ABSTRACT: Background: Essential tremor of voice (ETv) is characterized by involuntary oscillations of laryngeal and upper airway muscles, causing rhythmic alterations in pitch and loudness during both passive breathing and active laryngeal tasks, such as speaking and singing. Treatment of ET is challenging and typically less effective compared with treatment of ET affecting extremities.

Objective: We conducted a proof-of-concept, open-label phase II study to examine the efficacy and central effects of sodium oxybate in patients with alcohol-responsive ETv.

Methods: All subjects received 1.0 to 1.5 g of oral sodium oxybate and underwent brain functional magnetic resonance imaging. The primary endpoint was the number of patients (% from total) with reduced ETv symptoms by at least 10% at about 40 to 45 minutes after sodium oxybate intake based on the combined visual analog scale score of ETv symptom severity. The secondary endpoint included changes in brain activity after sodium oxybate intake compared to baseline.

Results: Sodium oxybate reduced ETv symptoms on average by 40.8% in 92.9% of patients. Drug effects were observed about 40 to 45 minutes after intake, lasting about 3.5 hours, and gradually wearing off by the end of the fifth hour. The central effects of sodium oxybate were associated with normalized activity in the cerebellum, inferior/superior parietal lobules, inferior frontal gyrus, and insula and re-established functional relationships between these regions.

Conclusions: Sodium oxybate showed high efficacy in ETv patients, with a likely central action on disorder pathophysiology. Sodium oxybate may be an effective novel oral drug for treatment of alcohol-responsive ETv patients. © 2023 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: voice tremor; sodium oxybate; treatment; alcohol

Introduction

Essential tremor (ET) is the most common movement disorder, with a prevalence of 5% among individuals aged 65 years and above.¹,² The voice is affected in up to 30% of ET patients, presenting either as an isolated symptom or combined with tremor of extremities.³⁻⁵ Essential tremor of voice (ETv) is characterized by
involuntary oscillations of laryngeal and upper airway muscles leading to rhythmic alterations in pitch and loudness during both passive breathing and active laryngeal tasks, such as speaking and singing.4,6

Treatment of ETv presents a significant therapeutic challenge. Trials of β-blockers, antipsychotics, anticonvulsants, and botulinum neurotoxin (BoNT) injections into the laryngeal or upper airway muscles, speech-language therapy, and rarely deep brain stimulation (DBS) have been employed. Typically, oral drugs have lower efficacy for ET symptoms affecting voice than extremities.1,7,8 BoNT injections are somewhat more effective for the isolated lateral variant of ETv involving intrinsic laryngeal muscles than tremor originating from extralaryngeal sources.7 Speech-language therapy provides temporary strategies for improving voice loudness and speech intelligibility but has widely variable outcomes across patients.9 Finally, DBS surgery targeting the thalamic ventral intermediate nucleus shows some efficacy in ETv patients, with better outcomes using bilateral than unilateral stimulation.10-12 Overall, the clinical management of ETv is lacking, primarily relying on temporary relief of symptoms rather than targeting disorder pathophysiology, which is thought to involve abnormal multisensory information processing in the cerebellar-thalamo-cortical network.13,14

In this proof-of-concept, open-label phase II study, we examined the therapeutic efficacy and central effects of sodium oxybate for treatment of patients with alcohol-responsive ETv. Sodium oxybate is a Schedule III controlled substance approved by the U.S. Food and Drug Administration to treat cataplexy in patients with narcolepsy. The drug is also approved in Canada and the European Union for the same indications, where it is classified as a Schedule III and Schedule IV controlled substance, respectively. Sodium oxybate is chemically identical to γ-hydroxybutyric acid (GHB), a naturally occurring neurotransmitter.15 After oral intake, it is quickly absorbed, crosses the blood–brain barrier, and is converted into γ-aminobutyric acid (GABA) within the brain.16 It acts on GABAergic and GHB receptors that bind to extrasynaptic GABA<sub>β</sub> receptors, with the highest density in the thalamus and cerebellum,17,18 both structures being relevant pathophysiological targets of tremor.

