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Novel strategies to treat alcohol dependence with sodium oxybate according to clinical practice

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Abstract. – OBJECTIVE: The treatment of alcohol dependence (AD) with sodium oxybate (SMO) was introduced in Italy and Austria more than 20 years and 15 years ago respectively, and it is now widely employed. In addition to the data obtained from clinical trials, little information is available on specific clinical practices. Thus, the aim of this study was to present and discuss the results of a consensus meeting held after twenty years of using SMO in clinical practice in Italy.

MATERIALS AND METHODS: A validated questionnaire study was conducted to investigate the modalities of treatment of AD with SMO currently used in Italy. A group of four referees first drew up the questionnaire which was distributed to fifty experts in the field of alcohol use disorders. The questionnaire consisted of 125 items with five different modalities of response and two or three answer possibilities.

RESULTS: The results of this survey showed a broad consensus on some issues regarding, for example, the duration of treatment, and the dose regimen of the drug; however, some aspects of the treatment of AD with SMO still remain controversial.

CONCLUSIONS: This is the first consensus study investigating the use of SMO for the treatment of AD through the opinions gained in over twenty years of clinical practice provided by fifty Italian expert clinicians. A consensus on good practice for the correct administration of SMO has clearly emerged; these opinions, along with those derived from previous clinical investigations, will help physicians to use SMO in a better way. However, some issues remain controversial, and others remain unresolved.

Key Words:
Alcohol dependence, Treatment, Sodium oxybate, Clinical practice.

Introduction

Sodium Oxybate (SMO) is a physiological short-chain fatty acid structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA). SMO is located in the mammalian central nervous system (CNS), and binds to $GABA_B$ receptors[1,2] exerting an ethanol-mimicking effect[3-5]. In the United States, the FDA approved SMO as a Schedule III Controlled Substance to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy[6].

In Europe, SMO is used as an anaesthetic for intravenous anaesthesia in Germany, and has been used for the treatment of alcohol dependence (AD) in Italy, since 1992, and in Austria since 1999. It has been demonstrated that exogenous SMO suppresses alcohol withdrawal syndrome (AWS) in humans by activating $GABA_B$ receptors directly, and $GABA_A$ receptors once it is converted to GABA[7]. A recent Cochrane review showed that SMO (50 mg/kg/day) is more

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effective than placebo and as effective as benzodiazepines (BDZs) for the treatment of AWS[8]. In addition, a recent multicentre study (GATE 1) showed that SMO was as effective as oxazepam in the treatment of uncomplicated AWS[9]. Moreover, SMO is superior to naltrexone (NTX) and disulfiram (DF) in maintaining alcohol abstinence, and to DF in reducing alcohol craving[8]. An increase in efficacy can result from the association of SMO with other drugs. In fact, the combination of SMO and NTX was superior to either SMO or NTX in inducing and maintaining alcohol abstinence, which was achieved in almost 70% of alcoholics after 3 months of treatment[10]. Finally, the combination of SMO and DF induced and maintained alcohol abstinence for 6 months in 65% of alcoholic patients not responding to SMO treatment alone[11].

Some concern has been raised about the risk of developing addiction to, misuse or abuse of SMO, especially in patients with AD and poly-drug addiction and psychiatric co-morbidity (borderline personality disorder). However, clinical trials have shown that episodes of craving for and abuse of SMO in alcoholics are a very limited phenomenon (~10%) and cases of death have not been documented[12-14]. Thus, following simple rules of administration (i.e. not to exceeding 50-100 mg/kg/day, adequately fractioned; see below), SMO can be considered a safe and efficient drug for the treatment of AD, both for the management of AWS and the prevention of alcohol relapse[1,2,8,15-18].

SMO is available as oral formulation and its approved dosages range from 50 to 100 mg/kg/day divided into three daily administrations[17,18]. Besides the data obtained from clinical trials, some other relevant information may be derived from clinical practice. In fact, in order to improve the efficacy of the drug, the way in which SMO is administered is often adjusted according to the overall clinical condition and to the patient's response. In this respect, specific recommendations do not emerge from available studies; thus, a study investigating the use of SMO in current clinical practice is warranted. The aim of this study was to present and discuss the results of a consensus meeting held after twenty years of using SMO in clinical practice in Italy.

