Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention

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Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention

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**Introduction:** Sodium oxybate (SMO) has been shown to be safe and effective in the treatment of patients with alcohol use disorders (AUDs); it was approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and for relapse prevention. The focus of this review is to discuss the clinical evidence on the therapeutic potential of SMO for AUDs.

**Areas covered:** This review covers the studies in patients with alcohol withdrawal syndrome who received SMO for the treatment of withdrawal symptoms and the studies in patients with AUDs who received SMO to achieve total alcohol abstinence, reduction of alcohol intake, and relapse prevention. Relevant medical literature on SMO was identified by searching databases including MEDLINE and EMBASE (searches last updated 20 September 2013), bibliographies from published literature, clinical trial registries/databases, and websites.

**Expert opinion:** SMO has proved safe and effective in the treatment of alcohol withdrawal syndrome and in the prevention of relapses. Craving for and abuse of SMO have been reported, in particular in some subtypes of alcoholic patients, e.g., those affected by co-addiction and/or psychiatric comorbidity. Future multicenter, multinational, randomized clinical trials should be useful to optimize the treatments in relation with patients’ characteristics, for example, pharmacogenetic, neurobiological, and psychological.

**Keywords:** alcoholism, gamma-hydroxybutyric acid, GHB, SMO

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Exogenous SMO is rapidly absorbed by the gastrointestinal tract; its peak plasma concentration appears after 15–45 min, and its clinical effects after 15–20 min. This drug has a dose-dependent and saturable elimination; however, the pharmacokinetics of SMO is linear in the AUDs therapeutic interval, and the elimination half-life of SMO in healthy subjects ranges between 20 and 53 min [11].

2.2 Neuromodulatory properties

In the central nervous system (CNS), SMO binds to GHB and GABA_B receptors with high and low affinity, respectively (Figure 2) [10]. The endogenous neurobiological activity of SMO is mediated through the GHB receptor, while many of the pharmacological and clinical effects of exogenously administered SMO appear to be mediated through the GABA_B receptor, where SMO may act both directly, as a partial GABA_B receptor agonist, and indirectly through GHB-derived GABA [10,12]. Irrespective of the brain SMO concentration, it is far from certain that SMO interacts directly with the GABA_A receptors [10–12]. However, the conversion of SMO to GABA induces an activation of GABA_B and GABA_A receptors [10–12] which may account for SMO sedative and anxiolytic effects. Moreover, a recent Australian study performed in rats’ brain cortex has documented the high affinity of GHB for an extra-synaptic α4-subunit of GABA_A receptor concluding that it may, likely, represent the elusive GHB receptor [13].

Both endogenous and exogenous SMO have a dual action on GHB receptors and GABA_B receptors. SMO binds with high affinity to presynaptic GHB receptors and decreases the release of GABA, while low-affinity binding of SMO to a low-affinity site on the GABA_B receptors increases the activation of cell-surface receptors. Therefore, the SMO administration primarily decreases the release of GABA from presynaptic GABA-ergic neurons through a direct activation of GHB receptors [10]. This may result in a disinhibition of dopaminergic neurons (DA) in the ventral tegmental area, an increase of dopamine within that circuitry, which is responsible of the alcohol-mimetic effect of SMO [10].

In summary, experimental data indicate that the sedative effect of SMO observed at medium to high doses may be due to a direct effect on GABA_B and indirect effects on GABA_A receptors: in the treatment of AUDs, doses up to 100 mg/kg/day are used to treat some severe AWS symptoms (e.g., anxiety) and from 4.5 to 9.5 g/day are used to treat cataplexy and excessive daytime sleepiness in narcoleptic patients. At low doses, SMO seems to have alcohol-mimetic effects due to a reduced release of GABA mediated by GHB receptors on presynaptic GABA-ergic and noradrenergic neurons, with a resultant disinhibition of DA release and increase in dopaminergic activity in the mesocorticolimbic circuitry [10]: these effects are observed at lower doses: mainly 50 mg/kg/day to suppress craving for alcohol and alcohol intake.

### Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Sodium oxybate (SMO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Product approved in Italy and Austria</td>
</tr>
<tr>
<td>Indication</td>
<td>Control of alcohol withdrawal syndrome (AWS) and prevention of relapse</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>It is believed that stimulation of GABA_B receptors in competition with alcohol, is a key mechanism of action of GHB in the CNS. SMO also binds to specific GHB receptors with low affinity for GABA. In addition, nonclinical pharmacology and clinical studies of SMO and alcohol have also shown many similarities between the acute effects of alcohol and SMO</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Chemical structure</td>
<td><img src="http://example.com/structure.png" alt="Chemical structure of Sodium oxybate" /></td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>[28, 29, 31, 40, 41, 44, 45, 48, 49, 52, 58, 62, 70, 84, 85]</td>
</tr>
</tbody>
</table>

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Italy and Austria for the treatment of alcohol withdrawal syndrome (AWS) and for relapse prevention and maintenance of abstinence. The present review reports and discusses the available clinical evidence studies supporting the use of SMO as an anti-alcohol medication.