In a recent open-label study in patients with alcohol-responsive laryngeal dystonia with co-occurring dystonic tremor of voice (DTv), we demonstrated that a single dose of 1.0 to 1.5 g of sodium oxybate was beneficial in 90.9% of these patients.19 Importantly, we found that sodium oxybate directly modulated the abnormal neural network in these patients.20 Building on this knowledge and taking into account the pathophysiology of ETv, we hypothesized that sodium oxybate would show similar efficacy in reducing ETv symptoms via modulation of brain activity within the tremor-inducing neural network.

Patients and Methods
Study Participants

A total of 17 ETv patients and 15 healthy controls were recruited for study participation. The study was powered based on the data from the study of sodium oxybate in patients with DTv,19 with sample size calculations showing that 12 ETv patients would have the effect size dz of 0.92 and the actual power of 83% to detect significant differences in voice symptoms after a single-dose drug intake at a two-sided α level of 0.05.

The inclusion criteria for all subjects, including patients and controls, were right-handedness, native monolingual English language, and normal cognitive status. Additional inclusion criteria for patients were a confirmed diagnosis of ETv based on detailed case history, perceptual voice/speech analysis, neurological and laryngological evaluations, fully symptomatic ETv presentation during study participation, and self-reported improvement of voice symptoms after alcohol intake, empirically measured as a 12-oz can of beer, 6-oz glass of wine, or 1-oz shot of hard alcohol. The exclusion criteria for all subjects, including patients and controls, were any past or present history of neurologic conditions (excluding ET in patients), psychiatric disorders, suicidal ideations, significant radiologic findings on brain magnetic resonance imaging (MRI), recent history (within 1 year) of voice and speech therapy, current use of centrally acting medications, presence of non-MRI-compatible tattoos or ferromagnetic implants, and pregnancy or breastfeeding during study participation.

Written informed consent was obtained from all subjects before study participation, approved by the Institutional Review Boards of Icahn School of Medicine at Mount Sinai and Mass General Brigham. Sodium oxybate was administered under the Investigational New Drug protocol (11,7954, date of registration: July 31, 2013), approved by the Food and Drug Administration (clinicaltrials.gov registration: NCT01961297). Brain imaging data from some subjects were reported in the previous study.13

Study Design and Sodium Oxybate Treatment

Sodium oxybate was administered only to ETv patients to assess the drug’s effects on voice symptoms compared to their baseline. Healthy controls did not receive sodium oxybate and participated only in the neuroimaging study as a comparative group for establishing baseline alterations in ETv.
ETv-Related Neural Alterations

Immediately prior to drug intake, all patients underwent baseline assessments, including vital signs, cognitive status using the Mini-Mental State Examination, drug-induced suicidal behavior screening using the Columbia-Suicide Severity Rating Scale, and daytime sleepiness using the Epworth Sleepiness Scale. Same assessments were also administered to all healthy controls. In addition, all patients completed a self-evaluation of voice and speech symptom severity using a 10-point visual analog scale (VAS), and their voice and speech samples were recorded during the production of continuous vowels, 20 symptom-provoking sentences, and spontaneous speech.

All ETv patients and healthy controls underwent baseline functional MRI (fMRI) on a 3.0-T Phillips scanner equipped with an eight-channel head coil. Whole-brain fMRI data were obtained using a gradient-weighted echo-planar imaging (EPI) pulse sequence and blood oxygen level-dependent (BOLD) contrast with sparse-sampling event-related design (repetition time (TR): 2 seconds per volume, 10.6 seconds between volumes, echo time (TE): 30.0 ms, flip angle (FA): 90°, field of view (FOV): 240 mm, voxel size: 3.75 × 3.75 × 4.00, 4-mm slice thickness, 36 slices). As described previously, this scanning protocol was used to minimize motion artifacts due to orofacial movements during speech production and to neutralize the scanner noise interference using acoustic stimulus presentation. To further reduce head movements during scanning, the patients’ head was tightly cushioned within the head coil, and patients were instructed to remain motionless throughout the scan.

