Efficacy and Safety of Sodium Oxybate in Isolated Focal Laryngeal Dystonia: A Phase IIb Double-Blind Placebo-Controlled Cross-Over Randomized Clinical Trial

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Objective: To examine the efficacy and safety of sodium oxybate versus placebo in a phase IIb randomized double-blind placebo-controlled 2-period cross-over clinical trial in patients with isolated laryngeal dystonia (LD).
Methods: The study was conducted from January 2018 to December 2021, pausing during the COVID-19 pandemic, at Massachusetts Eye and Ear in 106 patients with alcohol-responsive (EtOH+) and alcohol-non-responsive (EtOH−) LD (53 to receive 1.5g of sodium oxybate first, 53 to receive matching placebo first). The primary outcome was a change from baseline in LD symptom severity 40 minutes after drug intake. Safety was based on vital signs, cognitive function, suicidality, daytime sleepiness, and adverse events. Patients, investigators, and outcome assessors were masked to study procedures.
Results: Compared to baseline, EtOH+ but not EtOH− patients had a statistically significant improvement in LD symptoms following sodium oxybate versus placebo (EtOH+: 98.75% confidence interval [CI] = 0.6–26.9; $p = 0.008$; EtOH−: 98.75% CI = −6.2 to 18.7; $p = 0.42$). Statistically significant minimum drug efficacy in EtOH+ patients was found at ≥16% symptom improvement (OR = 2.09; 98.75% CI = 0.75–5.80; $p = 0.036$), with an average of 40.81% benefits (98.75% CI = 34.7–48.6). Drug efficacy waned by 300 minutes after intake without a rebound. No changes were found in cognitive function, suicidality, or vital signs. Common adverse events included mild dizziness, nausea, and daytime sleepiness.
Interpretation: Sodium oxybate showed clinically meaningful improvement of symptoms in EtOH+ LD patients, with acceptable tolerability. Sodium oxybate offers the first pathophysiologically relevant oral treatment for laryngeal dystonia.

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Dystonia is a movement disorder characterized by uncontrollable muscle contractions leading to abnormal movements, postures, or both. Laryngeal dystonia (LD) is a common form of dystonia, causing involuntary spasms in laryngeal muscles predominantly during speaking. Chronically impaired ability to communicate has a

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debilitating impact on nearly every aspect of a patient's life, causing social isolation, loss of employment, depression, anxiety, and suicidal ideations.[1,2] Approximately one-third of LD patients develop dystonic tremor of voice (DTv),[3] further challenging their vocal communication.[4,5]

Currently, LD symptoms are managed with botulinum neurotoxin (BoNT) injections. However, only 57% of LD patients are treated with BoNT, 40% of whom do not benefit from injections.[3,6,7] On a trial-and-error basis, approximately 6% of patients receive off-label oral medications, such as propranolol, primidone, or clonazepam, which provide only mild, if any, benefits.[7,8] None of these therapies directly target the underlying disorder pathophysiology, leaving patients to rely on short-term, often suboptimal management of their symptoms or remain untreated.[3]

Recent advances in the understanding of symptomatology and pathophysiology of dystonia opened opportunities for probing novel drugs for this disorder. However, randomized controlled trials in these patients remain scarce. Among 6 completed trials of oral drugs for dystonia, only 3 studies reported the outcomes (ClinicalTrials.Gov and PubMed search on March 15, 2024). Phase I/II single-group trial of perampanel in cervical dystonia[9] and phase II randomized double-blind placebo-controlled cross-over trial of levetiracetam in oromandibular and cranial dystonias[10] found no significant effects on symptom severity. Conversely, a phase II open-label single-dose trial of sodium oxybate showed a statistically significant symptom reduction in 82.2% of patients with alcohol-responsive (EtOH+) LD, with and without co-occurring DTv.[11] Drug efficacy was related to the direct modulation of pathophysiologically abnormal neural activity in these patients.[12]

Sodium oxybate is a centrally acting oral agent chemically identical to an inhibitory neurotransmitter, gamma-hydroxybutyric acid (GHB), which mimics some effects of alcohol.[13] Sodium oxybate is converted into GABA within the brain[14] and increases dopamine levels mediated by $GABA_B$ receptors.[15–17] It is a primary pharmacological agent approved by the United States (US) Food and Drug Administration (FDA) (schedule III), Canada (schedule III), and the European Union (schedule IV) to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy age 7 years and above. Sodium oxybate is available only by prescription through a restricted risk evaluation and mitigation strategy (REMS) program, which manages drug distribution, educates physicians and patients on its proper use, and ensures that the benefits of the drug outweigh its risks in each patient receiving the drug.[18] Contrary to illicit GHB, the reports of abuse, misuse, drug-facilitated sexual assault, and dependence on the pharmaceutical product sodium oxybate that is taken at therapeutic doses and according to the dosing schedule are extremely rare.[19–21]

The discovery of LD symptom responsiveness to alcohol in over 50% of patients[22,23] and concurrent pathophysiological deficiencies in GABAergic function[24] has been critical for the initial development of sodium oxybate as a potential treatment for LD.[11,12] The aim of this study was to examine the efficacy and safety of sodium oxybate compared to placebo in LD patients. We hypothesized that similar to alcohol and in contrast to placebo, sodium oxybate is effective in reducing dystonic symptoms with acceptable safety in EtOH+ but not alcohol-non-responsive (EtOH−) LD patients.

Methods

We conducted a phase IIb randomized double-blind placebo-controlled 2-period cross-over single-center clinical trial of a single dose of 1.5g oral sodium oxybate in patients with EtOH+ and EtOH− LD.

Participants

Written informed consent was obtained from all patients before study participation. Inclusion criteria were clinically documented LD with or without DTv, with (EtOH+) or without (EtOH−) benefits of alcohol on their voice symptoms; age from 21 to 80 years; native English language; and right-handedness. The latter two were criteria included as part of a follow-up study to examine the central effects of sodium oxybate (not reported here). Exclusion criteria were incapability of giving informed consent; pregnancy or breastfeeding until a time when they were no longer pregnant or breastfeeding; a past or present history of any neurological disorders (except for LD and DTv), any psychiatric problems, any brain and/or laryngeal surgery, grade 2 or higher hepatic or renal dysfunction according to the US National Cancer Institute (NCI) criteria, moderate to severe congestive heart failure, cognitive impairment, suicidal ideations, alcoholism or high risk for alcohol use disorder according to the National Institute on Alcohol Abuse and Alcoholism definition and Diagnostic and Statistical Manual of Mental Disorders-5 criteria; the use of prescribed or over-the-counter centrally acting medications at the time of the study; asymptomatic presentation because of the BoNT treatment at the time of the study until the time they were fully symptomatic and at least 3 months post their last injection, and no contraindications to magnetic resonance imaging (MRI) as part of the follow-up study to examine the central effects of sodium oxybate. All patients were required to confirm abstaining from alcohol and caffeine for 48 hours before study participation. All patients were required to confirm

that they would not drive or engage in important decision-making, financial, or legal obligations for at least 5 hours after each treatment and that they would not drink alcohol for at least 12 hours after each treatment period.

The diagnoses of LD and DTv were confirmed based on a detailed case history, a review of medical information from the referring physicians, perceptual voice and speech analysis, and neurological and laryngological evaluations.

Alcohol responsiveness of symptoms was established using a standardized alcohol challenge test using 0.8g/l of 40-proof vodka calculated based on the patient's total body water.[25–27] EtOH responsiveness was assessed by counting the number of LD-characteristic voice breaks in each sentence as well as voice harshness/strain, breathiness, and tremor using a visual analog scale (VAS, 0 = none, 10 = most severe/profound) at baseline and 4 time points (15, 30, 45, and 120 minutes) after EtOH intake. These measures were then averaged at each time point and used to calculate the change in symptom severity at 15, 30, 45, and 120 minutes after EtOH intake as ([baseline – EtOH intake]/baseline) × 100%, respectively. Patients with ≥10% symptom improvement from the baseline were considered EtOH+; patients with <10% symptom change were considered EtOH−.