2. Sodium oxybate

2.1 Metabolism

SMO (or GHB – Gamma-hydroxybutyric acid – as commonly called in pharmacokinetic and pharmacodynamic studies), is a short-chain 4-carbon fatty acid which occurs naturally in mammalian brain tissue [10]. The primary precursor of GHB in the brain is GABA, which is transformed into succinic semialdehyde (SSA) through a GABA-transaminase and then converted into GHB via a specific succinic semialdehyde reductase (SSR) (Figure 1). GHB can be reconverted to SSA via a GHB dehydrogenase, and then SSA can be converted back to GABA; SSA can also be transformed by succinic semialdehyde dehydrogenase into succinic acid and further metabolized via the mitochondrial Krebs cycle. GHB is primarily metabolized and eliminated by the liver, and only a modest quantity of it remains unmodified (2–5%) and eliminated in the urine and/or by a still not fully ascertained process of β-oxidation [10].

Both endogenous and exogenous SMO have a dual action on GHB receptors and GABA_B receptors. SMO binds with high affinity to presynaptic GHB receptors and decreases the release of GABA, while low-affinity binding of SMO to a low-affinity site on the GABA_B receptors increases the activation of cell-surface receptors. Therefore, the SMO administration primarily decreases the release of GABA from presynaptic GABA-ergic neurons through a direct activation of GHB receptors [10]. This may result in a disinhibition of dopaminergic neurons (DA) in the ventral tegmental area, an increase of dopamine within that circuitry, which is responsible of the alcohol-mimetic effect of SMO [10].

In summary, experimental data indicate that the sedative effect of SMO observed at medium to high doses may be due to a direct effect on GABA_B and indirect effects on GABA_A receptors: in the treatment of AUDs, doses up to 100 mg/kg/day are used to treat some severe AWS symptoms (e.g., anxiety) and from 4.5 to 9.5 g/day are used to treat cataplexy and excessive daytime sleepiness in narcoleptic patients. At low doses, SMO seems to have alcohol-mimetic effects due to a reduced release of GABA mediated by GHB receptors on presynaptic GABA-ergic and noradrenergic neurons, with a resultant disinhibition of DA release and increase in dopaminergic activity in the mesocorticolimbic circuitry [10]: these effects are observed at lower doses: mainly 50 mg/kg/day to suppress craving for alcohol and alcohol intake.
2.3 Clinical indications
SMO was identified and synthesized > 40 years ago [14]. SMO was first developed as a CNS depressant [15] and used as an anesthetic adjuvant for minor surgical procedures in the laboratory as well as in clinical settings [16-18]. The use of SMO as an anesthetic is now decreasing, although it is still approved in Germany for intravenous anesthesia [12]. In the 1970s, SMO was found to be effective in the treatment of narcolepsy [19,20]. In particular, nightly doses of SMO were shown to improve the structure of sleep in narcoleptic patients, reducing the number of nocturnal awakenings and daytime attacks of cataplexy [21]. In the USA, Canada, the European Union, and Switzerland, SMO has now been approved as an orphan drug status for the treatment of narcolepsy (Jazz Pharmaceuticals, Inc., Valeant Pharmaceuticals International, and UCB). In particular, in the USA, through a limited distribution program, the FDA approved SMO as a schedule III controlled substance to treat patients with narcolepsy who have episodes of weak or paralyzed muscles (i.e., cataplexy).

3. Sodium oxybate for the treatment of alcohol withdrawal syndrome

AWS is a life-threatening condition affecting alcohol-dependent patients who discontinue or decrease their alcohol consumption [22]. The main objectives of the clinical management of AWS are to decrease the severity of symptoms, prevent more severe withdrawal clinical manifestations such as seizure and delirium, and facilitate entry of the patient into a treatment program in order to attempt to achieve and to maintain long-term abstinence from alcohol [23]. At present, benzodiazepines (e.g., diazepam, 0.5 – 0.75 mg/kg/day) are the drugs of choice in the treatment of AWS [24]. However, the use of benzodiazepines is associated with several side effects, such as risk of excess sedation, memory deficits, and respiratory depression in particular in patients with liver impairment, as is often the case in alcoholics [25]. Consequently, the discovery of new potentially useful non-benzodiazepine GABA-ergic drugs for the treatment of AWS is of considerable practical importance [25].

The GABA-ergic action of SMO and its alcohol-mimicking effects on the CNS [26] represented the rationale for testing this compound in the treatment of AWS. Preclinical data showed the efficacy of SMO to suppress ethanol withdrawal syndrome in rats [26,27]. Subsequently a number of clinical studies versus placebo and active comparators have demonstrated the safety and efficacy of SMO in suppressing AWS symptoms. The proof-of-concept study in patients with AWS was performed by Gallimberti et al. [28]. This was a randomized double-blind placebo-controlled trial in 23 patients. A single oral dose of SMO (50 mg/kg) decreased significantly and very rapidly the AWS symptoms score as compared to placebo.

The efficacy of repeated doses of SMO (50 mg/kg/day in most studies given orally in three divided doses) was subsequently confirmed in comparative studies versus benzodiazepines [29,30] and versus clomethiazole [31,32]. SMO was tested in large samples of in- and outpatients who developed AWS symptoms of various levels of severity, after being admitted to different clinical settings (e.g., Psychiatry, Internal Medicine, Surgery, Intensive Care Unit (ICU)). In almost all studies of SMO in patients with AWS, the primary efficacy endpoint was the decrease of the Clinical Institute Withdrawal Assessment for Alcohol Scale-revised (CIWA-Ar) score and/or CIWA-Ar subscores, the validated and reference instrument to assess interventions in patients with AWS [33].

