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Alcohol and Alcoholism, 2023, **58(2)**, 125–133
https://doi.org/10.1093/alcalc/agac070
Advance access publication date 6 January 2023
Article

Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration

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Received: September 27, 2022. **Revised:** November 17, 2022. **Editorial decision:** December 6, 2022. **Accepted:** December 6, 2022

Abstract

Aims: The estimated effect of sodium oxybate (SMO) in the treatment of alcohol dependence is heterogeneous. Population severity and treatment duration have been identified as potential effect modifiers. Population severity distinguishes heavy drinking patients with <14 days of abstinence before treatment initiation (high-severity population) from other patients (mild-severity population). Treatment duration reflects the planned treatment duration. This study aimed to systematically investigate the effect of these potential effect moderators on SMO efficacy in alcohol-dependent patients.

Methods: Network meta-regression allows for testing potential effect modifiers. It was selected to investigate the effect of the above factors on SMO efficacy defined as continuous abstinence (abstinence rate) and the percentage of days abstinent (PDA). Randomized controlled trials for alcohol dependence with at least one SMO group conducted in high-severity and mild-severity populations were assigned to a high-severity and mild-severity group of studies, respectively.

Results: Eight studies (1082 patients) were retained: four in the high-severity group and four in the mild-severity group. The high-severity group was associated with larger SMO effect sizes than the mild-severity group: abstinence rate risk ratio (RR) 3.16, $P = 0.004$; PDA +26.9%, $P < 0.001$. For PDA, longer treatment duration was associated with larger SMO effect size: +11.3% per extra month, $P < 0.001$. In the high-severity group, SMO showed benefit: abstinence rate RR 2.91, $P = 0.03$; PDA +16.9%, $P < 0.001$. In the mild-severity group, SMO showed benefit only in PDA for longer treatment duration: +23.9%, $P < 0.001$.

Conclusions: In the retained studies with alcohol-dependent patients, high-severity population and longer treatment duration were associated with larger SMO effect sizes.

INTRODUCTION

Alcohol dependence (AD) is responsible for about two-thirds of the overall alcohol-attributable mortality (Rehm *et al.*, 2012). There is strong evidence that alcohol-related harm is mainly determined by the amount of alcohol consumed and the drinking pattern (Rehm *et al.*, 2010, 2012, 2018).

One of the treatment goals for AD is abstinence (European Medicines Agency, 2010). Currently, disulfiram, acamprosate and naltrexone are registered for the maintenance of abstinence in AD patients. Although effective on the group level, effects sizes are heterogeneous and limited, and many AD patients fail to respond to these medications (European Medicines Agency, 2010; van den Brink *et al.*, 2018). Therefore, additional pharmacological treatments are needed.

Sodium oxybate (SMO) as an oral solution has been approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and for maintenance of abstinence since 1991 and 1999, respectively (van den Brink *et al.*, 2018). SMO is the sodium salt of γ-hydroxybutyric acid (GHB), a short-chain fatty acid that is naturally synthesized in the mammalian brain. SMO is a low affinity agonist at $GABA_B$ receptors and also binds with high affinity to GHB-specific binding sites (Keating, 2014; van den Brink *et al.*, 2018; Leurs *et al.*, 2021). One proposed mechanism of SMO in the treatment of AD is its ability to mimic some effects of alcohol in the brain (Keating, 2014; Kamal *et al.*, 2016). SMO showed evidence of efficacy compared with placebo or naltrexone in AD patients in a series of randomized controlled trials (RCTs), including a Phase III trial, and in various (network) meta-analyses (Gallimberti *et al.*, 1992; Caputo *et al.*, 2003, 2007; Leone *et al.*, 2010; van den Brink *et al.*, 2018; Cheng *et al.*, 2020; Guiraud *et al.*, 2022). However, heterogeneity of the SMO treatment effect was identified within and across studies (van den Brink *et al.*, 2018; Guiraud *et al.*, 2021, 2022). In a recent network meta-analysis including 64 trials (43 interventions), evidence of inconsistency of SMO treatment effect between direct and indirect comparisons was identified (Cheng *et al.*, 2020), suggesting an unbalanced presence of effect modifier(s) across studies in the network (Dias *et al.*, 2011). No evidence was found of heterogeneity being explained by meta-regression on predefined study level characteristics (Cheng *et al.*, 2020). In another meta-regression analysis, including 51 RCTs for AD, treatment effect of approved medications for AD was significantly negatively correlated with the magnitude of the placebo response. No effect modifiers were identified among the factors tested (Litten *et al.*, 2013). Interestingly, these meta-regressions did not test the effect of population severity and (planned) treatment duration, two factors identified as effect modifiers of several approved medications for AD and/or predictors of placebo response.