Study Design

The initial study design included an additional control group of patients with EtOH− laryngeal pathology, vocal fold nodules (VFN), a non-neurological condition not related to dystonia or tremor. However, because the conduct of this trial was significantly impacted by the COVID-19 pandemic and could not be completed within the planned timeline, we interpreted these pandemic-related delays as extenuating circumstances and implemented mitigating strategies by excluding the EtOH− VFN group from the study design given that no data in VFN patients were yet acquired, these data were not directly relevant to the drug effects in LD patients, and had no direct impact on the primary outcome measure. This study design modification was reviewed and recommended by the Data Safety and Monitoring Board, approved by the Institutional Review Board of Mass General Brigham, and communicated to the National Institutes of Health and the Food and Drug Administration (FDA).

All EtOH+ and EtOH− LD patients recruited for the study were randomly assigned sodium oxybate in treatment period 1, followed by placebo in treatment period 2, or placebo in treatment period 1, followed by sodium oxybate in treatment period 2. A cross-over design was chosen for this study instead of the more traditional randomized, parallel-group design because the within-patient variation was less than the between-patient variation, and therefore, required fewer patients with this rare neurological disorder. In addition, some of the known disadvantages of the cross-over design (eg, larger dropout rate, instability of the patient's condition, and a potential carryover effect) were not expected in this study. Each treatment period was separated by a 24-hour washout, equating to more than 5 half-lives for either treatment, to allow the effective systemic elimination of the drug or placebo before initiating subsequent treatment.

The study was conducted at Massachusetts Eye and Ear, part of Mass General Brigham, Boston, and approved by the Institutional Review Board of Mass General Brigham (protocol 2019P001680). The study was conducted in accordance with the principles of Good Clinical Practice and the FDA guidelines for safety monitoring. The Data and Safety Monitoring Board met 7 times to provide oversight of this study, reviewed unmasked safety data to ensure the patient's safety, and recommended study design modifications as a mitigation strategy because of extenuating circumstances related to the COVID-19 pandemic. Sodium oxybate and alcohol were administered under the Investigational New Drug protocol (117954, registration July 31, 2013), approved by the FDA (ClinicalTrials.gov NCT03292458).

Randomization and Masking

EtOH+ and EtOH− patients were blindly randomized and allocated to treatment by the Massachusetts Eye and Ear Research Pharmacy using proprietary, publicly available, web-based randomization software (Research Randomizer) to generate the randomization scheme with permuted block randomization and varying block sizes. The randomization was performed before the inclusion of the first patient. Patients were randomized in a 1:1 allocation to 1 of 2 treatment periods—sodium oxybate/placebo or placebo/sodium oxybate—and received a single dose of each treatment (Fig 1).

Sodium oxybate (1.5g) and placebo were formulated in 50ml of water by the Massachusetts Eye and Ear Research Pharmacy. A pharmaceutically manufactured placebo was matched to sodium oxybate by its taste, smell, color, consistency, and appearance. Drug and placebo were delivered in identically appearing, sequentially numbered containers on the morning of each administration, according to the allocation sequence. The study dose was established before the enrollment of the first patient based on prior dose-finding studies.[11,28–31] The single oral dose of 1.5g of sodium oxybate did not change throughout the study.

All patients, investigators, and those assessing outcomes were masked to randomization and allocation until

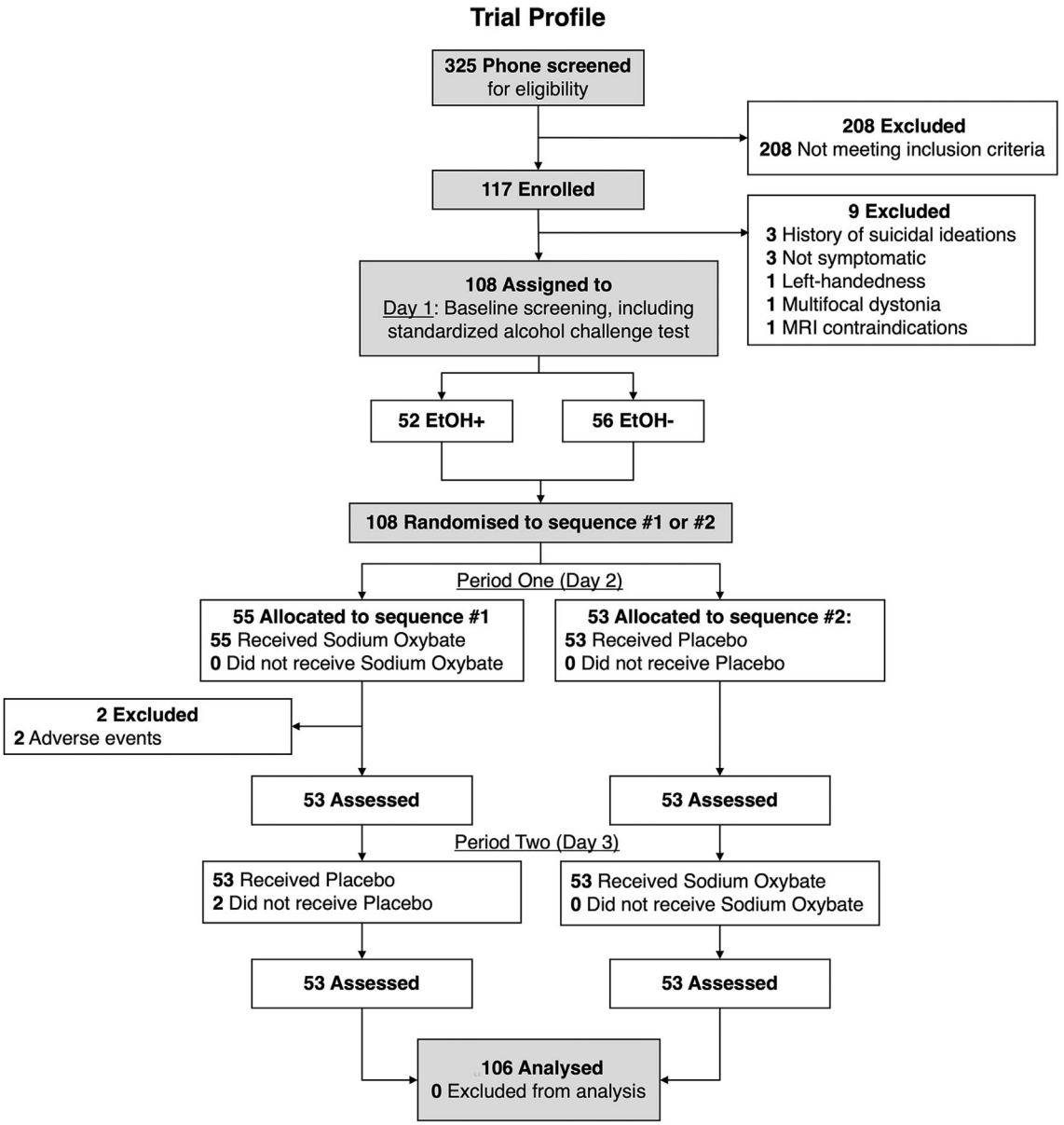

FIGURE 1: The clinical trial profile depicts the flowchart of study screening, enrollment, randomization, allocation, and analysis. EtOH+ = alcohol-responsive; EtOH− = alcohol-non-responsive.

all data were processed for the final statistical analysis. The Massachusetts Eye and Ear Research Pharmacy that generated the random allocation sequence and assigned patients to the sequence of interventions was not involved in the patient screening, enrollment, or the conduct of the study.