Materials and Methods

The way in which SMO is prescribed in the Italian Centres for the Treatment of Alcohol Dependence (CTAD) in clinical practice was assessed through a study by means of a standardised method questionnaire. A group of four referees chosen on the basis of their long-standing clinical experience in the treatment of AD with SMO first drew up the questionnaire which was distributed to fifty experts in the field of alcohol use disorders. These experts working in CTAD were homogenously distributed throughout Italy, and were selected on the basis of their experience in the use of SMO over a period of at least 20 years and of the number of treated patients (almost 20000 subjects per year). All fifty experts completed the questionnaire and met to discuss the results of the survey. Namely, the discussed topics were (1) therapeutic indications of SMO in clinical practice; (2) modalities of treatment with SMO; (3) adverse effects of SMO; (4) possibility of craving for and abuse of SMO; (5) possible association of pharmacological and (6) non-pharmacological treatment.

The meeting dedicated to the questionnaire set-up was held in Bologna in 2009. The resulting questionnaire consisted of 125 items with five different modalities of response and two or three answer possibilities: (1) no, yes; (2) no, sometimes, as a rule; (3) no, sometimes, often; d) I totally disagree, I partially agree, I totally agree; (4) no less, yes, no more. A classification of seven clusters of questions was added: 28 questions concerning the clinical indications for the use of SMO; 29 about the dosage and duration of treatment; 13 about dose fractioning of the drug; 15 about the combination with other medications; 13 about the entrustment of SMO and monitoring of patients; 21 about the onset of adverse effects and the risk of craving for and abuse of SMO; 6 about the association with non-pharmacological treatments.

Frequency distribution was analyzed for each cluster of questions. According to answers to every question, a threshold of at least 90% was considered as the cut-off level to be achieved to define: (1) clinical consensus (≥ 90%); (2) elements of controversy (< 90%).

Results

Besides the common indications derived from previous clinical trials[1,2,8,15-18] (Table I), some other relevant information emerged with a clear consensus regarding the following issues: (1) treating patients with SMO for a variable duration of

Table I. What it is widely known and demonstrated about SMO by pre-clinical and clinical studies.

- SMO is a short chain fatty acid that is structurally similar to GABA
- SMO appears to function as neurotransmitter and neuromodulator binding to GABA B receptors
- SMO has an alcohol-mimicking effect due to its role in inducing an increase in dopamine release
- Short half-life (25-30 minutes)
- Therapeutic dosage to suppress alcohol withdrawal syndrome: 50-100 mg/kg divided in three or six daily administrations
- Therapeutic dosage to prevent relapse: 50 mg/kg divided into three or six daily administrations
- Low risk of abuse (almost 10%) when SMO is administered at the recommended dosage under the supervision of a designated family member with continuous strict medical surveillance
- Risk of developing addiction to SMO in patients with poly-drug addiction and with psychiatric comorbidity (borderline personality disorders)

time according to improvement of patient motivation to abstain (consensus of 100%); (2) increasing the dosages of SMO until the craving for alcohol is suppressed (consensus of 98%); (3) SMO is not to be considered the "last chance" drug when no result has been achieved with other pharmacological and non-pharmacological treatments (consensus of 96%); (4) not waiting for abstinence from alcohol before introducing the treatment with SMO (consensus of 90%); (5) not avoiding SMO in patients treated with anti-HCV/HIV drugs or methadone (consensus of 90%); (6) efficacy of SMO is strictly connected with a counseling approach aimed at the prevention of relapses (consensus of 90%) (Table II).

Conversely, some issues remain full of controversy. In particular, it is still uncertain whether: (1) the "motivation" to abstain from alcohol can affect the efficacy of SMO (often = 72%; sometimes = 14%; no = 14%); (2) SMO can be avoided in patients with liver cirrhosis (no = 72%; sometimes = 28%; as a rule = 0%); (3) the craving for SMO occurs in chronic psychotic patients (no = 58%; sometimes = 30%; often = 12%); (4) the abuse of SMO is more frequent in patients seeking psychotropic effects (sometimes = 48%; often = 32%; no = 20%); (5) SMO should be entrusted to stabilized patients (as a rule = 42%; no = 34%; sometimes = 24%), to family members (sometimes = 48%; no = 34%; yes = 18%) or to friends (sometimes = 60%; no = 40%; as a rule = 0%); (6) the combination of SMO with BDZs can be dangerous (sometimes = 44%; no = 42%; often = 14%) or can induce bad outcomes (no = 42%; sometimes = 36%; often = 22%); (7) > 100 mg/kg/day of SMO can be prescribed (as a rule = 48%; sometimes = 38%; no = 14%); (8) SMO can be used in "harm reduction" (no = 54%; sometimes = 24%; often = 22%); (9) SMO can be prescribed both to Cloninger I type patients (as a rule = 40%; sometimes = 34%; no = 26%) and Cloninger II type patients (sometimes = 44%; as a rule = 30%; no = 26%) (Table III).