Population severity distinguishes AD patients with heavy alcohol consumption (>40 g/day for women and > 60 g/day for men) at baseline and with a short abstinence duration (<14 consecutive days) before treatment initiation from other AD patients. With respect to their level of response to placebo treatment, these patients have been defined in the literature as the high-severity population and the complement population as the mild-severity population (van den Brink *et al.*, 2018; Scherrer *et al.*, 2021). Recent subgroup analyses in studies for the treatment of AD showed that the placebo response in double-blind RCTs is lower and treatment effect size is higher in the high-severity population than in the mild-severity population (van den Brink *et al.*, 2013, 2014, 2018; Mann *et al.*, 2016; Pierce *et al.*, 2018; Scherrer *et al.*, 2021). Furthermore, longer planned treatment durations were associated with lower placebo response within and across RCTs conducted in populations with a certain severity level (Scherrer *et al.*, 2021).

Therefore, the aim of this study was to simultaneously investigate the potential moderating effect of population severity and treatment duration on SMO efficacy in RCTs directed at the maintenance of abstinence in AD patients. A method to test these interactions across studies is network meta-regression analysis (NMRA) (Higgins *et al.*, 2022) and thus, this analysis was selected to systematically investigate SMO efficacy heterogeneity in the treatment of AD. In addition, separate analyses were performed to assess the credibility and plausibility of our findings.

METHODS

The protocol for this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022347817).

Eligibility criteria

We included all published RCTs conducted in AD patients to maintain abstinence in an outpatient setting and which included at least one group treated with SMO. Only full text articles in English were selected.

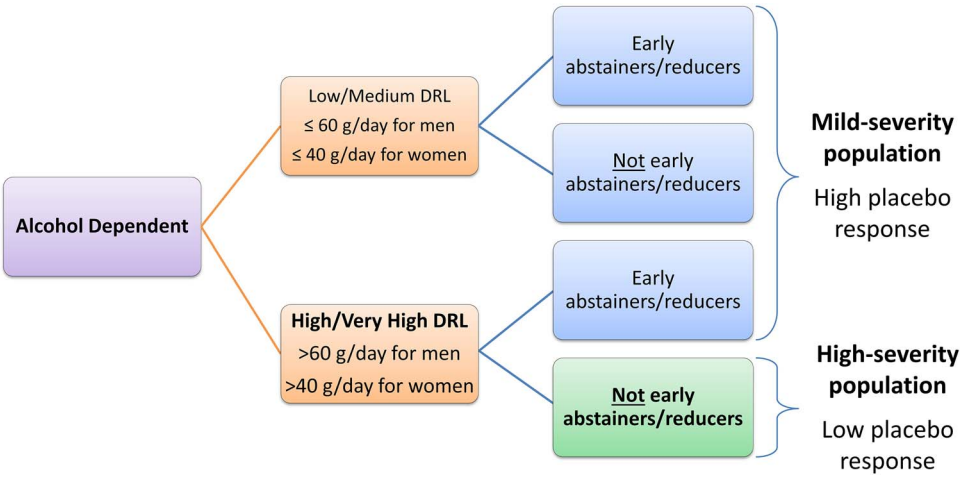

Fig. 1. Definitions of alcohol-dependent subpopulations according to van den Brink *et al*. (2018). DRL: drinking risk level see Supplementary Table S1; early abstainers: patients with > 14 consecutive days of abstinence before treatment initiation; early reducers: patients who reduce their alcohol consumption to a low or medium DRL prior to treatment initiation.

Population

Selected studies included AD patients according to DSM (IV or earlier), ICD (10 or earlier) or equivalent criteria. Patients needed to be abstinent before starting the study medication.

Determination of population severity and treatment duration

For those articles not reporting efficacy separately for severity subgroups, studies were assigned to one of the severity groups with the Scherrer *et al*. (2021) method: studies reporting a long abstinence duration before treatment and/or non-heavy alcohol consumption at baseline at study level were assigned to the group of mild-severity studies (Fig. 1). Studies reporting a short abstinence duration before treatment and heavy alcohol consumption at baseline at study level were assigned to the group of high-severity studies (Fig. 1). For studies reporting on efficacy separately for each severity subgroup, data of each subgroup (mild-severity and high-severity) were treated as a standalone study allocated to the group of mild-severity or the group of high-severity studies, respectively.

Treatment duration was a continuous variable expressed in months and reflecting the planned treatment duration for each retained RCT. See supplementary material for additional information.

Interventions/comparators

All studies with SMO as one of the pharmacological interventions for maintaining abstinence in AD patients in an outpatient setting were included in the analysis. In a network meta-analysis, each treatment is compared directly and/or indirectly with all other treatments, therefore any treatment can be the comparator. In the current report, placebo was used as main comparator (Fig. 3).