Procedures

The study was conducted during 3 visits on 3 consecutive days (days 1–3), with study procedures starting between 9 AM and 10 AM each day in all patients. On day 1, all patients underwent baseline assessments, which included evaluations of vital signs (blood pressure, pulse rate), cognitive status using the Montreal Cognitive Assessment (MoCA), handedness using the Edinburgh Handedness Inventory, suicidal behavior screening using the Columbia-Suicide Severity Rating Scale (C-SSRS), daytime sleepiness using the Epworth sleepiness scale, and alcohol responsiveness using the standardized alcohol challenge test. All patients completed a 9-point self-evaluation of voice and speech symptom severity using a visual analog scale (VAS: 0 = no effort; 9 = constant struggle) (Data S1). The patients marked the score that reflected their symptom severity at the time of evaluation. In addition, voice and speech samples in all patients were recorded during the production of continuous and repeated vowels, vocal glides, humming, shouting, singing, repetition of 20 LD symptom-provoking sentences, including 10 sentences loaded with vowels to evoke

symptoms of adductor LD and 10 sentences loaded with voiceless consonants to evoke symptoms of abductor LD, and spontaneous speech (Data S1).

On days 2 and 3, the baseline assessments (except for the standardized alcohol challenge test) were repeated immediately before drug or placebo intake. A single dose of 1.5g of sodium oxybate and matching placebo were administered orally according to the allocation sequences on 2 consecutive days to ensure an adequate washout period. The expected duration of treatment effects was 3.5 to 4 hours based on prior studies of this drug in patients with LD and voice tremor.[11,32] All patients were re-assessed 40 minutes after drug/placebo intake for changes in their vital signs (blood pressure, pulse rate), cognitive status (MoCA), drug-induced suicide risk (C-SSRS), daytime sleepiness (Epworth sleepiness scale), voice and speech symptoms, as well as adverse events. The 40-minute time point was chosen based on the results of 2 prior phase II open-label clinical trials of sodium oxybate in patients with LD and essential tremor of voice, respectively, where symptom improvement was observed 30 to 45 minutes following 1.0 to 1.5g of sodium oxybate intake.[11,32] All patients were monitored for 300 minutes after treatment, during which their vital signs, MoCA, C-SSRS, Epworth sleepiness scale, voice and speech samples, symptom self-evaluation, and adverse events were collected at 180 and 300 minutes after intake.

At the time of discharge, patients were required to be stable, with vital signs within 10% of their baseline and no adverse events present. All patients were followed up in person or by phone 24 hours after each study visit to inquire about their voice symptom severity and adverse events. All assessments, from baseline to follow-up, were conducted using the same protocol in all patients.

Outcomes

The primary outcome measure was selected before the study as the change from baseline in LD symptom severity 40 minutes after sodium oxybate intake compared to placebo. The primary outcome was assessed based on a combined clinician-objective and patient-subjective VAS score of symptom severity as defined in the clinical trial protocol. As described previously,[32] voice and speech recordings at baseline and 40 minutes after drug and placebo intakes were de-identified, randomized, and blindly perceptually rated for symptom severity by an experienced speech-language pathologist. LD-characteristic voice breaks were quantified in each sentence; voice harshness/strain, breathiness, and DTv were evaluated using VAS (0 = none; 100 = most severe) (Data S1). The intra-rater reliability of perceptual ratings of baseline symptoms between treatment periods 1 and 2 was excellent at Cronbach's $\alpha = 0.9$). Each patient's symptom self-evaluation VAS ratings (0 = no effort, 9 =constant struggle) were extracted at baseline and 40 minutes after drug and placebo intakes. To ensure data comparability, linear normalization was applied to both perceptual ratings and self-evaluation data points by computing scaled variables that have a standard deviation of 1 and a minimum-maximum (min-max) of 0 to 100. The normalized data points in each patient, including the mean number of voice breaks in sentences, harshness/strain, breathiness, tremor, and self-evaluated effort, were averaged to derive a combined clinician-objective and patient-subjective VAS score of symptom severity.[32] The Pearson's correlation coefficients between clinician-rated perceptual and patient-rated symptom severity at baseline and 40 minutes after treatment showed that there were statistically significant correlations between these 2 measures following drug and placebo treatments, respectively (EtOH+: $R_{\text{BASELINE}} \geq 0.40$, $p_{\text{BASELINE}} \leq 0.03$; $R_{40\text{-MIN}} \geq 0.50$, $p_{40\text{-MIN}} \leq 0.008$; EtOH−: $R_{\text{BASELINE}} \geq 0.37$, $p_{\text{BASELINE}} \leq 0.03$; $R_{40\text{-MIN}} \geq 0.38$, $p_{40\text{-MIN}} \leq 0.03$). Therefore, the combined VAS score was assumed to have equal weights of the clinician's perceptual measures and the patient's self-reported assessment and was unlikely to be skewed by either of these measures, ensuring a robust evaluation of symptom severity before and after treatment. Drug and placebo treatment efficacy in each patient was quantified as $\Delta\text{VAS} = ((\text{baseline}_{\text{VAS}} - \text{treatment}_{\text{VAS}})/(\text{baseline}_{\text{VAS}}) \times 100\%$ and used as a measure of primary outcome.

The secondary outcomes were the treatment efficacy dependent on LD clinical form (LD, LD/DTv, adductor, and abductor), the length of treatment efficacy, and the relationship between treatment-induced symptom change, alcohol responsiveness, and clinical characteristics of the disorder, including LD duration, age of onset, and baseline symptom severity.

Safety was documented as a change from baseline in vital signs (blood pressure, pulse rate), cognitive function (MoCA), suicidality (C-SSRS), and daytime sleepiness (Epworth sleepiness scale). Adverse events were assessed using a structured side effects questionnaire and unstructured patient reporting (unprompted self-reporting by patients) as none, mild, moderate, or severe.

Sample Size

The study was powered using data from the open-label study of sodium oxybate in LD and LD/DTv patients,[11] with sample size calculations showing that a total of 22 patients would provide actual power of 0.82 at a significance level of ≤0.01. This more conservative significance level for sample size calculations was chosen to mitigate the potential bias of trials in sequence. Moreover, because

the previous open-label study[11] recruited only EtOH+ LD patients, we increased statistical power for this study by considering the minimum sample size of 22 subjects for each of the EtOH+ and EtOH− groups. Additionally, although our a priori-defined hypothesis was to examine the effects of sodium oxybate versus placebo in EtOH + versus EtOH− patients and not each in LD and LD/DTv phenotypes separately, we aimed to recruit at least 22 patients of each phenotype to ensure the balanced clinical representation of these patients in our study cohorts, therefore further expanding the sample size for increased power. Finally, we aimed to recruit up to 35 patients per EtOH+/EtOH− LD and LD/DTv cohorts to account for study dropouts.

Statistical Analysis

The primary efficacy outcome of mean symptom change at 40 minutes after drug intake compared to baseline was analyzed using a restricted maximum likelihood (REML)-based linear mixed-effect model (LMM). The analysis included group (EtOH+, EtOH−), treatment (sodium oxybate, placebo), and treatment period (day 2, day 3) as interacting fixed effects and subject as random effect. An unstructured covariance structure was used to model the within-patient errors. Significance tests of statistically significant interactions between the fixed effects were based on the linear contrast of least-squares means for the fitted model using a 2-sided $\alpha = 0.01$ (2-sided 98.75% confidence interval [CI]). The multiplicity adjustment was performed using the conservative Scheffé's test to account for testing of all possible linear combinations of groups. The primary treatment comparisons were the contrast between the drug and placebo at 40 minutes after intake. The minimum and average efficacy (in ΔVAS %) of sodium oxybate versus placebo in improving symptoms compared to the baseline were determined using binomial logistic regression.

