has been produced about ACM in association with other drugs [10]. However, no study examined the possible efficacy of the combination SO with ACM in patients with AUD. Therefore, our case series aimed to evaluate the outcomes of a combined therapy of SO plus ACM in maintaining alcohol abstinence in a cohort of patients with AUD.

METHODS

We enrolled 48 AUD patients consecutively admitted over 24 months to the Unit of Alcohol Addiction Treatment, SerD, Caserta and in the Centre for the Study and Treatment of Alcohol-Related Diseases, SS. Annunziata Hospital, Cento, Ferrara. AUD was defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria [15]. Patients with severe liver and/or renal failure were excluded. After the resolution of the acute phase of alcohol withdrawal syndrome [16], only patients with the persistence of symptoms of alcohol withdrawal were recruited. All recruited patients were treated with oral doses of SO (50-100 mg/kg of body weight, tid), and they needed the treatment with SO for at least 12 weeks. In addition, ACM (666 mg three times daily, reduced in those patients with a body weight <60 kg) was combined with SO for 12 weeks too. Each subject underwent weekly outpatient visits for 12 weeks, recording the degree of abstinence from alcohol and the amount of daily alcohol intake (expressed as standard US drinks; one standard US drink = 12 g of absolute alcohol) [1]. Complete abstinence was assessed based on interviews with patients and their relatives, and by measuring ethyl glucuronide in urine [17]. Laboratory parameters related to alcohol abuse – aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), and mean red blood cell volume (MCV) – were assessed at the beginning and after three months of treatment. An accurate investigation on the amount of abused SO was carried out with the assistance of patients and their family members to whom the SO had been entrusted. In addition to weekly counseling sessions and pharmacological therapy, self-help groups, such as Alcoholics Anonymous and social services, were recommended.

The study was performed in accordance with the ethical standards of the 1975 Declaration of Helsinki, as revised in 2013, and all participants gave verbal informed consent.

Statistical analysis

The characteristics of the study participants were expressed as median and interquartile range (IQR) for quantitative variables (due to the non-normal distribution) and as count and percentages for categorical variables. Sociodemographic and treatment-related variables were compared between participants who were abstinent *vs* those who were not abstinent at the end of the observation period using the Mann-Whitney U test and the Chi-square or Fisher test, as appropriate. Intra-individual changes in laboratory parameters from the start of treatment to the 12-week visit within the groups of abstinent and not abstinent individuals were assessed through the non-parametric Wilcoxon test for paired samples. All analyses were performed using the IBM SPSS version 25.0 statistical software. All analyses were two-tails, and a p-value <0.05 was defined as statistically significant.

RESULTS

The sample included 48 AUD patients (34 males and 14 females) with a median age of 47.5 years, whose clinical and demographic characteristics are shown in *Table 1*. Patients who resulted abstinent and those who were not abstinent at the 3-month visit did not differ in terms of age, education, baseline units of alcohol intake, duration of alcohol consumption, and laboratory markers of alcohol misuse, while the former group was more likely to use illegal drugs at the first visit *(Table 1)*.

At the 3-month visit, continuous abstinence from alcohol was maintained by 34 patients (70.8%). During the observation period, all laboratory markers of alcohol misuse significantly decreased both in abstinent and not abstinent patients *(Table 2)*. Concerning side effects *(Table 3)*, 15 (31.3%) patients reported mainly nausea (20.8%), dizziness (8.3%), and abdominal pain (2.1%), without significant differences between abstinent and not abstinent patients. A significantly higher dropout rate was observed in patients who were not abstinent than abstinent (50% *vs* 5.9%). At the end of treatment, no patient developed cravings or episodes of abuse of SO, and none showed withdrawal symptoms at SO discontinuation. No additional sedative effects due to alcohol/SO interaction were observed in patients failing to maintain abstinence.