The fMRI experimental task included eight symptom-provoking English sentences and a resting condition. After the acoustic presentation of a sample sentence (3.6 seconds) via the MR-compatible headphones, patients were cued with an arrow to produce the same sentence (5 seconds) and then remain silent for brain volume acquisition (2 seconds). Task and resting conditions were pseudorandomized within and between functional runs and patients. A total of 32 speech production trials were acquired in each patient during four functional runs. A two-way audio communication system was used during scanning to monitor the patients and ensure correct task performance. A high-resolution T1-weighted MRI image using a 3D-magnetization-prepared rapid acquisition gradient echo sequence (TR: 7.5 ms, TE: 3.4 ms, FA: 8°, FOV: 210 mm, 1-mm slice thickness, 172 slices) was acquired as an anatomical reference.

Following all baseline assessments, ETv patients received a single dose of 1.0 or 1.5 g of sodium oxybate (Xyrem) administered orally during one study visit in the clinical setting. The dose was established based on the combination of our clinical experience, prior dose-finding studies, and each patient’s description of his or her alcohol tolerance. That is, patients who reported alcohol benefits after one drink received 1.0 g of sodium oxybate, whereas patients who reported alcohol benefits from two or more drinks received 1.5 g of sodium oxybate. Patients who reported limited tolerance for alcohol received 1.0 g.

The aforementioned baseline assessments, except for fMRI, were repeated in ETv patients at two time points, 40 to 45 minutes and 5 hours after drug intake. Additionally, a side effects questionnaire was administered to capture adverse events at both time points. ETv patients repeated the fMRI study 1 hour after sodium oxybate intake.

All patients remained in the clinic for 5 hours after drug administration to monitor the drug efficacy and possible adverse events. During the monitoring period, patients were verbally asked about the status of their symptoms (improved, worsened, and no change from baseline) at about 30-minute intervals, except for the time they were in the MRI scanner. If there were no changes from baseline in the patient’s vital signs or behavioral measures and no adverse events at the end of the fifth hour, they were discharged with the instructions not to drive and not to engage in any activity requiring sustained attention and decision-making for at least 12 hours after drug intake.

All patients were followed up by phone the next day after study participation to assess their ETv symptoms and possible side effects. Those patients who expressed interest in obtaining sodium oxybate prescription for continuous treatment of their ETv symptoms were referred to a movement disorders neurologist outside of this study. All patients were followed up about 1 year after study participation to inquire about their potential off-label use of sodium oxybate prescribed by their treating physician to manage ETv symptoms.

All assessments and questionnaires administered throughout the study and at the 1-year follow-up were performed using the same version.

Data Processing

In each patient, symptom severity ratings based on their self-evaluation VAS scores (0: normal/no ETv, 10: most severe/profound ETv) before and after drug intake were extracted to derive patient-subjective measures of sodium oxybate efficacy. Additionally, voice and speech recordings in all patients at baseline and 40 to 45 minutes after drug intake were perceptually analyzed to derive clinician-objective measures of drug efficacy. For this, recordings were anonymized, randomized, blinded by an investigator not related to this study, and blindly perceptually acoustically rated using a 10-point VAS (0: normal/no voice tremor, 10:
most severe/profound ETv). Each patient’s self-
evaluation VAS score and perceptual acoustic VAS score were then averaged to derive a combined measure of ETv severity before and after drug intake, respectively, thus incorporating both clinician-objective and patient-subjective assessments.