The secondary outcome of the length of drug/placebo efficacy in EtOH+ and EtOH− patients was examined using the multivariate repeated measures analysis of variance (ANOVA) of the combined ΔVAS score changes from 40- to 180-minute and 300-minute time points, followed by post hoc paired t tests at $p \le 0.01$. The differences in drug/placebo efficacy dependent on the clinical form of LD (LD vs LD/DTv and adductor vs. abductor types) were assessed using 2-sample t tests at corrected $p \le 0.01$. The relationships between drug/placebo-induced symptom changes, alcohol responsiveness, and clinical characteristics of the disorder, including the duration, age of onset, and baseline symptom severity, in EtOH+ and EtOH− patients were examined using Pearson's correlation coefficients at corrected $p \le 0.01$.

For safety endpoints, the treatment effects on vital signs in EtOH+ and EtOH− patients were quantified as a median change from baseline (in %). Multivariate repeated measures ANOVAs were used to analyze the treatment effects on daytime sleepiness, cognitive function, and suicidality at corrected $p \le 0.01$ (2-sided CI, 98.75%). Adverse events were graded as mild, moderate, or severe according to the NCI Common Toxicity Criteria (CTC) scale (grades 0–4) and summarized as a number of patients (% of total), with calculated relative risk and risk difference (2-sided CI, 98.75%) between drug and placebo.

There were no missing values in any patient group. Statistical analysis was implemented using Systat 13, IBM SPSS Statistics, and StatPlus:mac AnalystSoft software.

Results

The study was conducted between January 22, 2018, and December 29, 2021. The COVID-19 pandemic and the associated lockdown of human research activities fully paused patient recruitment and the conduct of study procedures between March 2020 and December 2020.

A total of 325 patients were screened for eligibility for study participation; 208 patients were found ineligible according to the extensive exclusion criteria (see Fig 1). A total 117 patients were enrolled in the trial, of whom 9 patients were excluded because of a history of suicidal ideations as determined using C-SSRS (n = 3), absence of symptoms at the time of study participation (n = 3), left-handedness (n = 1), presence of multifocal dystonia (n = 1), and contraindications to MRI (n = 1). Two patients developed moderate (NCI CTC grade 2) adverse events within 35 minutes of treatment, including drowsiness, dizziness, headache, nausea, vomiting, and blurred vision. Their treatment was unblinded by the Massachusetts Eye and Ear Research Pharmacy for clinical evaluations, and the study was discontinued by investigators with no research data collection. Despite the side effects, both patients reported substantial improvement in their voice symptoms after drug intake. Both patients were discharged by the emergency department licensed physician in the presence of a caregiver. Both patients were followed up by phone the next day, during which neither reported any adverse events.

The final study cohort included 106 patients (74 females/32 males; mean age, 58.6 ± 11.7 years) who received cross-over sodium oxybate and placebo and completed all study procedures (Table 1). Among these, 53 patients had isolated focal LD, and 53 patients had co-occurring DTv as an additional clinical feature of LD. Eight patients reported a family history of dystonia.

TABLE 1. Demographics of Patients with LD

	EtOH+ (n = 50)		EtOH− (n = 56)	
	LD	LD/DTv	LD	LD/DTv
n (%)	23 (21.7)	27 (25.5)	30 (28.3)	26 (24.5)
Gender, n (%)				
Female	15 (14.2)	24 (22.6)	17 (16.0)	18 (17.0)
Male	8 (7.5)	3 (2.8)	13 (12.3)	8 (7.5)
Age (yr), median (IQR)	56.0 (48.5 to 61.5)	62.0 (51.0 to 68.0)	57.0 (48.0 to 63.8)	66.5 (54.3 to 71.8)
Race, n (%)				
Black or African American	3 (2.8)	1 (0.9)	1 (0.9)	2 (1.9)
White	20 (18.9)	26 (24.5)	29 (27.4)	24 (22.6)
Ethnicity, n (%)				
Non-Hispanic or Latino	23 (21.7)	27 (25.5)	30 (28.3)	26 (24.5)
Handedness	Right (Edinburgh Handedness Inventory)			
Language	Monolingual Native English			
Cognitive status	MoCA ≥26			
Dystonia phenotype, n (%)				
Adductor type	12 (11.3)	13 (12.3)	17 (16.0)	16 (15.1)
Abductor type	10 (9.4)	10 (9.4)	12 (11.3)	9 (8.5)
Mixed adductor and abductor type	1 (0.9)	4 (3.8)	1 (0.9)	1 (0.9)
Family history of dystonia, n (%)	3 (2.8)	2 (1.9)	2 (1.9)	1 (0.9)
Age of onset (yr), median (IQR)	38.0 (31.5 to 46.0)	51.0 (32.5 to 56.5)	43.5 (32.5 to 52.8)	46.5 (31.0 to 60.0)
Dystonia duration (yr), median (IQR)	13.0 (9.5 to 20.0)	13.0 (8.5 to 21.5)	11.0 (5.3 to 23.5)	13.5 (7.3 to 28.0)
Botulinum toxin treatment, n (%)	20 (18.9)	25 (23.6)	26 (24.5)	21 (19.8)
Time since last injection (mo), median (IQR)	5.5 (3.0 to 19.3)	10.0 (4.0 to 46.0)	8.5 (6.0 to 24.0)	13.0 (9.0 to 52.0)
Centrally acting medications, n (%)	4 (3.8)	7 (6.6)	7 (6.6)	5 (4.7)
Time since last intake (weeks), median (IQR)	2.0 (0.0 to 0.0)	2.0 (0.0 to 0.0)	2.0 (0.0 to 0.0)	2.0 (0.0 to 0.0)

Abbreviations: DTv = dystonic tremor of voice; EtOH+ = alcohol-responsive; EtOH− = alcohol-non-responsive; IQR =interquartile range; LD = laryngeal dystonia; MoCA = Montreal Cognitive Assessment.

The average duration of LD was 16.0 ± 11.0 years, with an average age of symptom onset of 42.6 ± 14.9 years. Ninety-two patients (45 EtOH+ and 47 EtOH−) received BoNT injections as part of their standard of care, with the last injection administered on average 39.0 ± 61.0 months before study participation. No patient had their last injection less than 3 months before study. Twenty-three patients had a past history of use of centrally acting medications for the management of LD or DTv, including benzodiazepines (n = 10), selective serotonin reuptake inhibitors (n = 8), sedatives (n = 4), barbiturate antiepileptics (n = 2), beta-blockers (n = 2), norepinephrine and dopamine reuptake inhibitors (n = 2), dopamine agonists (n = 2), and serotonin and norepinephrine reuptake inhibitors (n = 2). No patient was on any centrally acting medication for at least 2 weeks before study participation. Detailed demographics and disease characteristics are provided in Table 1.

Efficacy

LMM analysis of the primary outcome measure (ΔVAS score of LD severity 40 minutes after treatment

administration) found a statistically significant group (EtOH+, EtOH−) × treatment (sodium oxybate, placebo) interaction ($F_{3,101} = 4.38$, $p = 0.006$), but not treatment × visit day ($F_{2,101} = 0.37$, $p = 0.69$) or group × treatment × visit day ($F_{2,101} = 0.80$, $p = 0.45$) interactions. Least squares means for statistically significant group x treatment effect found that sodium oxybate at 40 minutes after intake was superior to placebo in EtOH+ patients (98.75% CI = 0.6 to 26.9, $p = 0.008$) but not in EtOH− patients (98.75% CI = −6.2 to 18.7, $p = 0.42$), therefore meeting the a priori primary outcome measure (Fig 2A, Table 2). Statistically significant minimum efficacy following drug vs. placebo intake in EtOH+ patients was found at ≥16% symptom improvement (OR = 2.09, 98.75% CI = 0.75 to 5.80, $p = 0.036$), with an average of 40.81% drug benefits (98.75% CI = 34.7 to 48.6, min–max benefit = 16.4% to 84.6%) (Table 2).