A single-blind, randomized study compared a 10-day treatment course of oral SMO (50 mg/kg in three divided doses) and oral diazepam in 30 patients [29]. The daily dose of diazepam was 0.50 – 0.75 mg/kg body weight for the first six days; from the seventh day onwards, the dose of diazepam was reduced by at least 25%/day and stopped on day 10. SMO and diazepam were effective in decreasing CIWA-Ar score and no statistically or clinically significant difference was observed between SMO and diazepam in CIWA-Ar total score at baseline and at any subsequent time of assessment. This study showed that SMO is as effective as diazepam, widely considered as the gold-standard pharmacotherapy in the treatment of AWS. Interestingly, a statistically significantly higher decrease in several CIWA-Ar subscores was observed with SMO as compared to diazepam. This was the case of the mean score of anxiety on day 4 and the mean score of agitation on day 5. This observation suggests a more rapid effect of SMO in reducing and suppressing these symptoms [29].

A comparative study with a similar design was performed in 42 inpatients with severe AWS [30]. The study drugs were SMO (50 mg/kg/day q.i.d) or diazepam (0.5 mg/kg/day q.i.d) for three weeks, using a randomized, open-label design. SMO was more effective than diazepam in reducing both CIWA-Ar total score and CIWA-Ar mean subscores (tremor,
paroxysmal sweats, anxiety, and agitation) and in reducing cortisol levels at different times of observation [30].

A further comparative study was carried out to compare the efficacy of two daily doses of SMO (50 or 100 mg/kg in three divided doses), and of clomethiazole, an effective non-benzodiazepine AWS pharmacotherapy [31]. No significant difference in CIWA-Ar and other secondary efficacy endpoints was found between the three treatment arms and there was no rebound of withdrawal symptoms after tapering off study medications [31].

An additional study compared the efficacy of intravenous SMO (30 mg/kg initially, followed by 15 mg/kg) and orally administered clomethiazole (250 mg every 4 h) in patients affected by AWS and treated in a medical ICU setting. Intravenous SMO was found to be more effective than oral clomethiazole in the treatment of AWS symptoms in this patient population [32].

In all these trials [29-32], no severe side effects have been reported. Mild side effects included vertigo, drowsiness, dizziness, rhinitis, diarrhea, and nausea. In the study where two different doses of SMO were tested, the 100 mg/kg daily dose was not more effective than the 50 mg/kg daily dose, but was associated with more frequent non-serious side effects (especially vertigo and diarrhea) [31].

A meta-analysis of the safety and efficacy of SMO in the treatment of AD (AWS and maintenance of alcohol abstinence) was performed in 2010 by The Cochrane Collaboration [34]. The AWS review included six trials which met the methodological requirements defined by The Cochrane Collaboration. These trials had included 286 patients with various levels of AWS severity and clinical settings. The meta-analysis showed that SMO (50 mg/kg/day) is more effective than placebo in reducing AWS symptoms score; the efficacy of SMO was at least equivalent to that of benzodiazepines and clomethiazole. No differences between the groups were observed for side effects and numbers of drop-outs between treatments [34].

Another meta-analysis evaluated a variety of drugs in six controlled trials for AWS prevention and eight trials for AWS therapy in ICU [35]. In this meta-analysis, no study with SMO was available for AWS prevention, and all evaluated drugs (benzodiazepines, SMO, and clomethiazole as single agents and phenobarbital, clonidine, and haloperidol as adjuncts) in randomized controlled trials were found to

Figure 2. —► Activity of meso-corticolimbic system in physiological condition. —► Activity of meso-corticolimbic system during exogenous administration of sodium oxybate (SMO).

—► Dopamine neurons (DA) originate from ventral tegmental area (VTA) and project their fibers to the nucleus accumbens (NAC) and to the pre-frontal cortex; DA neurons play a relevant role in physiological reward (i.e., food, sleeping, sexual activity); this circuit is often inhibited by noradrenergic and GABA-ergic neurons originated from the nucleus ceruleus (LC).

—► Sodium oxybate (SMO) induces disinhibition of DA originated from VTA through direct activation and inhibition of GABA-ergic and noradrenergic neurons with a consequent increase in dopamine release from NAC and pre-frontal cortex; this mechanism is on the basis of the alcohol-mimicking effect of SMO.
be effective for AWS therapy. In particular, benzodiazepines appeared as slightly superior to SMO and clomethiazole, although the authors stated that caution was needed because of the large methodological differences between studies that were included in the meta-analysis.