Discussion

This is the first study investigating the use of SMO for the treatment of AWS and of the maintenance of alcohol abstinence through the expert opinions gained in over 20 years of clinical practice provided by fifty clinicians working in 50 Italian CTADs.

In the last twenty years, several clinical trials aimed at investigating the efficacy of SMO in the treatment of AWS and in the prevention of relapses have been performed[2,8,17,18]. Data emerging from these studies have been very useful as guidelines for physicians involved in the pharmacological treatment of AD with SMO. Since

Table II. Novel strategies of good clinical practice for the treatment of alcohol dependence with SMO.

- Do not treat all patients for a fixed period of time, but for a period that varies from patient to patient according to their improvement in motivation to abstain
- Do not use low doses (< 50 mg/kg/day) to prevent the onset of craving for SMO, but use doses at which the patient can control his/her craving for alcohol, maintaining the maximum limit of 100 mg/kg/day
- Do not consider SMO as a drug to be used only when no result has been achieved with other pharmacological anti-craving approaches
- Do not wait for the patient to stop drinking before starting treatment with SMO
- Do not avoid the treatment with SMO in patients affected by HIV or HCV infections
- In association with the use of SMO, a psychosocial approach with counselling focused on the prevention of relapses is mandatory

Table III. Issues, regarding the use of SMO, remaining full of controversy.

- Can the "motivation" to abstain from alcohol affect the efficacy of SMO?
- Can SMO be avoided in patients with liver cirrhosis?
- Do craving for and abuse of SMO occur more frequently in patients seeking a psychotropic effects?
- Should SMO be entrusted to stabilized patients?
- Can more than 100 mg/kg/day of SMO be prescribed?
- Can SMO be used in "harm reduction"?
- Can SMO be prescribed independently of the typology of alcoholic patients?

some data emerging form this consensus confirmed those derived from previous clinical investigations, these do not need any further discussion. On the other hand, the present results have shown other significant information which, contrarily, needs to be discussed.

First, there is no agreement on the maximal duration of the treatment with SMO before its discontinuation. In clinical trials, SMO was administered from 3 up to 12 months[8,17,18]. The present study clearly showed that a maximum period of administration of SMO after maintenance of abstinence has been achieved cannot be identified. All interviewed clinicians stated that the decision to discontinue SMO mainly depends of the improvement of the patient's motivation to remain completely abstinent, a factor that plays a crucial role. This was also supported by a recent guideline issued by the European Medicines Agency (EMEA)[19]: the management of AD requires a treatment with an active substance for at least twelve months, but preferably fifteen, to consolidate the long-term maintenance of alcohol abstinence[19].

Second, the possibility to increase the dosage until full suppression of craving for alcohol is achieved may guide the clinicians' decisions to use higher and more adequate dosages of SMO for the treatment of every single patient using a sort of adaptation regimen. This mechanism may avoid the risk of confusing craving for alcohol and craving for SMO, which remains a crucial point of discussion; to support this hypothesis, data emerging from a recent study showed that half of the patients presenting a supposed craving for SMO prefer alcohol when asked if they were in a condition to choose between alcohol and SMO. This suggests that craving for SMO was not real, but was masking the persistence of craving for alcohol.

Third, the craving for alcohol is likely suppressed by increasing the dosages of SMO[20]. However, due to the very short half-life (25-30 minutes) of the drug[16], before prescribing > 100 mg/kg/day of SMO (the maximum approved daily dose), fractioning of the drug from three to six daily administrations could be considered a safer approach[21]. On the other hand, due to their lack of efficacy, doses of SMO < 50 mg/kg/day are not suggested. Indeed, the results of the GATE 2 study showed that those patients (66%) who received a daily dose of SMO lower than 50 mg/kg (the lowest dose of the therapeutic interval defined by the Summary of Product Characteristics of SMO in Austria and in Italy) were responsible for the borderline statistical significance achieved by SMO versus placebo[18].