Brain image analysis in ETv patients and healthy controls was performed using AFNI software. Following the standard image processing afni_proc.py pipeline, the first two volumes were removed from individual time series to account for scanner magnetization equilibrium. Using heptic polynomial interpolation, time series were registered to the volume collected closest in time to the anatomical scan and aligned to the anatomical reference image. Time series were then spatially normalized to the AFNI standard Talairach–Tournoux space, spatially smoothed using a 4-mm Gaussian filter, and normalized to the percentage signal change. A regressor for the task was convolved with a canonical hemodynamic response function and entered into a multiple regression model to estimate the BOLD response. Control for motion artifacts included regression of motion parameters, censoring of TRs, and censoring of outlier TRs, as described earlier. Regression of motion parameters was based on six motion parameter estimates calculated during the realignment of the EPI volumes, which were included as covariates of no interest, and three quadratic polynomials, which were used to model baseline drifts for each imaging run. Censoring of TRs excluded those with Euclidean norm of the motion derivative ≥1.0 based on simulations of motion artifacts in the presence of a slow effective TR of 10.6 seconds. Because outliers capture residual motion in cases where the motion parameters do not, additional censoring of outlier TRs was performed to ensure the stringent removal of TRs containing residual motion artifacts.

**Statistical Analysis**

The primary endpoint was the number of patients (% from total) with reduced ETv symptoms by at least 10% at about 40 to 45 minutes after sodium oxybate intake based on the combined VAS score of ETv symptom severity. The secondary endpoint included changes in brain activity after sodium oxybate intake compared with baseline.

The Wilcoxon matched-pairs test examined the drug effects on ETv symptoms by comparing the individual combined VAS scores at baseline and 40 to 45 minutes after drug intake at P ≤ 0.05, corrected for ties and zeros. Nonparametric statistics were employed to account for a small sample size in determining the effects of sodium oxybate on ETv symptoms, despite normally distributed data (all W ≥ 0.87, P ≥ 0.052). Sodium oxybate efficacy in each patient was quantified as ((baselineVAS – drug intakeVAS)/[baselineVAS]) × 100%. The relationships between ETv severity, duration, and age of onset at baseline and 40–45 minutes after drug intake were examined using Spearman’s rank correlation coefficients at Bonferroni-corrected P ≤ 0.05. In addition, Friedman tests examined cognitive function, daytime sleepiness, and drug-induced suicidal ideations at baseline compared to 40 to 45 minutes and 5 hours after drug intake at corrected P ≤ 0.05. Statistical analysis was performed in StatPlus:mac software, AnalystSoft Inc.

To determine ETv-specific brain activity at baseline (i.e., prior to drug intake), a 2-tailed independent t test was computed contrasting ETv patients and healthy controls at family-wise error (FWE)-corrected P ≤ 0.05 with minimum cluster size threshold ≥343 mm³ as determined using 3dClustSim program in AFNI software. To examine changes in brain activity after sodium oxybate intake, a paired t test was computed contrasting activity at baseline and 1 hour after drug intake in ETv patients at FWE-corrected P ≤ 0.05, with minimum cluster size threshold ≥858 mm³. To identify the effects of sodium oxybate on the pattern of functional connectivity, individual mean percentage BOLD signal changes were extracted in all patients from brain regions that showed significant drug modulatory effects, and Spearman’s rank correlation coefficients were computed to assess the functional relationships between these regions at baseline and 1 hour after drug intake at R ≥ 0.5 and corrected P ≤ 0.05. Finally, Spearman’s rank correlation coefficients were computed between ETv clinical characteristics (duration, onset, and severity) and mean percentage BOLD signal change from regions of significant drug effects at Bonferroni-corrected P ≤ 0.05. Statistical analysis was performed using AFNI software.

**Results**

**Patient Characteristics**

Of 17 recruited patients, 3 patients were found ineligible due to unclear diagnosis (n = 1), profound hearing loss (n = 1), and the presence of a history of a brain lesion unrelated to tremor (n = 1). The final study cohort included 14 ETv patients (12 women/2 men, mean age: 62.5 ± 13.5 years) and 15 age- and sex-matched healthy controls (12 women/3 men, mean age: 56.2 ± 7.4 years) (see detailed demographics and disease characteristics in Table 1). Seven patients were diagnosed with isolated ETv, and 7 patients were diagnosed with combined ET of extremities, head, and voice. Five patients reported a family history of ET. The average duration of ETv was 8.6 ± 5.9 years, with the average age of symptom onset of 53.9 ± 15.3 years.