Outcome

The selected primary outcome was the abstinence rate which is the primary endpoint recommended by regulatory agencies for the demonstration of efficacy in the maintenance of abstinence (European Medicines Agency, 2010; US Food and Drug Administration, 2015). Our definition of abstinence was continuous abstinence (no relapse to any alcohol use) throughout the treatment period.

In accordance with the European Medicines Agency (EMA) guideline, the percentage of days abstinent (PDA) was selected as a secondary measure (European Medicines Agency, 2010). If cumulative abstinence duration was reported and PDA was not reported and since both endpoints are closely related, the cumulative abstinence duration was transformed into PDA by dividing the reported cumulative abstinence duration in each treatment group by the planned treatment duration. Other outcomes were reported in no more than two studies and were, thus, not included in the analyses.

Search strategy

We performed a systematic search considering articles assessed for eligibility (after exclusion of duplicates) in previous systematic reviews and meta-analyses with similar research questions related to similar populations (AD) and study designs (RCTs) as our NMRA (Fig. 2 and full list in supplementary material). However, since these searches only covered articles published up to March/October 2020, we also conducted a systematic screening of original articles published from March 2020 to July 2022 in MEDLINE based on PRISMA guidelines (see search strategy in supplementary material).

Study selection

Articles identified through this search strategy were screened by three reviewers and information related to the inclusion/exclusion criteria are presented in a bespoke Excel spreadsheet. Any disagreement between reviewers or uncertainty related to the study selection was discussed and resolved.

Data extraction

Data were extracted from the publication in duplicate in a pre-piloted Excel spreadsheet and were reviewed by a third reviewer. When multiple articles from one study existed, all reports were considered, data were retrieved from these different sources and the related articles were referenced in the Excel spreadsheet.

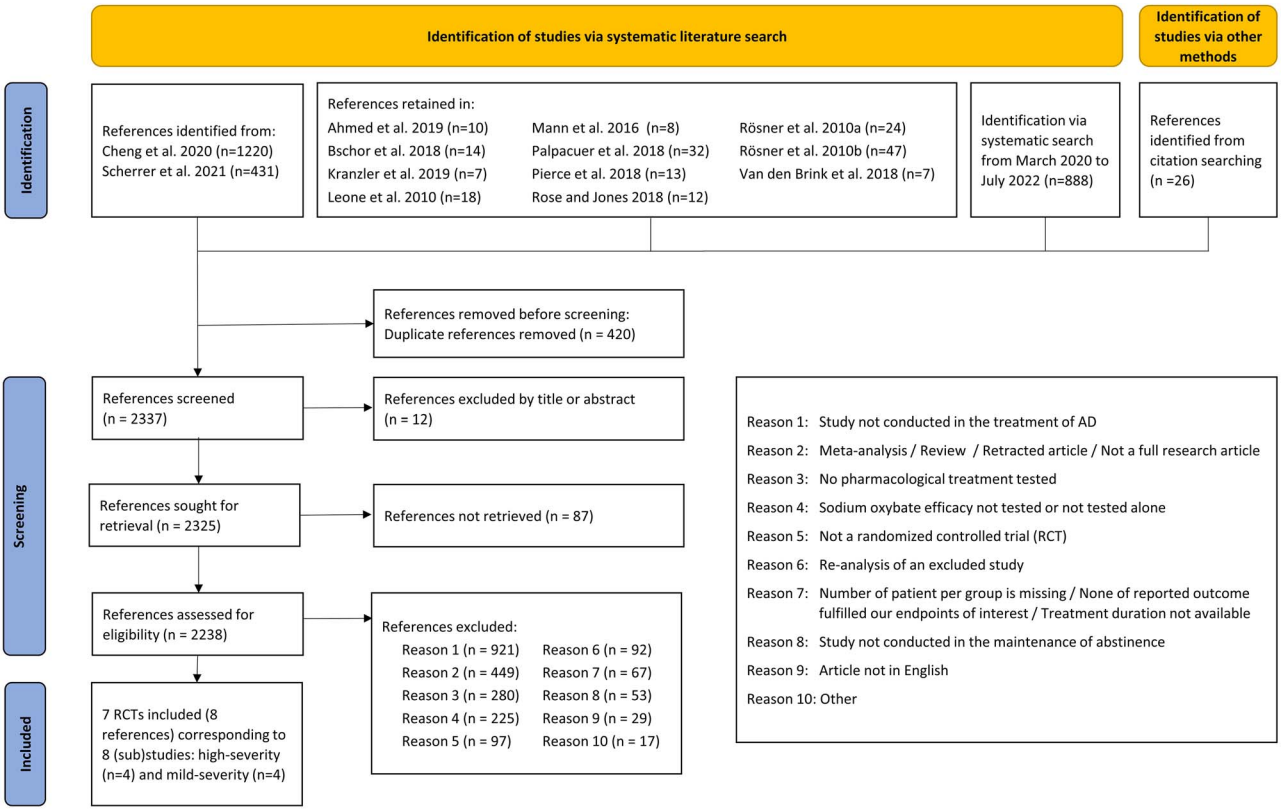

Fig. 2. Flow diagram of study selection.