DISCUSSION

To our knowledge, this is the first case series that evaluated the outcomes of the combined therapy with SO and ACM for AUD. In particular, the present study suggests that the association of these drugs may be effective in maintaining complete alcohol abstinence in almost 70% of AUD patients. These results align with previous experiences of SO combined with other compounds. Indeed, we previously showed that the degree of abstinence ranged from 68% to 72% in patients treated with SO plus DF [12] and SO plus NTX [11], respectively. Moreover, the therapeutic combination between SO and ACM seems more promising than other pharmacological regimens. For instance, recent studies found that the abstinence rate was about 50% in patients treated with ACM plus NTX, while considering therapies with SO or ACM alone, it did not overcome 40% [18]. Of note, the high number of patients (almost two-thirds of the sample) achieving complete abstinence at the end of treatment exhibited a sig-

Table 1
Baseline characteristics of the patients in the sample as a whole and by treatment outcome

Characteristics	All (n=48)	Not abstinent (n=14, 29.2%)	Abstinent (n=34, 70.8%)	p-value
Age	47.5 (41.25-54)	47.5 (41.25-53)	47.5 (40.75-54.5)	0.81
Sex (male)	34 (70.8)	9 (64.3)	25 (73.5)	0.52
Scholarity				0.11
Primary	19 (39.6)	4 (28.6)	15 (44.1)	
Secondary	24 (50)	10 (71.4)	14 (41.2)	
Degree or above	5 (0.4)	0 (0)	5 (14.7)	
Pre-treatment UA/day	11.5 (8.25-16)	11 (8-16)	11.5 (9-16)	0.75
Duration of addiction (months)	18 (10-26.5)	16.5 (10.75-28.25)	18 (10-25)	0.75
Current or past substances use				0.02
Current	3 (6.3)	3 (21.4)	0 (0.0)	
Past	12 (25)	3 (21.4)	9 (26.5)	
Type of substance used				0.96
Heroin	3 (6.3)	1 (7.1)	2 (5.9)	
Cocaine	5 (10.4)	2 (14.3)	3 (8.8)	
Cannabis	7 (14.6)	3 (21.4)	4 (11.8)	
Psychiatric comorbidities	16 (33.3)	6 (42.9)	10 (29.4)	0.37
Biochemical parameters				
GGT	97.5 (55.75-188.75)	162.5 (59.5-573)	90.5 (54.5-167)	0.21
GPT	39.5 (23.25-78.25)	46 (30-77.75)	32 (22-81.5)	0.11
GOT	31 (22-78.25)	51 (29.75-80.75)	25.5 (20.75-82)	0.10
MCV	95.5 (92-102)	102 (94.75-107.25)	94.5 (91.8-100)	0.02

UA: unit of alcohol; GGT: γ-glutamyl transpeptidase; GPT: glutamic pyruvic transaminase; GOT: glutamic oxaloacetic transaminase; MCV: mean red blood cell volume.

Table 2
Changes in biochemical parameters and alcohol intake in abstinent (n=34) and not abstinent (n=14) individuals at the 3-month control

	Time 0	Time 1	ΔT1-T0	p-value
GOT				
Abstinent	25.5 (20.75-82.0)	16.5 (14.75-21.5)	-11.5 (- 56.75, -3)	<0.001
Not abstinent	51 (29.75-80.75)	22 (20-36)	-28 (- 44.25, -9.50)	0.001
GPT				
Abstinent	32 (22-81.5)	16.0 (13-22.25)	-14.5 (-49, -7)	<0.001
Not abstinent	46 (30-77.75)	26.5 (18.50-36.5)	-19 (-48, -12.5)	0.001
GGT				
Abstinent	90.5 (54.5-167)	28 (18.75-33)	-66 (-141.5, -27.25)	<0.001
Not abstinent	162.5 (59.5-573)	56 (28-112.75)	-60 (-468.25, -29.5)	0.001
MCV				
Abstinent	94.50 (91.75-100)	88 (86.75-91.25)	-5.50 (-8.25,-4)	<0.001
Not abstinent	102 (94.75-107.25)	95 (90.50-99)	-5.50 (-12.75,-3)	0.001
Alcohol (Unit/day)				
Abstinent	11.50 (9-16)	0 (0.0)	-11.5 (-16, -9)	<0.001
Not abstinent	11 (8-16)	2.00 (1.75-3.25)	-9.5 (-13.25, -6)	0.001

GGT: γ-glutamyl transpeptidase; GPT: glutamic pyruvic transaminase; GOT: glutamic oxaloacetic transaminase; MCV: mean red blood cell volume.