Thirteen patients never received BoNT injections; 1 patient received the last injection 6 months prior to study participation, with full symptom presentation.


**TABLE 1  Participant demographics**

<table>
<thead>
<tr>
<th>Demographic/clinical feature</th>
<th>ETv patients (n = 14)</th>
<th>Healthy controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>12 women/2 men</td>
<td>13 women/3 men</td>
</tr>
<tr>
<td>Age (y, mean ± SD)</td>
<td>62.5 ± 13.5</td>
<td>56.2 ± 7.4</td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive status</td>
<td>MMSE ≥27</td>
<td></td>
</tr>
<tr>
<td>Age of ETv onset (y, mean ± SD)</td>
<td>53.9 ± 15.3</td>
<td>na</td>
</tr>
<tr>
<td>Duration of ETv (y, mean ± SD)</td>
<td>8.6 ± 5.9</td>
<td>na</td>
</tr>
<tr>
<td>Baseline ETv severity (mean ± SD)</td>
<td>6.1 ± 1.8</td>
<td>na</td>
</tr>
<tr>
<td>ET distribution</td>
<td>7 isolated voice/4 voice and hands/3 voice, hands, and head</td>
<td>na</td>
</tr>
</tbody>
</table>

Abbreviations: ETv, essential tremor of voice; SD, standard deviation; MMSE, Mini-Mental State Examination; na, nonapplicable.

during the study. Eight patients received centrally acting medications as the standard of care for ET, including β-blockers (n = 2), muscle relaxants (n = 3), anticonvulsants (n = 2), selective serotonin reuptake inhibitors (n = 2), and dopamine promoters (n = 1). All eight patients refrained from taking these medications for at least 2 weeks prior to their study visit; thus, no patient was on any centrally acting drug or BoNT during study participation. All patients abstained from alcohol and caffeine for 24 hours prior to the study to be fully symptomatic at the time of participation.

All patients reported that their ETv symptoms improved for ~3 to 4 hours after at least one alcoholic drink. Patients’ self-reports of alcohol responsiveness were confirmed by a family member or friend.

**Efficacy and Central Effects of Sodium Oxybate**

All patients tolerated sodium oxybate well, without major adverse effects. The vital signs and cognitive status were stable, there were no drug-induced suicidal ideations, and daytime sleepiness was within the normal range at baseline and remained unchanged 40 to 45 minutes and 5 hours after drug intake (all corrected $\leq 0.41$, $P \geq 0.57$). Transient minor side effects were observed in 9 of 14 patients (64.3%), which were present regardless of drug efficacy and included lightheadedness (n = 9, 100%) or dry mouth (n = 1, 11.1%). All side effects in all 9 patients resolved within 45 to 60 minutes after drug intake. No rebound effects with increased ETv severity were found either at the fifth hour after the drug intake or on the next day after the study.

Based on the combined clinician-objective and patient-subjective VAS score of ETv symptom severity, 13 of 14 patients (92.9%) showed an average of 40.8 ± 18.4% reduction in ETv symptoms, ranging from 12.5% to 66.7%, after a single dose of 1.0 to 1.5 g of oral sodium oxybate. One of 14 patients (7.1%) had no symptom changes (either improvement or worsening) after drug intake. Sodium oxybate showed a significant effect on ETv severity (corrected $Z = -3.2$, $P = 0.001$) at 40 to 45 minutes after intake, thus meeting the primary endpoint (Fig. 1A). There were no significant correlations between ETv severity, duration, and age of onset either before drug intake ($R_S \leq 0.52$, $P \geq 0.06$) or 40 to 45 minutes after treatment ($R_S \leq 0.47$, $P \geq 0.09$). Based on patients’ reports and our observations during the monitoring period, symptom improvement lasted on average of 3.5 hours, gradually wearing off by the end of the fifth hour.