Dealing with missing data

We used results from the intention-to-treat population. Since relapse was the main documented reason for dropout in previous trials (Guiraud *et al*., 2022), dropouts were treated as treatment failures for abstinence rate (patient not continuously abstinent) in all retained studies. For PDA, we used the efficacy results and thus the imputation method for missing data reported in the article.

Assessment of risk of bias

The revised Cochrane risk of bias tool for randomized trials (RoB2) (Sterne *et al*., 2019) was used to assess the risk of bias in five domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Three reviewers conducted the assessment of the risk of bias. Any disagreement between reviewers or uncertainty was discussed and resolved. Information supporting the risk of bias assessment was presented in a bespoke Excel spreadsheet (see supplementary material).

Data synthesis

SMO efficacy was investigated using a NMRA with population severity and treatment duration as covariates and was then explored in each population severity group separately using a network meta-analysis. Network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. NMRA is a technique to investigate whether certain study characteristics are associated with the intervention effects in the network meta-analysis (Higgins *et al*., 2022).

To address the risk of overfitting, a sensitivity analysis using a NMRA with only population severity as a covariate was conducted for the primary endpoint on the overall sample of retained studies. A second sensitivity analysis using NMRA was performed with only double-blind RCTs.

Results for all comparisons were synthetized using risk ratio (RR) for abstinence rate and mean difference for PDA, including the 95% confidence interval. For evaluations of consistency in the network, we used the design-by-treatment interaction model (Higgins *et al*., 2012). Analyses assumed random effects for intervention effects within a frequentist framework.

The statistical software that we used was STATA® SE 14.2. NETWORK META was used for performing NMRA and network meta-analysis models.

Credibility and plausibility of findings

The following criteria defined by the EMA and the Cochrane were used to assess the reliability of the subgroup findings: (a) a statistically persuasive and clinically relevant treatment effect has to be demonstrated in the whole population, (b) existence of external evidence defining the subgroup of interest, (c) existence of a pharmacological rationale of the difference of treatment effect between subgroups, (d) the magnitude of the difference of treatment effect between subgroups is statistically significant and practically important, (e) differences of treatment effect between subgroups are observed within and between studies and existence indirect evidence in support of the findings and (f) the subgroup analysis was pre-specified

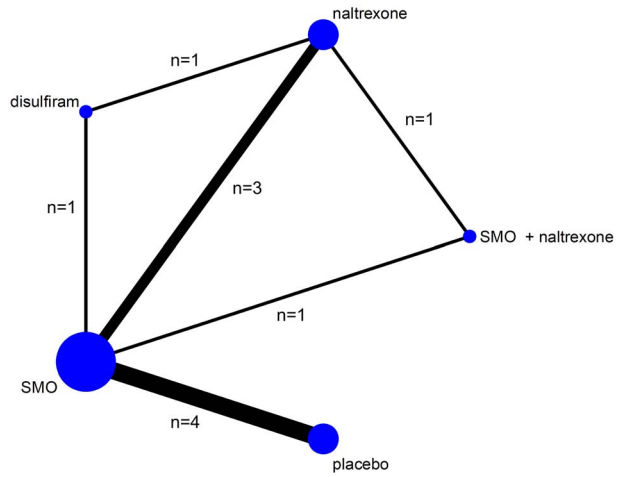

Fig. 3. Network plot of efficacy studies in abstinence rate. SMO: sodium oxybate. Nodes represent the interventions in the network and lines show the available direct comparisons between pairs of interventions, e.g. SMO vs. placebo. The size of the nodes corresponds to the number of participants assigned to each treatment. The thickness of the line and the reported number both indicate the number of trials evaluating the specific comparison.

(European Medicines Agency, 2019; Higgins *et al.*, 2022). See supplementary material for additional information.

RESULTS

Study selection

In total, 2337 references were screened and 2329 were excluded. The main reasons for exclusion were the following: study not about the treatment of AD ($n = 921$), review, meta-analysis, retracted article, not a full-length original research paper (e.g. conference paper, poster) ($n = 449$), no pharmacological treatment tested ($n = 280$) and SMO efficacy not tested ($n = 225$) (Fig. 2 – see list in supplement).