4. Sodium oxybate for the treatment of alcohol relapse prevention and maintenance of alcohol abstinence

4.1 Sodium oxybate as an anti-craving drug in the treatment of AUDs

As mentioned above, SMO exerts an ethanol-mimicking effect on the CNS [36-38]. Consistent with this rationale, SMO has been shown to be capable of inhibiting voluntary ethanol consumption in rats that have a preference for ethanol [36-39]. In humans, a randomized double-blind study treating patients with SMO at dose of 50 mg/kg (divided into three daily administrations) or placebo for three months showed that SMO was significantly superior to placebo in increasing the number of abstinent days, in reducing the number of daily drinks and in reducing alcohol craving [40]. A subsequent open multicenter study confirmed the efficacy of SMO in improving the abstinence rate and in reducing craving for alcohol [41]. SMO also proved to be manageable, with few side effects, such as dizziness, sleepiness, and tiredness early on during treatment (usually resolved after 2 – 3 weeks). About 30 – 40% of alcoholics treated with SMO fail to achieve complete abstinence from alcohol even though they sometimes describe a temporary reduction of alcohol craving. Taking into account the short half-life of SMO [42,43], a study was conducted to investigate the efficacy of the administration of a greater fractioning (six times a day) of the same dose (50 mg/kg) of SMO in those subjects who have not achieved alcohol abstinence after the administration of the conventional three daily doses [44]. The results showed a significant reduction of alcohol craving in a greater percentage of alcoholics who were able to achieve complete abstinence from alcohol.

The already mentioned meta-analysis by The Cochrane Collaboration evaluated the safety and efficacy of SMO in prevention of alcohol relapse [34]. The meta-analysis evaluated 7 clinical trials having included 362 alcoholic patients who received SMO and a placebo or an active comparator to prevent alcohol relapses and maintain alcohol abstinence. Compared to placebo, SMO administered at the daily dose of 50 mg/kg significantly increased the number of patients with complete abstinence or controlled drinking and reduced the number of daily drinks and the craving score. SMO was more effective than NTX and DSF in reducing craving and promoting abstinence.

More recently, a one-year open-label study tested the efficacy of SMO (doses ranging between 25 and 100 mg/kg/day) in “treatment-resistant” chronic alcoholics defined as patients who have previously followed at least two attempts at treatment [i.e., use of psychoactive drugs such as selective serotonin reuptake inhibitors, mood stabilizers, tricycles, and/or self-help group intervention] without achieving alcohol abstinence or who relapsed into heavy drinking during attendance at self-help groups or who were not helped in achieving alcohol abstinence by their precarious psycho-social or environmental conditions [45]. The results of the study showed that 60% of patients were “responders”, that is, patients who successfully achieved complete abstinence from alcohol together with social adjustment (full-responders) or patients who reduced their alcohol intake but did not accomplish complete alcohol abstinence (partial responders) [45]. The retention rate during treatment with SMO was significantly higher than the retention rate of the same sample previously treated with other pharmacotherapies. Furthermore, this study confirmed that the only significant predictor of the retention rate was the six-times/daily fractionated administration of SMO [45], a result in close agreement with the previous study [44].

Two laboratory studies in healthy subjects investigated the effects of a concomitant administration of single doses of alcohol and SMO. Both studies had a randomized, double-blind, placebo-controlled, four-way crossover design. These studies are of interest, since they investigate possible side effects in case of alcohol intake during treatment with SMO.

The first study compared the effect of single doses of SMO (50 mg/kg), alcohol, the combination of SMO and alcohol, both at the same doses, and placebo in eight healthy volunteers [46].

A similar study was performed in 24 healthy volunteers with the same dose of alcohol but a smaller dose of SMO was used (2.25 g or 30 mg/kg) [47]. This dose is close to the upper limit of the therapeutic interval (33.3 mg/kg). The primary objective of that study was to investigate the effects of study drugs on objective and subjective psychometric tests. SMO was found to have less sedative effects than alcohol. Antagonistic and less frequently synergistic interactions without potentiation between SMO and alcohol were found in a small number of psychometric tests. The combination was associated with a nonsignificantly increased number of non-serious adverse events.

The daily dose of SMO used to treat alcohol dependence (3 – 6 g) is much smaller than the dose used in the treatment of narcolepsy (4.5 – 9 g).

This may account for the absence of reported serious adverse effects (SAEs) when alcohol-dependent patients treated with SMO have an alcohol relapse. In fact, no side effects due to the combination of SMO 50 mg/kg/day (divided into 3 – 6 daily administrations) and alcohol were observed in SMO-treated alcoholics who were still drinking during the treatment [40,41,44,48,49]. It is conceivable that the use of the same dose of 50 mg/kg divided into 3 – 6 daily administrations was able to prevent the occurrence of adverse effects when associated with ethanol [50].
4.2 Results of the “GHB in alcohol-dependence treatment efficacy” study

GHB in Alcohol-dependence treatment efficacy (GATE 2) trial was a randomized, double-blind, placebo-controlled, multicenter study which was conducted in 11 centers in 4 European Countries (Austria, Germany, Italy, and Poland) [51,52]. The objective of the study was to confirm the efficacy and the safety of oral SMO in the long-term treatment of alcohol dependence in a large patient population. A total of 314 patients, who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for alcohol abuse and dependence, but without history of any other drug dependence except nicotine, were randomized. Among them, 154 patients were randomized to the SO group, and 160 patients to the placebo group.