When brain activity was examined in ETv patients compared with healthy controls prior to sodium oxybate intake (baseline), patients exhibited increased activity in the left primary sensorimotor cortex, supplementary motor area, middle occipital gyrus, cerebellar lobule VIIa, right inferior frontal gyrus and inferior parietal lobule (IPL, area PGp), bilateral superior parietal lobule (SPL, area 7), and middle orbital gyrus (Fig. 1B; Table 2). About 1 hour after sodium oxybate intake, ETv patients showed decreased activity in the right inferior frontal gyrus, insula, IPL (area PGp), middle occipital gyrus, cerebellum (lobules IV–V and vermis), and bilateral SPL (area 7 and precuneus) compared to their individual baseline, thus meeting the secondary endpoint (Fig. 1C; Table 2).

Brain regions modulated by sodium oxybate established strong functional relationships with each other after but not before treatment. At baseline before sodium oxybate treatment, the only significant relationship was present between IPL and occipital cortex ($R_S = 0.56$, $P = 0.05$). Conversely, after treatment, correlated activity was strengthened between IPL and
FIG. 1. (A) ETv severity at baseline and 40 to 45 minutes after sodium oxybate intake in all patients, including drug responders and drug nonresponders. (B) Statistically significant differences in brain activation during symptomatic speech production at baseline (prior to drug intake) between ETv patients and healthy controls. Brain slices are shown in AFNI standard Talairach–Tournoux space. Color bars represent t scores. (C) Statistically significant differences in brain activation during symptomatic speech production before and 1 hour after drug intake in ETv patients. Brain slices are shown in AFNI standard Talairach–Tournoux space. Color bars represent t scores. (D) Functional correlations between regions with statistically significant differences in brain activity before and 1 hour after drug intake in ETv patients. The dashed line represents the functional relationship between brain regions present before and after drug intake; solid lines represent reestablished functional relationships 1 hour after drug intake. (E) Scatter plots show Spearman’s rank correlation coefficients between cerebellar BOLD (blood oxygen level-dependent) signal change (%) and ETv duration (years) before and 1 hour after drug intake. Cbl, cerebellum; ETv, essential tremor of voice; IFG/Ins, inferior frontal gyrus/insula; IPL, inferior parietal lobule; MOccG, middle occipital gyrus; PreC, precuneus; SPL, superior parietal lobule; VAS, visual analog scale.
Thus making it a potent treatment choice. Sodium oxybate is structurally similar to GABA and mimics the effects of alcohol, known to modulate the inhibitory neurotransmitter GABA, deficiencies of which are thought to be critical in ET pathophysiology. 

SODIUM OXYBATE FOR VOICE TREMOR

**TABLE 2** Differences in brain activity during speech production

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Cluster peak</th>
<th>Cluster size</th>
<th>Cluster peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x y z</td>
<td>(mm³)</td>
<td>t score</td>
</tr>
<tr>
<td>ETv patients &gt; healthy controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L primary sensorimotor cortex</td>
<td>-23, -29, 48</td>
<td>1929</td>
<td>3.5</td>
</tr>
<tr>
<td>L supplementary motor area</td>
<td>-2, -32, 62</td>
<td>1072</td>
<td>3.6</td>
</tr>
<tr>
<td>L middle occipital gyrus</td>
<td>-44, -81, 3</td>
<td>1029</td>
<td>3.4</td>
</tr>
<tr>
<td>L cerebellum (lobule VIIa)</td>
<td>-23, -81, -32</td>
<td>858</td>
<td>4.1</td>
</tr>
<tr>
<td>R. inferior frontal gyrus</td>
<td>58, 10, 10</td>
<td>943</td>
<td>3.2</td>
</tr>
<tr>
<td>R. inferior parietal lobule (area PGp)</td>
<td>47, -67, 13</td>
<td>1372</td>
<td>3.8</td>
</tr>
<tr>
<td>L/R superior parietal lobule (area 7)</td>
<td>16, -67, 36</td>
<td>2015</td>
<td>3.4</td>
</tr>
<tr>
<td>L/R middle orbitobulgy</td>
<td>2, 45, -11</td>
<td>4416</td>
<td>4.3</td>
</tr>
</tbody>
</table>