Table 3
Treatment outcomes of the patients involved

Treatment outcomes	All (n=48)	Not abstinent (n=14, 29.2%)	Abstinent (n=34, 70.8%)	p-value
Drop-out	9 (18.8)	7 (50)	2 (5.9)	<0.001
Side effects	15 (31.3)	5 (35.7)	10 (29.4)	0.669
Type of effects				0.662
Nausea	10 (20.8)	4 (28.6)	6 (17.6)	
Abdominal pain	1 (2.1)	0 (0)	1 (2.9)	
Dizziness	4 (8.3)	1 (7.1)	3 (8.8)	

nificant reduction of all laboratory markers of alcohol misuse. In the not abstinent group, we also observed a significant decrease in all laboratory markers of alcohol misuse confirming that the reduction of alcohol intake improved liver function too.

The high potential of the efficacy of this treatment is likely ascribable to the different actions of SO and ACM. These medications affect the two major signaling systems, i.e. GABA and NMDA both involved in AUD. SO has an alcohol-mimicking effect on GABA receptors and acts as a replacement therapy, while ACM is an antagonist of glutamate and modulates the upregulation of the NMDA system.

An important issue to be considered is craving and the potential abuse of SO [6, 7]. In our study none of the treated patients showed craving for SO. It is well known that both abuse of and craving for SO may limit the use of this drug, although clinical trials suggested that these effects are relatively rare at therapeutic doses [7, 19, 20]. Craving and the abuse of SO are more frequent in patients with psychiatric comorbidities or poly-drug use [19, 20]. In the case series herein reported, conversely to previous experience [19], craving and abuse were not documented although about one-third of patients experienced previous or current substance abuse.

A further aspect that needs to be considered is the prescription of SO. In Italy, SO has been used for over 30 years for the treatment of AUD in the absence of specific indications [21]. 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 from alcohol and the prevention of relapse. For this reason, in the guidelines of the treatment of AUD recently published on the Italian National Guidelines System, SO has been included only with the indication for the treatment of alcohol withdrawal syndrome since it is an off-label medication for the maintenance of alcohol abstinence and the prevention of relapse [21]. Indeed, after the resolution of the acute phase of alcohol withdrawal syndrome [16], all reported patients in our case series showed the persistence of symptoms of alcohol withdrawal which allowed the treating physicians to use SO for at least 12 weeks. In favor of the safety and efficacy outside the specifically authorized use for the treatment of alcohol withdrawal syndrome, essential data on the use of SO for maintaining alcohol abstinence and relapse prevention have been recently published. At this regard, a meta-regression analysis showed that SO was more effective in AUD patients with higher severity, and undergone longer treatments [22].

In conclusion, this case series suggests that SO and ACM are safe and may be effective in patients with AUD. Well-designed, controlled clinical trials are needed to establish whether the combination of drugs might become a key step in the therapeutic approach to AUD.

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Conflict of interest statement

The Authors declare no conflict of interest.

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REFERENCES

1. World Health Organization. Global status report on alcohol and health and treatment of substance use disorders. Geneva: WHO; 2024.
2. Haber PS. Identification and treatment of alcohol use disorder. N Engl J Med. 2025;392(3):258-66. doi: 10.1056/NEJMra2306511
3. Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2023;1(1):CD012557. doi: 10.1002/14651858.CD012557.pub3
4. Guiraud J, van den Brink W. Sodium oxybate: A comprehensive review of efficacy and safety in the treatment of alcohol withdrawal syndrome and alcohol dependence. Int Rev Neurobiol. 2024;178:213-81. doi: 10.1016/bs.irn.2024.07.005
5. Naglich AC, Lin A, Wakhlu S, Adinoff BH. Systematic review of combined pharmacotherapy for the treatment of alcohol use disorder in patients without comorbid conditions. CNS Drugs. 2018;32(1):13-31. doi: 10.1007/s40263-017-0484-2