There were no statistically significant differences between LD and LD/DTv forms in response to either sodium oxybate (EtOH+: $t_{47} = 0.95$, 98.75% CI = −10.22 to 21.99, $p = 0.35$; EtOH−: $t_{54} = 0.14$, 98.75% CI = −11.30 to 12.62, $p = 0.89$) or placebo (EtOH+: $t_{47} = -0.98$, 98.75% CI = −26.36 to 11.94, $p = 0.33$; EtOH−: $t_{54} = 1.50$, 98.75% CI = −2.98 to 11.23, $p = 0.14$) (Fig 3A, Table 3). Similarly, there were no differences between adductor LD and abductor LD forms to sodium oxybate (EtOH+: $t_{43} = -1.03$, 98.75% CI = −24.28 to 10.57, $p = 0.31$; EtOH−: $t_{52} = -1.33$, 98.75% CI = −18.85 to 6.07, $p = 0.19$) or placebo (EtOH+: $t_{43} = -0.06$, 98.75% CI = −21.20 to 20.26, $p = 0.95$; EtOH−: $t_{52} = -0.59$, 98.75% CI = −9.41 to 5.92, $p = 0.56$) (see Fig 3B, Table 3).

The drug efficacy gradually tapered off from 40 to 300 minutes after intake, independent of the treatment period, in EtOH+ patients (98.75% CI = −6.22 to 22.15, $F_{47} = 8.68$, $p = 0.001$) and EtOH− patients (98.75% CI = −0.44 to 15.67, $F_{53} = 11.84$, $p = 0.001$) (Fig 3C–I,II, Table 3). There were no statistically significant differences in placebo effects, independent of the treatment period, between 40 and 300 minutes in EtOH + patients (98.75% CI = −7.13 to 12.74, $F_{47} = 1.88$, $p = 0.16$) and EtOH− patients (98.75% CI = −3.32 to 8.38, $F_{53} = 3.25$, $p = 0.05$) (Fig 3C-I,II, Table 3).

There was a statistically significant positive correlation between alcohol-responsiveness of symptoms and drug-induced symptom improvement in EtOH+ patients ($R = 0.45$, 98.75% CI = 0.10 to 6.88, $p = 0.001$), but not in EtOH− patients ($R = 0.09$, 98.75% CI = −0.024 to 0.35, $p = 0.53$) (Fig 3D-I,II, Table 4). There were no statistically significant correlations between alcohol responsiveness and the placebo-induced symptom change in EtOH+ patients ($R = 0.06$, 98.75% CI = −0.034 to 0.39, $p = 0.68$) and EtOH− patients ($R = 0.22$, 98.75% CI = −0.10 to 0.55, $p = 0.10$) (Fig 3D-I,II, Table 4). There were no statistically significant correlations between drug- or placebo-induced symptom changes and the disorder duration, age of onset, or baseline symptom severity in EtOH+ and EtOH− patients (all $R \le 0.24$, $p \ge 0.88$) (Table 4).

Safety

All 106 study participants tolerated sodium oxybate sufficiently well without serious adverse events (NCI CTC grade ≤1). The vital signs (blood pressure, pulse rate) in all patients were stable throughout the study and at discharge, with a median change from baseline of ≤4.65% at 40 minutes, ≤ 3.99% at 180 minutes, and ≤2.47% at 300 minutes after drug or placebo intake in both EtOH+ and EtOH− patients. No rebound treatment effects with increased LD severity were observed in any patient either at 300 minutes after the drug/placebo intake or 24 hours after the study.

Cognitive function as assessed by MoCA was unchanged after drug or placebo intake, independent of the treatment period, in EtOH+ patients (drug: $F_{2,47} = 1.54$, 98.75% CI = −0.53 to 0.33, $p = 0.23$; placebo: $F_{2,47} = 1.61$, 98.75% CI = −0.78 to 0.34, $p = 0.21$) and EtOH− patients (drug: $F_{2,53} = 1.12$, 98.75% CI = −0.53 to 0.24, $p = 0.33$; placebo: $F_{2,53} = 0.89$, 98.75% CI = −0.54 to 0.32, $p = 0.42$).

There were no treatment-induced suicidal ideations in any patient based on the C-SSRS questionnaire performed at baseline, 40, 180, and 300 minutes after intake.

Compared to baseline, increased daytime sleepiness after sodium oxybate intake was reported by 18 patients (16.9%), including 10 EtOH+ patients and 8 EtOH− patients (Fig 2B). Three EtOH+ patients (2.8%) reported increased daytime sleepiness after placebo (Fig 2C). A statistically significant difference in daytime sleepiness was found 40 minutes after drug intake compared to placebo in both EtOH+ and EtOH− patients, independent of the treatment period ($t_{105} = -3.33$, 98.75% CI = −0.29 to −0.04, $p = 0.001$). Daytime sleepiness returned to normal baseline at the time of the 180-minute assessment after treatment in all patients ($t_{105} = 1.55$, mean difference = 0.09, 98.75% CI = −0.06 to 0.25, $p = 0.12$).

All adverse events were study emergent; none of the adverse events were of special interest. Adverse events after drug intake were reported by 27 (54.0%) of 50 EtOH+ patients and 36 (64.3%) of 56 EtOH− patients (Fig 2B). Adverse events after placebo were observed by 7 (14.0%) of 50 EtOH+ patients and 13 (23.2%) of 56 EtOH− patients (Fig 2C). Table S1 presents the absolute risk,