It should also be noted that, in our study, complete abstinence from alcohol is not an exclusion criteria for treatment with SMO. In all clinical trials investigating the efficacy of SMO in short-, medium- and long term periods, in order to avoid the onset of AWS, all patients were detoxified within 7 days, and abstinence from alcohol for at least 7-10 days was always considered as an inclusion criteria. In addition, in order to explore the "per se" efficacy of SMO in maintaining complete alcohol abstinence, those patients who had been treated with SMO to suppress AWS were always excluded from these trials[8,17,18]. Taking into account that SMO is the only drug able to suppress symptoms of alcohol withdrawal and to prevent relapses, it is easy to understand that all physicians who prescribe SMO to suppress AWS do not require patients to be abstinent. Consequently, according to the characteristics of the patients, they usually prescribe SMO both as an anti-craving drug and to maintain abstinence from alcohol. To support this approach, it can be added that no additive sedative effects are induced by drinking during treatment[8].

Furthermore, it clearly emerged that SMO can be used in combination with anti-viral drugs such as interferon or anti-retroviral therapy, as well as with methadone. Indeed, even though SMO is metabolized by the liver, no interaction between SMO and these drugs has been reported. The reason is that the anti-viral drugs used to treat HBV,

HCV and HIV infections are mostly metabolized by the liver through the cytochrome P450 pathway[22] which is not involved in SMO metabolism[17,18]. In addition, a clinical trial reported that no additive effect was observed in patients receiving the combination of methadone and SMO in heroin addicts abusing alcohol[23]. So, it could be speculated that the use of SMO to maintain alcohol abstinence in patients infected by HBV or HCV infection may help them to be more complaint to anti-viral therapy.

Finally, the indication to combine a psychosocial approach with SMO clearly emerged. In previous clinical investigations we employed simple weekly counselling sessions and only a few patients attended self-help groups to avoid masking the efficacy of SMO[8]. On the contrary, in the majority of studies investigating the efficacy of anti-craving and aversive drugs to treat AD (i.e. DF, NTX, acamprosate and nalmefene), self-help groups, medical management, motivation-enhancing therapy or cognitive behavioural therapy were always combined with the pharmacological approach[24] and this played an important role in increasing the rate of alcohol abstinence. It could also be speculated that the association of SMO with a non-pharmacological program of relapse prevention could further enhance the treatment compliance and, therefore, the efficacy of the drug.

This study poses several critcisms, mainly related to the lack of a standardized instrument and the lack of data on the outcome of the study cohort. Despite these conditions and the heterogeneity of responses about the ranking of other modalities of SMO administration, the results were very similar across all groups of physicians. The different views recorded on many clinically relevant issues warrants further investigations/discussions. However, the large size of the participant groups from different Italian regions reinforces the possibility of generalizing our findings.

Conclusions

A consensus on good practice for the correct administration of SMO has clearly emerged; these opinions, along with those derived from previous clinical investigations, will help physicians to use SMO in a better way. However, some issues remain controversial, and others remain unresolved. Thus, further controlled clinical studies are warranted.

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Conflict of Interest

Fabio Caputo, MD, PhD, reports, as consultant, personal fees from D&A Pharma, from CT Pharmaceutical Industries, Sanremo, and from Lundbeck Italia during the last two years; Giovanni Addolorato, MD, reports, as consultant, personal fees from Ortho McNeil Janssen Scientific Affairs, LLC, from D&A Pharma, from Lundbeck Italia, and from CT Pharmaceutical Industries, during the past three years; Mauro Bernardi MD, reports being a consultant or speaker for CLS Behring GmbH, PPTA Europe, and Baxter Healthcare SA during the past three years. All other authors declare that they have no conflicts of interest.

References

1) Caputo F, Bernardi M. Medications acting on the GABA system in the treatment of alcoholic patients. Curr Pharm Des 2010; 16: 2118-2125.
2) Caputo F, Vignoli T, Grignaschi A, Cibin M, Addolorato G, Bernardi M. Pharmacological management of alcohol dependence: from mono-therapy to pharmacogenetics and beyond. Eur Neuropsychopharmacol 2014a; 24: 181-191.
3) Colombo G, Agabio R, Lobina C, Reali R, Fadda F, Gessa GL. Cross-tolerance to ethanol and gamma-hydroxybutyric acid. Eur J Pharmacol 1995; 273: 235-238.

4) Agabio R, Colombo G, Loche A, Lobina C, Pani ML, Reali R, Gessa GL. Gamma-hydroxybutyric acid reducing effect on ethanol intake: evidence in favour of a substitution mechanism. Alcohol Alcohol 1998; 33: 465-474.