Seven RCTs (reported in eight references) totaling 1082 treated patients fulfilled the selection criteria and were included: four double-blind, placebo-controlled trials testing SMO efficacy and safety (Gallimberti *et al.*, 1992; Di Bello *et al.*, 1995; van den Brink *et al.*, 2018; Guiraud *et al.*, 2021, 2022), one open-label RCT comparing SMO to naltrexone (Caputo *et al.*, 2003), one open-label study comparing SMO to naltrexone and the combination of SMO and naltrexone (Caputo *et al.*, 2007) and one open-label study comparing SMO to naltrexone and disulfiram (Nava *et al.*, 2006) (Fig. 3). All retained studies reported the abstinence rate in each treatment group, whereas three (double-blind placebo controlled) RCTs reported PDA or the cumulative abstinence duration (Gallimberti *et al.*, 1992; Guiraud *et al.*, 2021, 2022). The retained RCTs recruited patients from sites in nine European countries. See Supplementary Table S2 for additional information on included studies.

Risk of bias assessment

Risk of bias assessment showed a low risk or only some concerns for all domains except for the risk of bias due to missing outcome data and for the risk of bias in measurement of the outcome. The dropout rates and the lack of sensitivity analyses for missing data imputation may have affected the treatment effects for four studies, although we considered dropout as relapse/failure for abstinence rate analysis. The high-risk bias in measurement of the outcome for five studies was mainly due to the treatment allocation not being blind in four studies (Supplementary Table S3).

Study allocation to population severity subgroups

One RCT recruited both mild-severity and high-severity patients and the related article reported efficacy data per severity subgroups (Guiraud *et al.*, 2021). For this RCT, each population severity subgroup was considered as a standalone study in the NMRA and was assigned to the group of mild-severity and high-severity studies, respectively. In addition, three RCTs were allocated to the mild-severity group of studies, whereas three RCTs were allocated to the high-severity group of studies (see Supplementary Table S2). Consequently, the mild-severity group in the NMRA consisted of 4 (sub)studies totaling 756 patients and 4 (sub)studies totaling 326 patients were allocated to the high-severity group (Table 1).

Main characteristics of retained studies

Mean age at baseline, percentage of men and mean alcohol consumption at baseline were similar in the two population severity subgroups. However, mean abstinence duration before treatment initiation in the high-severity and in the mild-severity group of studies were very different: 4.7 and 17.4 days, respectively (Table 1). The assignment of studies to the mild-severity group was driven by a long abstinence duration before treatment initiation for three studies and by a non-heavy alcohol consumption at baseline for one study (Supplementary Table S2). Other baseline characteristics scores were available in less than two studies or were expressed differently (e.g. categories vs mean score) and are not reported here.

Primary analysis

In the main analysis, simultaneously including population severity and treatment duration as covariates, the SMO treatment effect in abstinence rate (compared to placebo) was significantly dependent on population severity ($P = 0.004$) and it was increased by an RR (95% CI) of 3.16 (1.45; 6.85) in the high-severity group of studies compared with SMO treatment effect in the mild-severity group of studies (Table 2). In this analysis, treatment duration was not a significant effect modifier of SMO in abstinence rate ($P = 0.139$; Table 2). The sensitivity analysis using only double-blinded RCTs provided very similar results as the main analysis, both in terms of point estimates and statistical significance. The NMRA using only population severity as covariate also showed a significant effect of population severity on SMO treatment effect in abstinence rate with a point estimate very similar to the one in the main analysis.

Secondary analysis

In the secondary analysis, simultaneously including population severity and treatment duration as covariates, the SMO treatment effect in PDA (compared with placebo) was also dependent on population severity ($P < 0.001$) and the SMO treatment effect was increased by a mean difference of +26.9% in the high-severity group compared with SMO treatment effect in the mild-severity group (Table 2). In contrast to the abstinence rate analysis, SMO efficacy in PDA was also significantly dependent on treatment duration:

Table 1. Descriptive statistics and main characteristics in retained studies

Characteristics	Statistical parameters	Overall	Mild-severity population	High-severity population
Retained studies	N studies	8	4	4
Sample size	N patients total	1082	756	326
	Mean (SD)	135 (125)	189 (162)	82 (52)
	Min; Max	17; 339	17; 339	35; 154
Treatment duration (months)	Mean[a] (SD)	4.9 (3.2)	6.8 (3.8)	3.0 (0.0)
	Min; Max	3.0; 12.0	3.0; 12.0	3.0; 3.0
Mean age of patients (years)	Mean[a] (SD)	45.2 (4.1)	44.7 (2.9)	45.6 (5.5)
	Min; Max	37.5; 48.8	40.7; 47.3	37.5; 48.8
% males	Mean[a] (SD)	75.7 (7.4)	80.3 (3.4)	71.1 (7.7)
	Min; Max	63.0; 84.8	76.5; 84.8	63.0; 78.2
Mean alcohol consumption at baseline (g/day)[b]	Mean[a] (SD)	103.0 (36.4)	95.9 (41.3)	113.6 (38.8)
	Min; Max	48.2; 141.1	48.2; 121.2	86.1; 141.1
Mean abstinence duration prior to treatment (days)[b]	Mean[a] (SD)	11.0 (9.7)	17.4 (10.3)	4.7 (2.6)
	Min; Max	1.0; 30.0	5.5; 30.0	1.0; 7.0