| ETv patients: baseline > sodium oxybate intake | | | |
| R. inferior frontal gyrus, extending to insula | 44, 13, -1 | 1415 | 5.1 |
| R. inferior parietal lobule (area PGp) | 44, -57, 13 | 4631 | 4.9 |
| R. middle occipital gyrus | 30, -78, 34 | 1801 | 3.5 |
| R. cerebellum (lobules IV–V and vermis) | 12, -39, -8 | 900 | 3.7 |
| R. superior parietal lobule (area 7) | 9, -71, 48 | 858 | 3.8 |
| L/R superior parietal lobule (precuneus) | 5, -53, 27 | 1072 | 3.8 |

Abbreviations: ETv, essential tremor of voice; L, left; R, right.

occipital cortex \( (R_S = 0.59, P = 0.03) \) and established between the IPL and SPL/area 7 \( (R_S = 0.79, P = 0.001) \), IPL and SPL/precuneus \( (R_S = 0.76, P = 0.003) \), IPL and insula \( (R_S = 0.60, P = 0.03) \), IPL and cerebellum \( (R_S = 0.65, P = 0.02) \), SPL/precuneus and middle occipital cortex \( (R_S = 0.80, P = 0.001) \), SPL/area 7 and occipital cortex \( (R_S = 0.68, P = 0.01) \), SPL/area 7 and SLP/precuneus \( (R_S = 0.82, P = 0.001) \), and SPL/area 7 and cerebellum \( (R_S = 0.72, P = 0.006) \) (Fig. 1D). The cerebellar activity showed a significant negative correlation with ETv duration before drug intake \( (R_S = -0.65, P = 0.016) \) but not 1 hour after treatment \( (R_S = 0.01, P = 0.99) \) (Fig. 1E).

One year after study completion, 4 (28.6%) of 14 patients were lost to follow-up. Of the remaining 10 patients, 5 patients (50%) were successfully receiving sodium oxybate treatment prescribed by their treating physician outside of this study, 4 patients (40%) were interested in the treatment but unable to fill the prescription due to medical insurance reimbursements, and 1 patient (10%) was not interested in the treatment.

**Discussion**

In this open-label phase II study, we demonstrated that 1.0 to 1.5 g of oral sodium oxybate significantly reduces voice symptoms by an average of 40.8% in 92.9% of patients with self-reported alcohol-responsive ETv. The drug had no rebound effects and was well tolerated, although nearly two-thirds of patients showed transient mild side effects. Sodium oxybate had fast-acting (within 40–45 minutes after intake) but short-lived (on average, 3.5 hours) effects on ETv symptoms. Thus, to maintain the therapeutic benefits, sodium oxybate may require daily repeated intake on average every 4 hours; however, due to its fast-acting mechanism, drug intake may be administered as needed to manage ETv symptoms in a particular setting. The absence of significant relationships between ETv severity and the drug effects suggests that sodium oxybate can be successfully used independent of disorder severity in both mild and severe cases. Importantly, drug-induced symptom improvement is associated with central modulation of abnormally increased brain activity and restoration of functional connectivity within the voice tremor neural network, as discussed later.