Patients were stratified according to Lesch’s typology [53,54], which classifies alcohol-dependent subjects into four clinically defined groups. Patients with body weight < 65 kg received 3.06 g of the SMO solution per day, and patients with body weight > 65 kg received 3.50 g of SMO, split into three doses. Patients remained on the allocated double-blind treatment for 6 months, and entered a 6-month untreated follow-up period. The primary efficacy outcome was the cumulative abstinence duration (CAD); CAD is the number of days of abstinence during the observed period. Secondary outcomes were i) the number and percentage of patients abstinent from alcohol each month, at the end of the 6-month treatment period, and at the end of the 6-month untreated follow-up period, ii) the time to first relapse (assessed by the Kaplan-Meier abstinence survival curve), iii) the proportion of drop-outs, and alcohol relapses and slips, respectively, defined by an increase of at least 1.0 and 0.5% in Carbohydrate Deficient Transferrin (%CDT); and iv) alcohol craving and desire for medication assessed by the Lübecker Craving Risiko Rückfall (LCCR) scale.

A total of 74 (48.1%) and 40 (26.0%), respectively, of SMO-treated patients completed the 6-month treated period and the 6-month untreated follow-up period. Corresponding figures were 58 (36.2%) and 31 (19.4%) in the placebo group. These figures are slightly higher than retention rates in published long-term trials in alcohol-dependent patient populations. At the end of the treated period, the difference of the mean values of CAD between the SMO group and the placebo group reached borderline statistical significance using analysis-of-variance testing: 90.4 days vs 73.9 days (p = 0.050). In addition, a statistically significant difference between SMO group and placebo group in maintaining a continuous abstinence from alcohol at the end of the first month (67.5 vs 55.6%; p = 0.030) and of the fifth month (40.9 vs 30.0%; p = 0.043) of treatment was found.

At the end of the 6-month untreated period, the mean values of CAD were 136.0 days in the SMO group and 108.9 days in the placebo group (p = 0.071). Tests of normality showed that the distribution of CAD significantly deviates in both study groups from a Gaussian distribution. In this case, the median value of CAD is a better index of centrality than the mean value. At the end of the treated period, the median values of CAD were 90.5 days and 57.5 days in the SMO group and the placebo, respectively, and at the end of the follow-up period, median values were 91.5 days and 58.0 days in the SMO group and the placebo group, respectively. Though GATE 2 trial was not designed and powered to demonstrate the persistence of the efficacy of SMO over a long time after drug discontinuation, these analyses strongly suggest that the therapeutic advantage of SMO is maintained for a long time after drug cessation. The median time to first relapse estimated by Kaplan-Meier methodology was 77.00 days in the SMO group and 46.00 days in the placebo group (p = 0.133). Interestingly, the effect of SMO differed according to Lesch’s typologies [53,54]. Indeed, in Lesch type II patients, the SMO group showed a statistically significant higher CAD than the placebo group (p = 0.035). No statistically significant difference was found between study groups at any visit in terms of desire for medication. Alcohol craving, assessed by LCCR, significantly decreased in both groups with no significant intergroup difference. Alcohol biomarkers (liver function tests, MCV, %CDT) improved throughout the study, but without any significant difference between study groups. This may be related to the fact that almost 50% of patients had normal baseline values of alcohol craving and alcohol biomarkers. The long screening period (at least 20 abstinence days prior to randomization) may account for normalized values at randomization. SAEs were very uncommon in both groups and were unrelated with study medications: injury, poisoning, and procedural complications in 3 (1.9%) patients in the SMO group and 2 (1.3%) patients in the placebo group.

When interpreting the efficacy outcomes of GATE 2 study, it is important to underline some limitations of the study which may have contributed to an underestimation of SMO’s efficacy compared to previous trials:

- The dose level of SMO was significantly lower than in previous studies. The average daily doses in patients with body weight below 65 kg and over 65 kg were 44.3 mg/kg or more, and 52.5 mg/kg or less, respectively. This means that 66% of patients received daily doses significantly 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.
- The number of dropped-out patients was much higher than in the protocol assumptions underlying sample size calculation.
- The study protocol required at least 20-day complete alcohol abstinence prior to randomization; such a long time interval may enhance placebo effect [55].

4.3 Sodium oxybate compared and combined with other medications in the treatment of alcohol dependence

A 3-month open randomized comparative study evaluating the efficacy of SMO (50 mg/kg of body weight t.i.d)
compared with NTX (50 mg o.d.) in maintaining abstinence from alcohol in patients with mostly moderate alcohol dependence. SMO was significantly more effective than NTX in maintaining alcohol abstinence (66.7 vs 35.3%; p < 0.02) [48]. Nevertheless, in the same study, in the NTX group, patients who failed to be abstinent did not relapse into heavy drinking, confirming the ability of this drug to reduce alcohol relapses, while in the SMO group all the patients who did not maintain abstinence relapsed into heavy drinking (~11%). This finding had been reported in another SMO trial in alcoholic patients [49]. However, in both studies, the difference between SMO and NTX did not reach the statistical significance.

Craving for SMO was not observed, and no sedative additive effects due to an alcohol–SMO interaction in patients who relapsed were found. Similarly, an SMO withdrawal syndrome or symptoms and signs related to drug suspension or discontinuation were reported. Moreover, a 12-month comparative study showed that SMO, administered at a dose of 50 mg/kg/day, NTX at a dose of 50 mg/day, and DSF at a dose of 200 mg/day did not statistically differ, although the abstinence rate was higher in SMO group (65%) compared to NTX (49%) and DSF (40%) [50]. No patient treated with SMO developed craving for this drug, and only mild-to-moderate side effects were found in all groups.