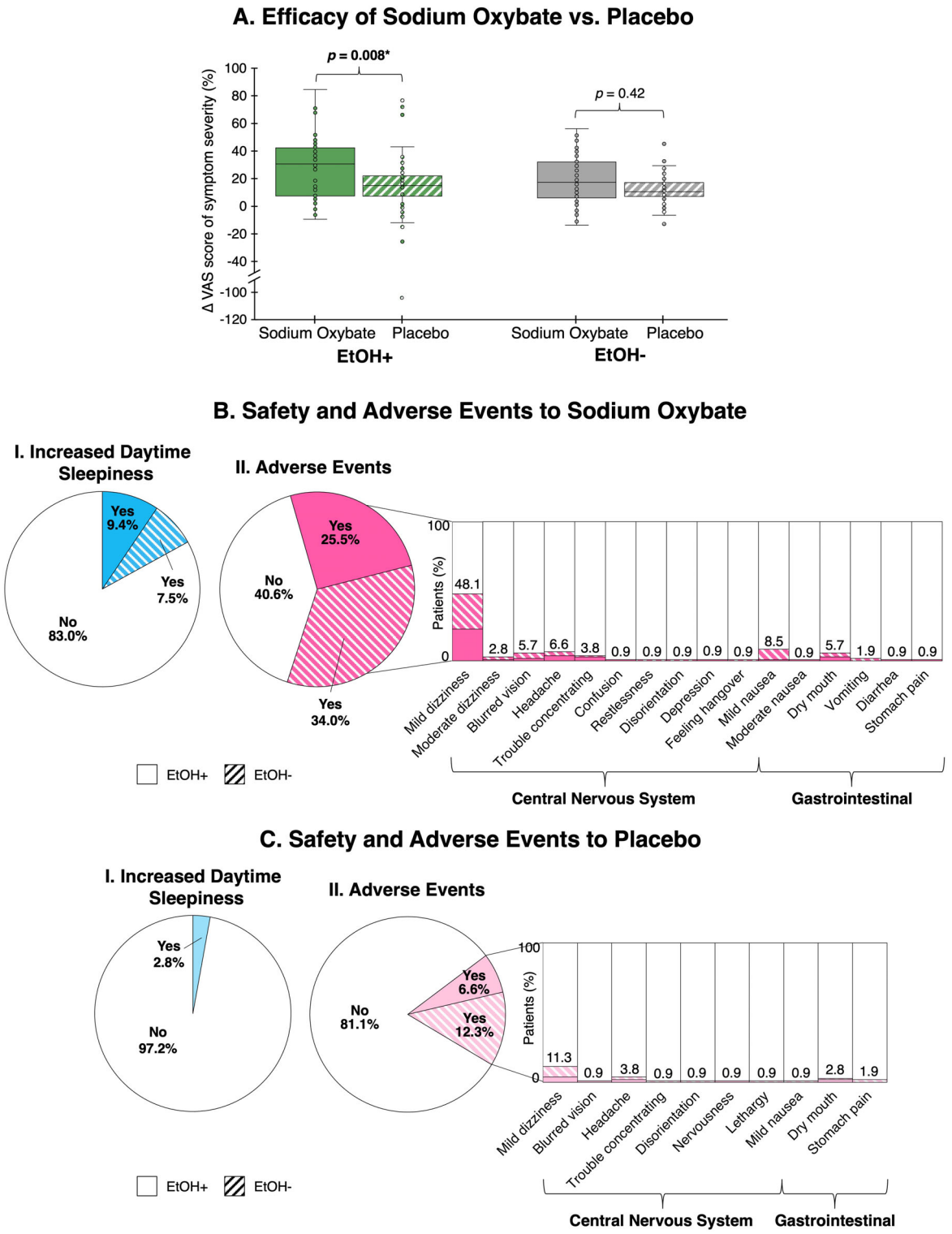

FIGURE 2: (A) Efficacy of sodium oxybate versus placebo in patients with alcohol-responsive (EtOH+) and alcohol-non-responsive (EtOH−) laryngeal dystonia (LD). The asterisk indicates the statistically significant difference between sodium oxybate and placebo based on the change in the visual analog scale (ΔVAS) score of voice symptom severity. (B) Safety and adverse events of sodium oxybate in EtOH+ and EtOH− patients, including (I) increased daytime sleepiness and (II) other adverse events. (C) Safety and adverse events of placebo in EtOH+ and EtOH− patients, including (I) increased daytime sleepiness and (II) other adverse events.

relative risk, and the estimates of risk difference between drug and placebo in EtOH+ and EtOH− patients. All drug-associated adverse events were resolved between 30 and 60 minutes after intake in 40 patients (37.7%) and between 2 and 5 hours after intake in 23 patients (21.7%). All placebo-associated adverse events were

TABLE 2. Primary Efficacy Outcomes of Sodium Oxybate and Placebo in Patients with LD

Treatment-induced ΔVAS score of symptom severity

Variable	LD Patient Group	Drug	Placebo	Treatment difference (drug-placebo)	SE	*p*
n		106	106	106	–	–
LS mean	EtOH+	28.0	14.2	13.8	3.9	0.008
98.75% CI		21.0 to 35.0	7.2 to 21.2	0.6 to 26.9	–	–
LS mean	EtOH−	18.6	12.3	6.3	3.7	0.42
98.75% CI		12.0 to 25.2	5.7 to 19.0	−6.2 to 18.7	–	–

Minimum treatment efficacy

LD patient group	ΔVAS score of symptom severity	Drug event (n)	Mean (98.75% CI)	Placebo event (n)	Mean (98.75% CI)	OR (98.75% CI)	*p*
ETOH+	≥16%	32	40.81 (34.7 to 48.6)	23	30.53 (22.7 to 39.6)	2.09 (0.75 to 5.80)	0.036
	<16%	18	4.76 (1.1 to 8.1)	27	0.24 (−13.4 to 8.5)		

Note: Mean indicated ΔVAS score of symptom severity.
Abbreviations: CI = confidence interval; EtOH+ = alcohol-responsive; EtOH− = alcohol-non-responsive; LD = laryngeal dystonia; LS = least squared means; OR = odds ratio; SE = standard error.

resolved within 15 and 60 minutes after intake in 12 patients (11.3%) and within 2 and 5 hours after intake in 8 patients (37.7%). No drug- or placebo-associated adverse events were reported on the 24-hour follow-up in any patient.

Discussion

This phase IIb randomized double-blind placebo-controlled 2-period cross-over single-center clinical trial demonstrated that a single dose of 1.5g of oral sodium oxybate is superior to placebo in patients with isolated focal EtOH+ LD. The strong positive relationship between alcohol-responsiveness of dystonic voice symptoms and sodium oxybate efficacy in EtOH+ LD patients and the lack of substantial drug benefits in EtOH− LD patients support the premise that the mechanism of action of sodium oxybate is similar to that of alcohol via modulation of pathophysiologically deficient GABAergic function in this disorder.[12,24] We, therefore, recommend careful clinical evaluation and selection of EtOH+ LD patients as candidates for sodium oxybate treatment, preferably using a standardized alcohol challenge test.[25,26]

Given the overall efficacy of sodium oxybate in EtOH+ LD patients, it is notable that no differences in symptom improvement were found across different LD phenotypes, including those with adductor, abductor, and tremor features. Similarly, no relationship was observed between sodium oxybate efficacy and voice symptom severity, indicating that patients with mild to severe EtOH+ LD may equally benefit from this drug. The finding of sodium oxybate efficacy being independent of dystonia phenotype contrasts starkly with the suboptimal efficacy of BoNT injections,[3,6,7] the benefits of which highly depend on LD clinical presentation, leading to the majority of patients with abductor LD and moderate to severe vocal tremor receiving little to no benefits from injections.[6,33] Taken together, the data from the current and prior[11] clinical trials demonstrate that the full spectrum of EtOH+ LD patients, including those with different clinical features and symptom severity as well as those who do not benefit from BoNT injections or choose to forgo injections because of personal or medical reasons, may benefit from sodium oxybate treatment.

The dosage of sodium oxybate is an important aspect of its benefits and prospective clinical use in EtOH + LD patients. The robust improvement of EtOH+ LD