Alcohol responsiveness of tremor symptoms is a well-documented feature of the disorder.\(^{23,28}\) Alcohol is known to modulate the inhibitory neurotransmitter GABA, deficiencies of which are thought to be critical in ET pathophysiology.\(^{10}\) Sodium oxybate is structurally similar to GABA and mimics the effects of alcohol,\(^{17,31}\) thus making it a potent treatment choice likely directly acting on tremor pathophysiology. The
therapeutic benefits of sodium oxybate have previously been explored in small cohorts of alcohol-responsive ET patients and shown to significantly reduce kinetic and postural tremor severity. Our study expands on these initial findings while focusing on voice symptoms in ET patients, for whom the existing strategies provide only suboptimal treatments to manage their disorder. Our findings parallel those of the previous study in patients with another tremor variant, DTv co-occurring with laryngeal dystonia, which demonstrated that 90.9% of DTv patients have an average of 46.8% reduction in symptom severity. Overall, these data suggest that sodium oxybate is efficacious across the spectrum of alcohol-responsive ET phenotypes, in general, and voice tremor variants, in particular.

In developing novel treatments for ETv, the considerations of disorder pathophysiology are of critical importance. Recent studies have reported functional and structural alterations in the primary sensorimotor cortex, IPL, SPL, inferior temporal gyrus, prefrontal cortex, insula, thalamus, and cerebellum across different forms of ET, including ETv, suggesting abnormal integration of multisensory information for coordination of motor sequence execution in these patients. These studies implicated GABAergic system disturbances as one of the underlying contributors to reduced inhibitory synaptic transmission, leading to increased activity in the cerebello-thalamo-cortical network. Our current findings of changes in brain activity during symptomatic speech production in ETv patients compared to healthy controls replicate the results of the previous studies and provide the foundation for examining the effects of sodium oxybate on brain function.

In particular, we show that the central effects of sodium oxybate include the modulation and reduction of abnormally increased activity in the cerebellum, IPL, SPL, inferior frontal gyrus, and insula and the re-establishment of functional relationships between these regions. Cerebellar alterations may be one of the main targets of sodium oxybate as GABA_A receptors and GHB receptors that bind to extrasynaptic GABA_A receptors are found at the highest density in the cerebellum. Parietal and prefrontal areas are known targets of the cerebellar output, therefore, the normalization of cerebellar function with sodium oxybate likely has a further impact on cortical activity. The latter is seen in attenuated IPL, SPL, inferior frontal, and insular activity after drug intake. These regions are known to be critical hubs in the speech production network, supporting multimodal information processing and integration for speech motor output. The restoration of functional connectivity between within cerebellar and cortical regions is another prominent neuromodulatory effect of sodium oxybate, which supports the recently proposed cerebellar decoupling hypothesis in ET pathophysiology. Our data point to the reversibility of such regional decoupling with sodium oxybate, leading to the amelioration of ETv symptoms.

The limitations of this study must be acknowledged. One limitation is related to the inclusion of ETv patients based on self-reported responsiveness of symptoms to alcohol. Although we confirmed their assessments of alcohol responsiveness with family members or friends, there might be variability in the degree of alcohol-induced ETv improvement that could not be captured without additional objective measures. Another limitation is that placebo effects cannot be ruled out, given the experimental design of this proof-of-concept open-label study. However, the reproducible kinetics of sodium oxybate in the vast majority of ETv patients and its modulatory effects on brain regions involved in disorder pathophysiology suggest that the drug efficacy may not exclusively be driven by placebo. Importantly, this study warrants future double-blind, placebo-controlled, randomized clinical trials of sodium oxybate in a larger cohort of ETv patients.

In summary, we provide the first experimental evidence that 92.9% of alcohol-responsive ETv patients showed an average of 40.8% symptom reduction after a single-dose oral administration of sodium oxybate. Significant neuromodulatory effects of sodium oxybate involve the normalization of pathophysiological cerebellar and parietal-prefrontal cortical activity, which may be an underlying mechanism of sodium oxybate action in ETv.

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Data Availability Statement
The dataset used and analyzed in the current study is available from the corresponding author upon reasonable request.

References


Author Roles