[a]Unweighted estimate. [b]The threshold values from inclusion/exclusion criteria regarding alcohol consumption at baseline and/or abstinence duration prior to treatment initiation were used for descriptive statistics computation for studies not reporting mean values (see Supplementary material).
In the overall population, the mild- and high-severity subgroups from the RCT conducted by Guiraud *et al*. (2021) were considered as standalone studies for the computation of descriptive statistics.

Table 2. Effect of population severity and treatment duration on SMO versus placebo treatment effect

Covariates	Estimate	95% CI	*P* value
Main analysis: abstinence rate, 8 studies, 18 arms, 1082 participants			
Population Severity	RR 3.16	1.45–6.85	0.004
Treatment Duration	RR 1.14	0.96–1.35	0.139
Secondary analysis: PDA, 4 studies, 8 arms, 878 participants			
Population Severity	MD 26.9%	17.5–36.2	< 0.001
Treatment Duration	MD 11.3%	6.0–16.5	< 0.001

RR: risk ratio; MD: mean difference; CI: confidence interval; PDA: percentage of days abstinent

SMO treatment effect in PDA in a given severity group was increased by +11.3% per extra month of treatment duration ($P < 0.001$) (Table 2).

Network meta-analysis separately for each population severity subgroup

Given these results, the SMO treatment effect (compared to placebo) was further investigated using a network meta-analysis conducted separately in each severity group for abstinence rate and in each severity group and according to treatment duration for PDA. In the high-severity population and compared with placebo, SMO showed a clinically relevant effect in abstinence rate (RR 2.91; 95%CI 1.11–7.65) and in PDA after a 3-month treatment duration (mean difference + 16.9%; 95%CI 10.9–23.0). In the high-severity population, the combination SMO and naltrexone was also superior to placebo in abstinence rate (RR 5.94; 95%CI 1.42–24.96).

However, in the mild-severity population, the magnitude of the effect was numerically in favor of placebo for naltrexone and disulfiram and placebo was significantly superior to SMO in PDA at 3 months (Table 3). The exception was a significant benefit for SMO compared with placebo in PDA in the mild-severity population after a 6-month treatment duration (mean difference + 23.9%; 95%CI 15.9–32.0) (Table 3).

No evidence of inconsistency based on a random effects design-by-treatment interaction model was found in the network meta-analysis conducted in the high-severity group of studies ($\chi^2 = 1.31$, $P = 0.25$) or in the mild-severity group of studies ($\chi^2 = 0.14$, $P = 0.71$).

Credibility and plausibility of findings

Data support fulfilment of the EMA and Cochrane criteria for credibility and the plausibility of the findings: (i) SMO showed efficacy in the whole study population; (ii) external evidence for the definition of the selected subgroups exists; (iii) a pharmacological rationale of the difference of treatment effect between subgroups exists; (iv) the difference between subgroups was clinically important and statistically significant and treatment effect in the high-severity was larger than in the mild-severity group, (v) effects of population severity and treatment duration on SMO efficacy have been observed within and across trials and are supported by external evidence from trials on other AD medications; (vi) the protocol for this review was registered in PROSPERO. See supplementary material for the empirical justification of these statements and the supporting literature references.

DISCUSSION

SMO has shown evidence of efficacy in the treatment of AD in a series of RCTs and meta-analyses and treatment with SMO is safe and well-tolerated (van den Brink *et al*., 2018; Addolorato *et al*., 2020). However, substantial heterogeneity of SMO treatment effects has been identified within and across studies (van den Brink *et al*., 2018; Guiraud *et al*., 2021, 2022). Heterogeneity in the efficacy of pharmacotherapies is common in the treatment of AD (Rösner *et al*., 2010; Litten *et al*., 2013;van den Brink *et al*., 2018 ; Scherrer *et al*., 2021). It is, therefore, important to determine the moderators of the treatment effect as well as the target population in which these medications are (most) effective.