5) Gessa GL, Agabio R, Carai MA, Lobina C, Pani M, Reali R, Colombo G. Mechanism of the anti-alcohol effect of gamma-hydroxybutyric acid. Alcohol 2000; 20: 271-276.

6) Pardi D, Black J. gamma-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. CNS Drugs 2006; 20: 993-1018.

7) Snead OC, Gibson KM. Gamma-hydroxybutyric acid. N Engl J Med 2005; 352: 2721-2732.

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; 17: CD006266.

9) Caputo F, Skala K, Mirijello A, Ferrulli A, Walter H, Lesch O, Addolorato G. Sodium Oxybate in the Treatment of Alcohol Withdrawal Syndrome: A Randomized Double-Blind Comparative Study versus Oxazepam. The GATE 1 Trial. CNS Drugs 2014; 28: 743-752.

10) Caputo F, Addolorato G, Stoppo M, Francini S, Vignoli T, Lorenzini F, Del Re A, Comaschi C, Andreone P, Trevisani F, Bernardi M. Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomised comparative study. Eur Neuropsychopharmacol 2007; 17: 781-789.

11) Maremmani AG, 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: 2816-2827.

12) Addolorato G, Castelli E, Stefanini GF, Casella G, Caputo F, Marsigli L, Bernardi M, Gasbarrini G, and GHB Study Group. An open multicentric study evaluating 4-hydroxybutyric acid Sodium salt in the medium-term treatment of 179 alcohol-dependent subjects. GHB Study Group. Alcohol Alcohol 1996; 31: 341-345.

13) Beghe' F, Carpanini MT. Safety and tolerability of gamma-hydroxybutyric acid in the treatment of alcohol dependent patients. Alcohol 2000; 20: 223-225.

14) Gallimberti L, Spella MR, Soncini CA, Gessa GL. Gamma-hydroxybutyric acid in the treatment of alcohol and heroin dependence. Alcohol 2000; 20: 257-262.

15) Caputo F, Skala K, Mirijello A, Ferrulli A, Walter H, Lesch O, Addolorato G. Sodium Oxybate in the Treatment of Alcohol Withdrawal Syndrome: A Randomized Double-Blind Comparative Study versus Oxazepam. The GATE 1 Trial. CNS Drugs 2014b; 28: 743-752.

16) Addolorato G, Leggio L, Ferrulli A, Caputo F, Gasbarrini A. The therapeutic potential of gamma-hydroxybutyric acid for alcohol dependence: balancing the risks and benefits. A focus on clinical data. Expert Opin Investig Drugs 2009; 18: 675-686.

17) Keating GM. Sodium oxybate: a review of its use in alcohol withdrawal syndrome and in the maintenance of abstinence in alcohol dependence. Clin Drug Investig 2014; 34: 63-80.

18) Skala K, Caputo F, Mirijello A, Vassallo G, Antonelli M, Ferrulli A, Walter H, Lesch O, Addolorato G. Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. Expert Opin Pharmacother 2014; 15: 245-257.

19) European Medicines Agency (EMEA). Guidelines on the development of medicinal products for the treatment of alcohol dependence - 2010.

20) Caputo F, Del Re A, Brambilla R, Grignaschi A, Vignoli T, Vigna-Taglianti F, Addolorato G, Zoli G, Cibin M, Bernardi M. Sodium oxybate in maintaining alcohol abstinence in alcoholic patients according to Lesch typologies: a pilot study. J Psychopharmacol 2013; 28: 23-30.

21) Addolorato G, Cibin M, Capristo E, Beghe' F, Gessa G, Stefanini GF, Gasbarrini G. Maintaining abstinence from alcohol with g-hydroxybutyric acid. Lancet 1998; 351: 38.

22) Burger D, Back D, Buggisch P, Buti M, Craxí A, Foster G, Klinker H, Larrey D, Nikitin I, Pol S, Puoti M, Romero-Gómez M, Wedemeyer H, Zeuzem S. Clinical management of drug-drug interactions in HCV therapy: challenges and solutions. J Hepatol 2013; 58: 792-800.

23) Caputo F, Francini S, Stoppo M, Lorenzini F, Vignoli T, Del Re A, Comaschi C, Leggio L, Addolorato G, Zoli G, Bernardi M. 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: 883-890.

24) Starosta AN, Leeman RF, Volpicelli JR. The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. J Psychiatr Pract 2006; 12: 80-89.