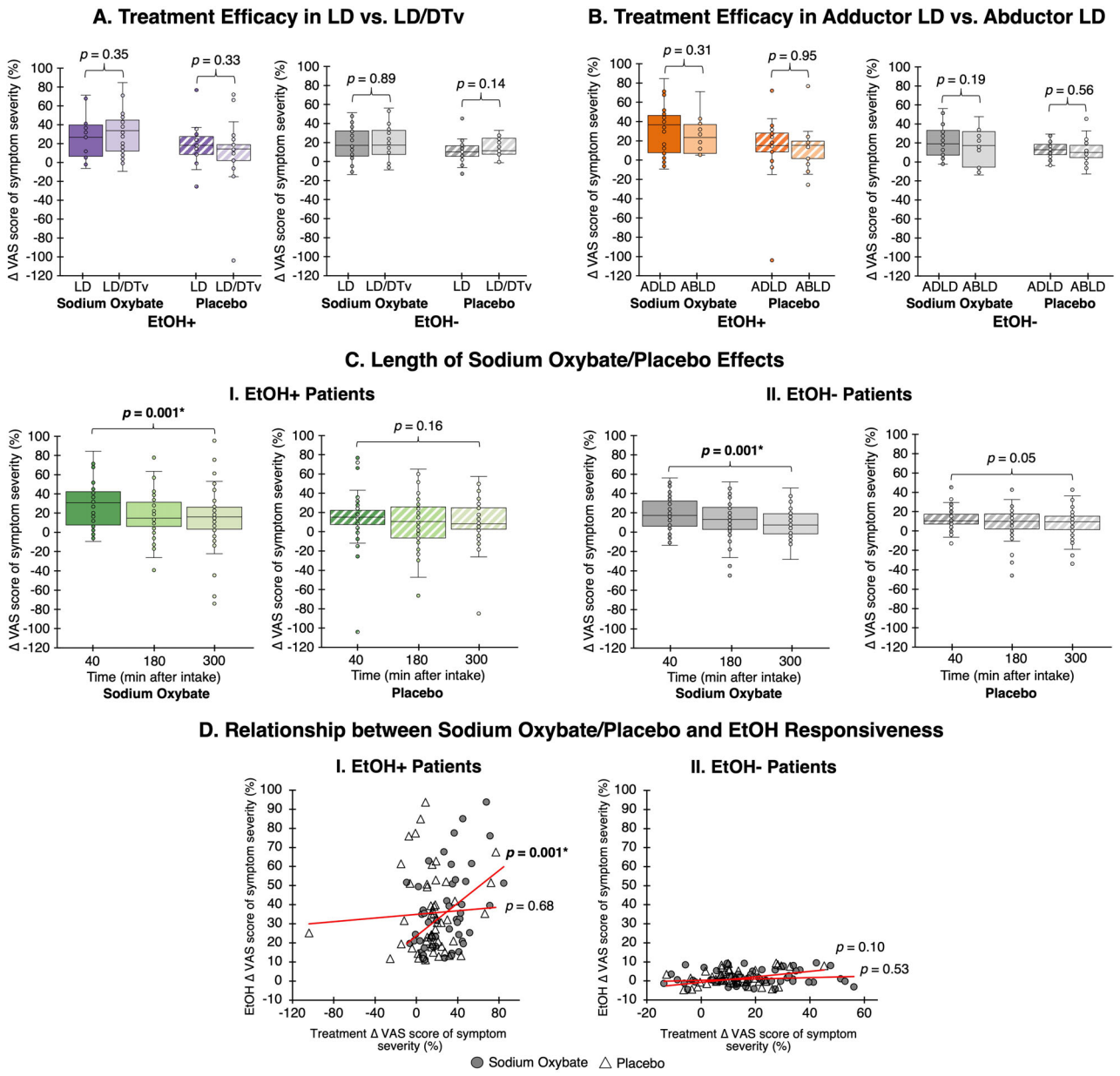

FIGURE 3: (A) Treatment efficacy in laryngeal dystonia (LD) patients with and without dystonic tremor of voice (DTv), stratified into alcohol-responsive (EtOH+) and alcohol-non-responsive (EtOH−) groups. (B) Treatment efficacy in LD patients with adductor (ADLD) and abductor (ABLD) forms, stratified into EtOH+ and EtOH− groups. (C) The length of sodium oxalate and placebo effects on voice symptoms at 40, 180, and 300 minutes compared to baseline in (I) EtOH+ patients and (II) EtOH− patients. (D) Relationships between sodium oxybate/placebo and alcohol responsiveness in improving voice symptoms in patients with EtOH+ and EtOH− LD. Change in symptom severity because of drug/placebo effects was quantified using a combined visual analog scale (ΔVAS) score. The asterisk indicates the statistically significant difference between group comparisons.

symptoms from a single 1.5-g dose 40 minutes after intake, with mild and transient side effects, gradual wearing off of benefits over the course of 5 hours, and without symptom rebound, indicates that the drug may be taken on an as-needed basis. Such a patient-facing treatment regimen is both cost-affordable and symptom-oriented, allowing patients, together with their treating physicians, to make informed decisions about when they are most in need of their symptom management without compromising the overall drug benefits, but minimizing its potential side effects.

Although sodium oxybate showed statistically significant improvement of symptoms in EtOH+ patients, there were 4 patients (8%) whose symptoms worsened by no more than 10% from baseline at 40 minutes after drug intake. However, this finding was not unique to EtOH+ patients as symptom worsening was twice as common (9, 16.1%) in EtOH− patients. Furthermore, similar symptom worsening was observed after placebo intake in both EtOH+ (9, 18.0%) and EtOH− (6, 10.7%) patients. These data suggest that symptom worsening in

Table 3. Secondary Efficacy Outcomes of Sodium Oxybate and Placebo in Patients with Laryngeal Dystonia

Variable	LD patient group	Phenotype	n	Drug	Placebo	Mean difference (98.75% CI)	*t*	*df*	*p*
Treatment effects on LD phenotypes									
Mean (SE)	EtOH+	LD	23	24.65 (4.45)	–	5.89 (−10.22 to 21.99)	0.95	47.32	0.35
		LD/DTv	27	30.54 (4.29)	–				
Mean (SE)	EtOH−	LD	30	18.30 (3.07)	–	0.66 (−11.30 to 12.62)	0.14	54.0	0.89
		LD/DTv	26	18.96 (3.49)	–				
Mean (SE)	EtOH+	LD	23	–	18.07 (3.99)	−7.21 (−26.36 to 11.94)	−0.98	48.0	0.33
		LD/DTv	27	–	10.85 (5.90)				
Mean (SE)	EtOH−	LD	30	–	10.34 (1.94)	4.13 (−2.98 to 11.23)	1.50	54.0	0.14
		LD/DTv	26	–	14.47 (1.93)				
Mean (SE)	EtOH+	AD	25	31.70 (5.08)	–	−6.85 (−24.28 to 10.57)	−1.03	43.0	0.31
		AB	20	24.85 (3.92)	–				
Mean (SE)	EtOH−	AD	33	21.36 (2.86)	–	−6.39 (−18.85 to 6.07)	−1.33	52.0	0.19
		AB	21	14.96 (4.04)	–				
Mean (SE)	EtOH+	AD	25	–	13.59 (6.07)	−0.47 (−21.20 to 20.26)	−0.06	43.0	0.95
		AB	20	–	13.10 (4.62)				
Mean (SE)	EtOH−	AD	33	–	13.07 (1.54)	−1.75 (−9.41 to 5.92)	−0.59	52.0	0.56
		AB	21	–	11.32 (2.83)				

Variable	LD patient group	Time point after intake (T; min)	n	Drug	Placebo	Mean difference (98.75% CI)	*F*	*df*	*p*
Length of treatment efficacy									
Mean (SE)	EtOH+	T1: 40	50	28.00 (3.06)	–	T1–T2: 9.38 (2.64 to 16.13)	8.68	47.0	0.001
		T2: 180	50	18.63 (3.36)	–	T2–T3: 3.16 (−6.22 to 12.53)			
		T3: 300	50	15.47 (4.32)	–	T1–T3: 12.54 (2.93 to 22.15)			
Mean (SE)	EtOH−	T1: 40	56	18.60 (2.31)	–	T1–T2: 5.93 (0.64 to 11.22)	11.84	53.0	0.001
		T2: 180	56	12.67 (2.40)	–	T2–T3: 4.34 (−0.44 to 9.11)			
		T3: 300	56	8.33 (1.98)	–	T1–T3: 10.27 (4.87 to 15.67)			
Mean (SE)	EtOH+	T1: 40	50	–	14.23 (3.71)	T1–T2: 4.97 (−2.80 to 12.74)	1.88	47.0	0.16
		T2: 180	50	–	9.26 (3.61)	T2–T3: −1.03 (−7.13 to 5.06)			
		T3: 300	50	–	10.30 (3.15)	T1–T3: 3.94 (−1.59 to 9.46)			
Mean (SE)	EtOH−	T1: 40	56	–	12.34 (1.39)	T1–T2: 3.03 (−2.32 to 8.38)	3.25	53.0	0.05
		T2: 180	56	–	9.31 (1.99)	T2–T3: 1.15 (−3.32 to 5.62)			
		T3: 300	56	–	8.16 (1.84)	T1–T3: 4.18 (−0.02 to 8.38)			

Note: Mean indicated ΔVAS score of symptom severity.