Table 3. Treatment effect of active compounds vs. placebo in each population severity group for abstinence rate and per population severity and treatment duration for PDA

Analysis	Treatment	No of arms[a]	No of participants[a]	Estimate (95% CI)	*P* value
Primary outcome: abstinence rate					
High-severity group of studies	SMO + NTX	1	18	RR 5.94 (1.42–24.96)	0.015
	SMO	4	192	RR 2.91 (1.11–7.65)	0.030
	NTX	2	34	RR 1.22 (0.35–4.28)	0.751
Mild-severity group of studies	SMO	4	473	RR 1.06 (0.77–1.47)	0.706
	NTX	1	27	RR 0.80 (0.42–1.51)	0.484
	DSF	1	31	RR 0.64 (0.33–1.25)	0.192
Secondary outcome: PDA					
High-severity – 3 months Tx	SMO	2	149	MD +16.9% (10.9–23.0)	< 0.001
Mild-severity – 3 months Tx	SMO	1	282	MD −9.9% (−17.7 to −2.2)	0.012
Mild-severity – 6 months Tx	SMO	1	154	MD +23.9% (15.9–32.0)	< 0.001

SMO: sodium oxybate; DSF: disulfiram; NTX: naltrexone; Tx: treatment duration; RR: risk ratio; MD: mean difference; CI: confidence interval; PDA: percentage of days abstinent; [a]Mild severity group included three placebo arms (225 participants) and high-severity group included two placebo arms (82 participants);

Here we studied population severity and treatment duration as two potential effect modifiers of SMO using NMRA. Population severity is a categorical variable with two categories that have been defined in literature as a potential effect modifier. It distinguishes heavy drinkers without 'spontaneous improvement' before treatment initiation (high-severity) from other patients (mild-severity) (van den Brink *et al*., 2018; Scherrer *et al*., 2021). Treatment duration is a continuous variable reflecting the planned treatment duration in the retained studies.

In our NMRA of eight studies with 1082 treated AD patients, the effect of SMO compared with placebo was dependent on population severity and was increased in the high-severity group of studies compared with the group of mild-severity: RR 3.16 ($P = 0.004$) for abstinence rate and mean difference + 26.9% ($P < 0.001$) for PDA. The relationship between SMO treatment effect and treatment duration was not significant ($P = 0.139$) for the abstinence rate analysis, but it was significant for the PDA analysis with an increase of 11.3% per extra month of treatment duration ($P < 0.001$). It should be recognized, however, that meta-regressions have low power to detect relationships (especially with dichotomous outcomes) and that at least 10 studies are generally required to detect a modifier effect (Higgins *et al*., 2022).

In the high-severity group of studies, SMO showed a clinically meaningful benefit vs. placebo both in abstinence rate (RR 2.91) and in PDA (mean difference + 16.9%). In contrast, no clinically relevant benefit in abstinence rate vs. placebo was shown in the mild-severity population. In this population, placebo was significantly superior to SMO in PDA at 3 months. This result is explained by data from the Guiraud *et al*. (2021) RCT where the placebo response in PDA at 3 months in the mild-severity subgroup was very high (mean 87.2%) and higher than in SMO group (mean 77.3%) (see supplementary material). The exception was a positive and clinically relevant effect of SMO in PDA for a treatment duration of 6 months in the mild-severity group, illustrating the significant effect of treatment duration on SMO efficacy in this endpoint. The placebo response in PDA was much lower for a 6-month than for a 3-month treatment duration in the mild-severity group (mean 37.9 vs. 87.2% – see supplementary material). At treatment group level, PDA measures the differences in abstinence rate as well as the differences in abstinence duration in relapsing patients. The significant beneficial effect of SMO in PDA in the mild severity population at 6 months can probably be explained by the combination of a longer abstinence duration in relapsing patients and a numerically higher abstinence rate in the SMO compared with the placebo group (Guiraud *et al*., 2022). Therefore, and in our network meta-analysis, SMO efficacy in PDA in the high-severity group of studies was mainly explained by a beneficial effect of SMO in abstinence rate, whereas in the mild-severity group of studies, the beneficial effect of SMO in PDA at 6 months was mainly driven by a longer abstinence duration in relapsing patients and a numerically higher abstinence rate.

Fortunately, and in contrast to a recent network meta-analysis (Cheng *et al*., 2020) that did not adjust treatment effects for population severity and treatment duration, no evidence of inconsistency between direct and indirect estimates of SMO treatment effects was found in the present network meta-analyses, suggesting that population severity and treatment duration are important sources of inconsistency. The lack of evidence of inconsistency may also be due to the small number of studies retained.