6. Antonelli M, Ferrulli A, Sestito L, Vassallo GA, Tarli C, Mosoni C, et al. Alcohol addiction - the safety of available approved treatment options. Expert Opin Drug Saf. 2018;17(2):169-77. doi: 10.1080/14740338.2018.1404025
7. Burnette EM, Nieto SJ, Grodin EN, Meredith LR, Hurley B, Miotto K, et al. Novel agents for the pharmacological treatment of alcohol use disorder. Drugs. 2022;82(3):251-74. doi: 10.1007/s40265-021-01670-3
8. Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database Syst Rev. 2010;(2):CD006266. doi: 10.1002/14651858.CD006266.pub2
9. De Witte P, Littleton J, Parot P, Koob G. Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action. CNS Drugs. 2005;19(6):517-37. doi: 10.2165/00023210-200519060-00004
10. Soyka M, Rösner S. Modern pharmacotherapy guidance for treating alcohol use disorders. Expert Opin Pharmacother. 2025;26(2):147-56. doi: 10.1080/14656566.2024.2445734
11. Caputo F, Addolorato G, Stoppo M, Francini S, Vignoli T, Lorenzini F, et al. Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomised comparative study. Eur Neuropsychopharmacol. 2007;17(12):781-9. doi: 10.1016/j.euroneuro.2007.04.008
12. Caputo F, Trevisan C, Vignoli T, Maremmani AGI, Montesano F, Carboni G, et al. Efficacy of sodium oxybate plus disulfiram for the maintenance of alcohol abstinence in treatment-resistant patients with alcohol use disorder: a multicentre retrospective study. Ann Ist Super Sanità. 2024;60(4):252-7. doi:10.4415/ANN_24_04_03
13. Maremmani AGI, Pani PP, Rovai L, Pacini M, Dell'Osso L, Maremmani I. Long-term γ-hydroxybutyric acid (GHB) and disulfiram combination therapy in GHB treatment-resistant chronic alcoholics. Int J Environ Res Public Health. 2011;8(7):2816-27. doi: 10.3390/ijerph8072816
14. Stella L, Addolorato G, Rinaldi B, Capuano A, Berrino L, Rossi F, et al. An open randomized study of the treatment of escitalopram alone and combined with gamma-hydroxybutyric acid and naltrexone in alcoholic patients. Pharmacol Res. 2008;57(4):312-7. doi: 10.1016/j.phrs.2008.03.001
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth Edition. Washington DC: American Psychiatric Publishing; 2013.
16. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? Addict Biol. 2010;15(2):169-84. doi: 10.1111/j.1369-1600.2009.00194.x
17. Jones AW. Brief history of the alcohol biomarkers CDT, EtG, EtS, 5-HTOL, and PEth. Drug Test Anal. 2024;16(6):570-87. doi: 10.1002/dta.3584
18. Cheng HY, McGuinness LA, Elbers RG, MacArthur GJ, Taylor A, McAleenan A, et al. Treatment interventions to maintain abstinence from alcohol in primary care: systematic review and network meta-analysis. BMJ. 2020;371:m3934. doi: 10.1136/bmj.m3934
19. Caputo F, Francini S, Stoppo M, Lorenzini F, Vignoli T, Del Re A, et al. Incidence of craving for and abuse of gamma-hydroxybutyric acid (GHB) in different populations of treated alcoholics: an open comparative study. J Psychopharmacol. 2009;23(8):883-90. doi: 10.1177/0269881108094620
20. Caputo F, Francini S, Brambilla R, Vigna-Taglianti F, Stoppo M, Del Re A, et al. Sodium oxybate in maintaining alcohol abstinence in alcoholic patients with and without psychiatric comorbidity. European Neuropsychopharmacology. 2011;21(6):450-6. doi: 10.1016/j.euroneuro.2010.12.005
21. Centro di Riferimento Alcologico Regione Lazio, Dipartimento Salute Mentale ASL Roma 1, Dipartimento di Epidemiologia del Servizio Sanitario Regionale – Regione Lazio ASL Roma 1. Linee guida trattamento del disturbo da uso di alcol. Roma: Sistema Nazionale Linee Guida dell'Istituto Superiore di Sanità; 2024.
22. Guiraud J, Addolorato G, Aubin HJ, Bachelot S, Batel P, de Bejczy A, et al. Sodium oxybate for alcohol dependence: A network meta-regression analysis considering population severity at baseline and treatment duration. Alcohol Alcohol. 2023;58(2):125-33. doi: 10.1093/alcalc/agac070