Abbreviations: CI = confidence interval; *df* =degrees of freedom; LD = laryngeal dystonia; OR = odds ratio; SE = standard error; VAS = visual analog scale.

TABLE 4. Secondary Efficacy Outcomes of Clinical Associations of Sodium Oxybate and Placebo in Patients with LD

Correlation	LD patient group	Treatment	n	R_P	98.75% CI	*p*
Clinical associations of treatment efficacy						
ΔVAS score of symptom severity × EtOH responsiveness	EtOH+	Drug	50	0.45	0.10 to 6.88	0.001
		Placebo	50	0.06	−0.034 to 0.39	0.68
	EtOH−	Drug	56	0.09	−0.024 to 0.35	0.53
		Placebo	56	0.22	−0.10 to 0.55	0.10
ΔVAS score of symptom severity × dystonia duration	EtOH+	Drug	50	−0.17	−0.51 to 0.16	0.25
		Placebo	50	0.18	−0.21 to 0.52	0.20
	EtOH−	Drug	56	0.10	−0.26 to 0.49	0.45
		Placebo	56	0.16	−0.17 to 0.44	0.24
ΔVAS score of symptom severity × age of symptom onset	EtOH+	Drug	50	0.16	−0.14 to 0.47	0.26
		Placebo	50	−0.18	−0.46 to 0.22	0.20
	EtOH−	Drug	56	−0.15	−0.43 to 0.18	0.26
		Placebo	56	−0.09	−0.40 to 0.30	0.58
ΔVAS score of symptom severity × baseline symptom severity	EtOH+	Drug	50	−0.05	−0.31 to 0.20	0.73
		Placebo	50	0.24	−0.20 to 0.58	0.09
	EtOH−	Drug	56	−0.04	−0.47 to 0.36	0.77
		Placebo	56	−0.11	−0.39 to 0.18	0.42

Abbreviations: CI = confidence interval; EtOH+ = alcohol-responsive; EtOH− = alcohol-non-responsive; LD = laryngeal dystonia; VAS = visual analog scale.

these patients might be attributed to general characteristics of this disorder, including LD symptom fluctuations and fatigue associated with the extended period of vocal communication, and is unlikely to be because of the direct drug effects. On the contrary, the lowest rate of symptom worsening in EtOH+ patients further supports the benefits of sodium oxybate in these patients.

There were several patients in the EtOH− group who seemingly benefitted from sodium oxybate. However, the reduction in their voice symptoms after drug intake was not statistically different from the placebo effects. Therefore, we cannot conclude or recommend that EtOH− patients may substantially benefit from sodium oxybate because its effects observed in a few patients during this study are similar to those of placebo and may be driven by external factors.

The safety profile of 1.5g of sodium oxybate was stable and consistent with the findings from previous studies.[11,28–31] There were no statistically significant changes in cognitive function, suicidality, or vital signs following drug administration in either EtOH+ or EtOH− LD groups. Relevant to the daytime intake of sodium oxybate, an important finding was transiently increased daytime sleepiness, which was reported 40 minutes after drug intake, returning to the normative baseline in all patients at the time of the 180-minute assessment. It is notable that, although daytime sleepiness was statistically significant following the drug than placebo intake, this side effect was observed only in 16.9% of all patients and relatively equally in EtOH+ and EtOH− patients. This finding suggests that daytime sleepiness is a drug-induced side effect independent of the patient population. It is recommended to monitor daytime sleepiness in these patients following sodium oxybate intake.

Among other commonly expected but mild adverse events of sodium oxybate in both EtOH+ and EtOH− patients were dizziness reported by a total of 48.1% of patients compared to a total of 10.4% of patients after placebo and nausea reported by a total of 8.5% of patients compared to a total of 0.9% of patients after placebo.

Other adverse events affecting the central nervous and gastrointestinal systems were found in less than 6.6% of all patients following sodium oxybate intake and less than 3.8% of all patients following placebo. Although most adverse events were mild, a smaller fraction of patients experienced moderate dizziness (2.8%) and moderate nausea (0.9%). Interestingly, an overall greater proportion of EtOH− patients (34.0%) than EtOH+ patients (25.5%) reported adverse events after sodium oxybate. As sodium oxybate is most beneficial for the treatment of EtOH+ patients, the effective adverse events in this cohort may be somewhat less frequent than in the general LD population. Most importantly, all side effects, including daytime sleepiness, dizziness, and nausea, were found to be transient and short-lived, without adverse effects at 24-hour follow-up. The next phase III clinical trial is warranted to provide further safety data on sodium oxybate in EtOH+ LD patients. In the meantime, sodium oxybate should be taken in accordance with the safety measures of its FDA-approved package insert, including the contraindications, warnings, and precautions. For example, sodium oxybate is contraindicated in combination with alcohol and sedative hypnotics. Providers should caution patients about operating hazardous machinery, including cars and airplanes, until they are reasonably certain that the drug does not affect them adversely.

Limitations

A potential limitation of this study includes a single-center trial. However, the patients were recruited across the United States as well as from the United Kingdom and Canada, therefore, expanding the generalizability of the findings. Another limitation may be the inclusion of a greater number of non-Hispanic White females. LD is well-documented to affect the non-Hispanic White population with a 4:1 female to male prevalence.[3,7] Therefore, the demographics of patients recruited for this trial reflect the clinical demographics of the disorder in general.

A potential indecision for the use of sodium oxybate might be its perceived association with illicit GHB used for non-medical purposes. However, empirical research has consistently shown that risks of misuse, abuse, and cognitive impairment are greater with the use of illicit GHB than pharmaceutical product because of the differences in the accessibility, purity, and dosing between these formulations.[20,34] The known rates of substance abuse, substance dependence, physical dependence, and diversion of pharmaceutical sodium oxybate at therapeutic doses taken at a prescribed dosing schedule have been extremely low since its introduction to the market in the United States in 2002, as well as in Europe and Canada.[21,35,36] This is partly owing to the robust risk management program (REMS) of this drug, which mandates the enrollment and certification of the prescribers and patients, drug dispensing only from a REMS-certified pharmacy, and extensive screening and counseling of patients before first dispense. Furthermore, given the dose-dependence of side effects of the drug,[37] the safety profile of a low 1.5-g dose of sodium oxybate in EtOH+ LD patients is found to be associated with mild and transient side effects compared to their greater incidence following intake of 4.5 to 9.0g dose of sodium oxybate indicated in narcolepsy patients. Together, the recognition of differences in the misuse and abuse liabilities for illicit GHB versus pharmaceutical product, the established pharmacovigilance of the REMS program, and the low profile of side effects of 1.5g-dose of sodium oxybate recommended in EtOH+ LD patients may help ensure that eligible patients have continuous access to this medication.

Summary

The results of this phase IIb randomized double-blind placebo-controlled 2-period cross-over single-center clinical trial demonstrate that sodium oxybate provides clinically meaningful improvement of voice symptoms in patients with EtOH+ LD, without a rebound and with acceptable tolerability. This study supports the future phase III multi-site randomized clinical trial for the potential translation of sodium oxybate as the first successful, pathophysiologically relevant oral treatment of LD. Moreover, given the common clinical feature of responsiveness of dystonic symptoms to alcohol,[22,23] sodium oxybate might be a potent oral drug for the treatment of other forms of alcohol-responsive dystonia.

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Author Contributions

K.S. contributed to the conception and design of the study; K.S., L.C.O., A.F.R., A.H.S., S.J.F, A.W., N.S.,

and P.C.S. contributed to the acquisition and analysis of data; K.S. and L.C.O. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

All data relevant to clinical and research information of the datasets used in this study are included in the manuscript. De-identified participant data and related study documents used in this study are available from the corresponding author, subject to the data user agreement and approval by the Mass General Brigham Data and Tissue Sharing Committee from the time of publication onward.

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