The present NMRA investigates differences between studies and individuals were not randomized to go in one trial or another. Hence, this analysis is observational with a risk of bias by confounding, chance findings and aggregation bias, especially when the sample of studies retained is relatively small compared with the number of covariates/moderators tested (Higgins *et al*., 2022). To address these risks, it is important to assess the reliability of the findings. The EMA and the Cochrane provided criteria to be fulfilled to reduce the risk of false causal relationship in meta-regression and to assess the credibility and the plausibility of exploratory subgroup findings (European Medicines Agency, 2019; Higgins *et al*., 2022). Our data support the fulfilment of these criteria and, thus a probable causal relationship between the tested covariates (population severity and treatment duration) and SMO treatment effect seems to exist.

The sensitivity analysis using only double-blind studies provided very similar results as the main analysis and the assignation of these studies to the population severity groups were only based on inclusion/exclusion criteria (see Supplementary Table S2). These data support a low risk of aggregation bias and indicate that results of the main analysis were not markedly affected by the potential bias due to the lack of blinding in some studies.

Drop-out rates in the retained studies were relatively high and were consistent with those commonly observed in AD trials and those in RCTs that were used to establish efficacy of approved compounds in the treatment of AD (Nice, 2011; European Medicines Agency, 2012). However, drop-outs were considered as treatment failures in the analysis of abstinence rate and relapse was the main documented reason for dropout in previous trials (Guiraud *et al*., 2022).

The combination of SMO and naltrexone showed promising results in abstinence rate in the high-severity group, whereas naltrexone and disulfiram did not show any significant benefit in both severity populations. These results have limitations and should be interpreted with caution since they were based on only one direct comparison with a small sample size for most of these interventions.

In conclusion, the present work provides data to explain heterogeneity of SMO efficacy in the treatment of AD. Results support the efficacy of SMO independent of treatment duration in high-severity populations and of long-term SMO treatments in mild-severity populations. Our results may help healthcare providers in the use of SMO for the treatment of AD. Other subgroupings, e.g. according to genetic, neurobiological, and other clinical features, might also be important effect modifiers of SMO (Lesch *et al*., 2020). They need to be further investigated to improve precision medicine for AD patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Alcohol and Alcoholism* online.

AUTHOR CONTRIBUTIONS

J.G. and W.v.d.B. designed the study. S.L., S.B. and J.G. conducted the systematic literature review and the risk of bias assessment. J.G. and B.S. were involved in the statistical analyses. All authors were involved in the data analysis and/or interpretation. J.G. wrote the manuscript and all authors contributed to and have approved the final manuscript.

FUNDING

This work was supported by D&A Pharma. The sponsor was not involved in the study design, data collection, data analysis and interpretation of the data. The corresponding author had final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST STATEMENT

Julien Guiraud is employed by Vergio, Clichy, France. Sylvie Lecoustey and Sylvie Bachelot are employed by D&A Pharma, Paris, France.

Wim van den Brink reports personal fees from D&A Pharma, Kinnov Therapeutics, Bioproject, Lundbeck, Novartis, Indivior, Angelini, Mundipharma, Takeda, Opiant Inc., Recordati, Camurus, Novo Nordisk and Clearmind Medicine.

Maurice Dematteis has provided expert advice to Camurus, Indivior, Molteni, D&A Pharma and Recordati Laboratories, and received fees for lectures from Accord Healthcare, Camurus, Indivior, Recordati and Molteni Laboratories.

Giovanni 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.

Henri-Jean Aubin received financial support from Kinnov Therapeutics, Ethypharm, Lundbeck, Bioprojet Pharma, and Pfizer. He was investigator in the SMO032 study (Guiraud *et al*., 2021).

Rolland Benjamin received fees from Ethypharm and Lundbeck.

David Nutt reports personal fees from D&A Pharma and Lundbeck.

Antony Gual reports grants from Novartis and D&A Pharma. He was investigator in the SMO032 study (Guiraud *et al*., 2021).

Otto Lesch served as a paid consultant for D&A Pharma. He was investigator in the SMO032 study (Guiraud *et al*., 2021) and in the GATE 2 study (Guiraud *et al*., 2022).

Icro Maremmani served as board member for Angelini, Camurus, CT Sanremo, D&A Pharma, Gilead, Indivior, Lundbeck, Molteni, MSD, Mundipharma.

Jürgen Rehm reported personal fees from D&A Pharma and Lundbeck.

Rainer Spanagel reported grants from Horizon 2020 program, Era-NET NEURON, BMBF, Deutsche Forschungsgemeinschaft (DFG), and personal fees from EMCCDA and D&A Pharma.

Andrea de Bejczy is founder and co-owner of Sobrera Pharma AB. She was investigator in the SMO032 study (Guiraud *et al*., 2021).

Philippe Batel reported fees from Lundbeck, D&A pharma, Kinnov therapeutics. He was investigator in the SMO032 study (Guiraud *et al*., 2021).

DATA AVAILABILITY

Database and STATA computer code are available in supplement.

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