Considering the data emerging from the comparative studies, a 3-month randomized study was performed in patients with mostly severe alcohol dependence [49]. In this 3-month open randomized comparative study, the combined treatment of SMO and NTX was shown to be more effective in maintaining abstinence from alcohol than single SMO and NTX therapies, with 72.2, 40, and 5.9% completely abstinent patients, respectively [49]. The number of relapses into heavy drinking also tended to occur less frequently in the combination group (no cases) than in either the SMO group or the NTX group. These data suggest that the two drugs may combine their different actions synergistically without suppressing the favorable effects of each other. In addition, as demonstrated by the absence of patients who developed craving for SMO in the combined group with respect to the group taking SMO alone (~10%) [49], it is possible that the anti-reward property of NTX prevents the onset of craving for SMO as previously observed in by three clinical experiences [57]. Another 6-month open randomized study compared the efficacy of SMO, NTX, and their combination in maintaining alcohol abstinence in patients treated by escitalopram, an SSRI anti-depressant agent [58]. In this study, the triple combination therapy (SMO + NTX + escitalopram) proved to be more effective than SMO plus escitalopram, NTX plus escitalopram, or escitalopram alone in preventing alcohol relapses: the abstinence rate was 83.3, 50, 33.3, and 18.1%, respectively [58]. In fact, the mechanism of alcohol craving may differ in the various subtypes of alcohol dependence [59,60]. In particular, a dopaminergic/opioidergic dysregulation has been hypothesized in reward craving, GABAergic/glutamatergic dysregulation in relief craving, and serotonergic dysregulation in obsessive craving [59-61]. Different craving conditions and profiles may coexist in a single patient, so that drug combinations (e.g., or i.e., SMO, NTX, and escitalopram) could be more effective than single or double drug therapies in preventing alcohol relapses. Finally, a recent Italian observational trial found that ~60% of patients not responding to a single-drug SMO therapy responded to the combination of DSF and SMO [62].

5. Craving for and abuse of sodium oxybate

SMO has a potential for abuse, misuse, dependence, and withdrawal symptoms in relation with its neurobiological properties. SMO has complex and biphasic effects on the dopaminergic system: initial stimulation followed by long-lasting inhibition. The acute stimulation underlies the euphorizing effects of SMO, usually observed at doses significantly higher than therapeutic doses used in AUDs or even narcolepsy. Chronic administration of SMO may result in compensatory mechanisms which offset the inhibition of dopamine release, and lead to an increase of dopamine, GABA, and/or glutamate release [63]. This scenario could contribute to the addictive liability of SMO. Addictive properties of SMO have been reported in both non-alcoholics and alcoholics [64]. However, there is a major difference between the use of SMO as a therapeutic agent to treat alcohol-dependent subjects and the illegal use, misuse, and abuse of illicit GHB in non-alcoholic subjects [65]. Euphorizing and disinhibiting effects of GHB have made it popular as a recreational drug [66] in the US and the UK where it is sold clandestinely mostly in the street or by internet sites [67]. More recently, the recreational use of GHB has also become popular in Europe and other countries [68]. GHB has also been used in the bodybuilding community because of its supposed ability to promote muscle growth and decrease body fat [69]; some studies suggest that high doses of SMO may stimulate the release of human growth hormone from the anterior pituitary gland. However, in alcoholics there is no evidence that treatment with SMO results in an increase in muscle mass [70]. The CNS depressant effects of GHB are somewhat comparable to those of sedative hypnotics such as barbiturates and benzodiazepines and explain the risk of GHB overdosage. The risk of overdosage of illicit GHB is also related to two aggravating factors: i) illicit GHB consumers commonly ingest preparations containing inaccurate/unknown doses of GHB and ii) these subjects also consume other illicit drugs in combination with GHB, including CNS depressants [57]. In addition, a recent Dutch paper has demonstrated that the most risky factor of GHB overdose, during its recreational use, is the drug itself, and taking GHB in a company of friends may reduce the risk of overdose of the drug [71]. The number of cases of GHB intoxication treated in Emergency departments of hospitals has been increasing in some countries and
decreasing in other countries during the last years [72,73]. Signs and symptoms induced by GHB intoxication have been reported at doses ranging from a few grams to 30 g or more. However, severe intoxications are usually observed for ingested doses in excess of 8 – 10 g, especially for doses higher than 30 g [74]. Adverse effects include dizziness, nausea, vomiting, myoclonic muscle movements (jerks), agitation, confusion, hallucinations, loss of peripheral vision, and delirium. In case of vomiting, there is a risk of pulmonary aspiration which may be life-threatening. Doses higher than 10 – 20 g can decrease cardiac output and may produce coma, seizure-like convulsions, and severe respiratory depression requiring respiratory assistance [74]. Psychosis, stroke, and possible long-term neurotoxic effects are much less common [75]. No specific antidotes are available for the treatment of GHB intoxication and the medical treatment is essentially supportive, based on respiratory assistance and maintenance of vital functions. Some uncontrolled clinical studies have suggested that opioid antagonists such as naloxone could be effective on GHB intoxication [68]. In some individuals who abuse GHB, repeated and persistent use of high doses may lead to the development of physical dependence including a risk of a withdrawal syndrome [76]. GHB withdrawal syndrome may include anxiety, insomnia, and tremor. If untreated, there is a risk of delirium, hallucinations, and/or acute psychosis. GHB withdrawal syndrome may require an out-of-inpatient treatment with administration of benzodiazepines depending on symptom severity [76,77]. Because of its abuse potential, FDA classified in 2000 GHB as a Schedule I controlled substance [78]. In 2002, FDA approved SMO as a therapeutic agent for the treatment of narcolepsy with cataplexy. In this case SMO has a Schedule III drug labeling, as a reflection of its reduced abuse potential as compared to illicit GHB [79]. A retrospective safety study on the 26,000 patients treated worldwide with SMO for narcolepsy during 6 years (2002 – 2008) evaluated the incidence of adverse events related to abuse, misuse, and addiction [80]. The number and incidence of the following DSM-IV-defined adverse events were, respectively, abuse (10 = 0.039%), dependence (4 = 0.016%), withdrawal symptoms (8 = 0.031%), drug-facilitated sexual assault (2 = 0.008%), overdose with suicidal intent (8 = 0.031%), and death, whichever the relatedness with the drug (21 = 0.080%). Overall, the incidence of patients with at least 1 of those adverse events was 0.2% [80].

A retrospective analysis included 732 alcohol-dependent outpatients treated with SMO in clinical trials [81]. Daily doses in these trials ranged between 50 and 100 mg/kg divided in three or more doses for an average duration of 132.2 ± 57.9 days. These patients also attended supportive psychosocial programs, and the administration of SMO was entrusted to a family member. A small percentage of these patients (2.6 – 10.1% depending on reports) showed craving for the drug and increased the dosage (up to 6 – 7 times the recommended dose) [41,81,82]. However, in these studies, craving assessment was based on spontaneous patient reports and not measured using a specific validated instrument. In the GATE 2 study performed in 314 alcohol-dependent patients, addictive symptoms were searched systematically through anamnesis and by the LCRR questionnaire [51,52]. Items 1 and 2 of LCRR questionnaire investigated desire for study medication; no significant difference was found between drug- and placebo-treated groups at any visit in terms of craving for medication. It has been suggested that craving for SMO observed in treated alcohol-dependent patients could be partly related to the consequences of the short elimination half-life of SMO [11]. This hypothesis is supported by clinical studies which showed that a greater fractioning of the daily amount of SMO (from 3 to 6 daily doses) not only enhanced the efficacy of SMO in preventing alcohol relapses, but also significantly reduced the incidence of drug abuse [44,83].

5.1 Risk factors of sodium oxybate in alcoholic patients

Craving for and abuse of SMO represent crucial aspects in the treatment of alcohol-dependent patients. Therefore, it is essential to identify subgroups of AUDs patients at risk for SMO abuse.

A recent study assessed the risk of developing craving for and abuse of SO in four groups of alcoholics, with or without history of co-addictions to heroin or cocaine [84]. In this study, AUDs patients were enrolled and treated with SMO orally administered (50 mg/kg of body weight t.i.d.) for 3 months. At the end of the study, SMO was found to be effective in promoting alcohol abstinence and in alcohol relapse prevention in all four study groups. Craving for SMO was found to be very uncommon in patients without co-addiction. However, craving for SMO was significantly higher in alcoholics with previous cocaine or heroin dependence than in alcoholic without co-addiction. This study suggests that the administration of SMO is safe and does not lead to addiction in alcohol-dependent patients without co-addiction but may be dangerous in alcoholics with history of cocaine or heroin dependence [84].

In a subsequent study performed in AUDs patients with and without psychiatric comorbidity, the efficacy of a 12-week treatment with SMO was similar in obtaining and maintaining complete abstinence in both groups. However, no patient without psychiatric comorbidity showed craving for or abuse of SMO, whereas 40% of patients with psychiatric comorbidity showed craving for the drug, without no statistically significant difference between DSM-IV-TR-defined Axis I or Axis II psychiatric comorbidity [85]. In particular, AUD patients with a borderline personality disorder seem to be at high risk of developing craving for SMO [85].

In conclusion, SMO abuse, misuse, and dependence during treatment for AUDs can be observed but with a very low incidence in patients without co-addiction and psychiatric comorbidity. The risk of SMO abuse must, however, be taken
into account in alcohol-dependent patients having these risk factors.

6. Conclusions

A large number of well-conducted clinical studies performed with SMO in alcohol-dependent patients have demonstrated that SMO is a safe and effective drug in the treatment of AWS as well as in alcohol relapse prevention. Several studies have provided preliminary evidence that SMO is more effective than NTX and DSF in the prevention of alcohol relapses. Recent studies have also suggested the possible benefits from combining medications acting on different neurobiological targets. The combination of SMO and NTX is of particular interest, because these two drugs have a different mechanism of action and neurobiological targets and can be synergistic. The risk of abuse is low, but still underlines the need to detect early evidence of abuse and/or misuse, and to avoid the administration of the drug to some of the alcoholic patients (co-addiction, psychiatric comorbidity). For these reasons, SMO must be prescribed and monitored by physicians with expertise in Addiction Medicine. In conclusion, SMO has been shown to be safe and effective in the treatment of AUDs, although further studies will be useful to optimize the use of SMO.

7. Expert opinion

Relapse prevention should be based on a multidisciplinary approach, where pharmacological treatment is combined with psychosocial interventions, including motivational or cognitive behavioral therapy and/or self-help groups. Up to recently, pharmacotherapy of AUD only included three approved drugs for the maintenance of alcohol abstinence: DSF, acamprosate, and NTX; these drugs are widely considered as having a modest efficacy. Nalmefene, an opioid antagonist, has recently been approved by European health authorities to reduce alcohol consumption without specifically targeting alcohol abstinence though the long-term consequences of the risk reduction approach are still unclear. Baclofen and topiramate are two promising GABA-ergic drugs but the risk-to-benefit ratio of these drugs has yet to be clarified.

SMO is approved in two European countries and has proved safe and effective in the treatment of AWS and in the long-term prevention of alcohol relapses. Convergent pilot trials suggest that SMO is more effective than NTX and DSF. Large-scale trials will be needed to confirm the superiority of SMO on existing drugs. The same is true for “treatment-resistant” patients who could particularly benefit from SMO.

As opposed to other chronic conditions such as hypertension or diabetes mellitus, combination therapy is not a common practice and has not been extensively assessed in patients with AUDs. A study has provided evidence that the combination of SMO and NTX has a strong pharmacological rationale and is more effective and possibly safer than single drug therapy. This finding must be confirmed with NTX or possibly nalmefene, another opioid antagonist.

Patients with alcoholic liver cirrhosis (ALC) are only considered for life-saving liver transplantation if they have been completely abstinent for a long duration. No approved drug has been shown to promote abstinence in this patient population. SMO should be assessed in a double-blind placebo-controlled study of 6 – 12-month duration. The objectives would be to determine if SMO can help patients meet the requirements for liver transplantation and modify the natural history of ALC.

However, AUDs are heterogeneous, complex disorders, and an “ideal” and effective drug for all types of AUD patients does not exist. Clinical evidence shows that many AUD patients may need and benefit from a substitution therapy [86,87], and SMO could be particularly useful for these patients. The future challenge will consist in tailoring personalized treatments [9] and basic research indicates that a pharmacogenomic approach to the treatment of AUD patients is conceivable [88]. Future multicenter, multinational, randomized clinical trials should be useful to deeply investigate the use and characteristics of SMO in the treatment of AUDs in a rigorous setting and to optimize the treatments in relation with patients’ characteristics, e.g., pharmacogenetic [89-91], neurobiological, and psychological.

Declaration of interest

G Addolorato served as a consultant for Ortho-McNeil Janssen Scientific Affairs, LLC, and D&A Pharma, and was paid for his consulting services. He has received lecture fees from D&A Pharma. F Caputo and O Lesch have served as a consultant for D&A Pharma, and they were paid for their consulting services. They have received lecture fees from D&A Pharma. All remaining authors have no conflicts of interest.
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Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

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In this study two doses of SMO (50 mg/kg and 100 mg/kg) were compared to clomethiazole in the treatment of alcohol withdrawal syndrome.

In this study the effects and interactions of the co-administration of SMO and alcohol in human volunteers were investigated.

In this study was confirmed the absence of adverse events by the co-administration of SMO and alcohol in human volunteers.

This study showed that the combination between SMO and naltrexone is useful in promoting alcohol abstinence and reducing the risk of SMO craving and abuse.

Sodium oxybate

In this study the usefulness of greater dosage fractioning of SMO in non-responder patients to the usual three administrations per day was investigated.

In this study was confirmed the absence of adverse events by the co-administration of SMO and alcohol in human volunteers.
and their classification procedures. Alcohol Alcohol 2009;44:46-54


**Large multicentric trial testing the combination between acamprosate, naltrexone and behavioural therapy in the treatment of alcohol dependence**


**This study showed that the combination of escitalopram, SMO and naltrexone is more effective to prevent relapse than either drug alone.**


**In this article authors suggested that the combination of SMO and disulfiram is more effective than SMO alone in treatment of alcoholic patients.**


**This study showed the absence of anabolic effects long-term treatment with SMO in alcoholic patients.**


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**In this article authors reviewed post-marketing and clinical safety experience with SMO in the treatment of cataplexy and narcolepsy, showing low risk of abuse and misuse of SMO.**


**In this article authors performed a retrospective analysis of 732 alcohol-dependent patients having been treated with SMO in clinical trials, showing as abuse of SMO is a limited phenomenon in clinical.**


** First evidence on the benefit of greater dosage fractioning of SMO (50 mg/kg/day divided into six daily doses) in non-responder alcoholics to the usual three administrations per day. No SMO misuse was found with the greater fractioning of the drug.


** In this study risk of SMO misuse and craving was showed in patients with previous cocaine or heroin addiction.


** In this study risk for SMO misuse and craving was showed in alcoholic patients with psychiatric comorbidity.


** In this study, the authors proposed a novel pharmacogenetical approach to treat alcoholic patients.


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