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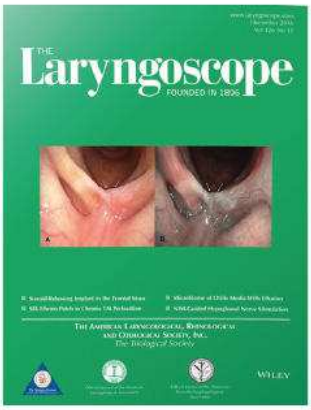

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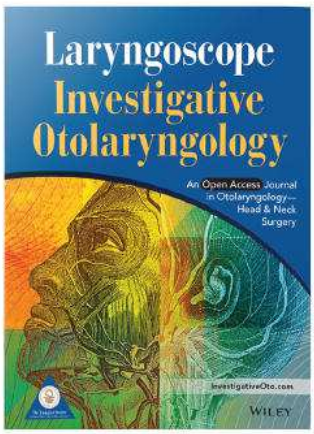

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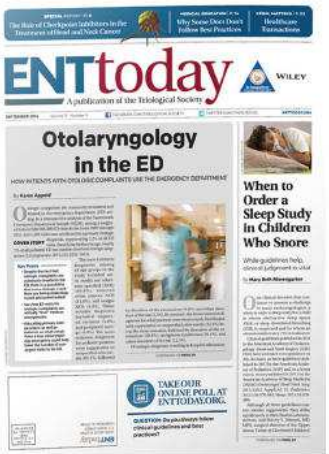

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An Open-Label Study of Sodium Oxybate in Spasmodic Dysphonia

Anna F. Rumbach, PhD; Andrew Blitzer, MD, DDS; Steven J. Frucht, MD; Kristina Simonyan, MD, PhD

Objectives/Hypothesis: Spasmodic dysphonia (SD) is a task-specific laryngeal dystonia that affects speech production. Co-occurring voice tremor (VT) often complicates the diagnosis and clinical management of SD. Treatment of SD and VT is largely limited to botulinum toxin injections into laryngeal musculature; other pharmacological options are not sufficiently developed.

Study Design: Open-label study.

Methods: We conducted an open-label study in 23 SD and 22 SD/VT patients to examine the effects of sodium oxybate (Xyrem), an oral agent with therapeutic effects similar to those of alcohol in these patients. Blinded randomized analysis of voice and speech samples assessed symptom improvement before and after drug administration.

Results: Sodium oxybate significantly improved voice symptoms ($P = .001$) primarily by reducing the number of SD-characteristic voice breaks and severity of VT. Sodium oxybate further showed a trend for improving VT symptoms ($P = .03$) in a subset of patients who received successful botulinum toxin injections for the management of their SD symptoms. The drug's effects were observed approximately 30 to 40 minutes after its intake and lasted about 3.5 to 4 hours.

Conclusions: Our study demonstrated that sodium oxybate reduced voice symptoms in 82.2% of alcohol-responsive SD patients both with and without co-occurring VT. Our findings suggest that the therapeutic mechanism of sodium oxybate in SD and SD/VT may be linked to that of alcohol, and as such, sodium oxybate might be beneficial for alcohol-responsive SD and SD/VT patients.

Key Words: Laryngeal dystonia, Xyrem, alcohol.

Level of Evidence: 4

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INTRODUCTION

Spasmodic dysphonia (SD) is an isolated task-specific dystonia that affects laryngeal muscles predominantly during speech production. SD is characterized by voice breaks on vowels and strained, strangled quality of voice in its adductor form (adductor spasmodic dysphonia [ADSD]) or by voice breaks on voiceless consonants and breathy quality of voice in its abductor form (abductor spasmodic dysphonia [ABSD]). About one-third of SD patients exhibit co-occurring dystonic voice tremor (VT), which often complicates the diagnosis and clinical management of SD.[1–3] The current treatment of SD with and without VT is directed to temporary improvement of voice symptoms with repeated injections of botulinum toxin into the laryngeal musculature. This treatment must be repeated every 3 to 4 months for life and is not effective in all SD patients (particularly ABSD) and even less so in combined SD/VT cases.[4,5] Other pharmacological interventions are not well established for these disorders.

To that end, we recently reported that ingestion of alcohol produces improvement of voice symptoms in up to 58% of SD and SD/VT patients, with potential benefits lasting 1 to 3 hours.[3] Although a significant proportion of patients reported the use of alcohol in professional and social situations to improve their voice quality, this type of symptom self-management may be problematic long term. Conversely, the use of a medication that delivers a similar effect may be highly desirable.[3]

In this open-label study, we examined the use of sodium oxybate (Xyrem; Jazz Pharmaceuticals, Dublin, Ireland), an oral agent with a therapeutic effect similar to that of alcohol, as a potential treatment option for patients with alcohol-responsive SD, both with and without VT. Sodium oxybate is a schedule III controlled substance that is chemically identical to gamma-hydroxybutyric acid, a naturally occurring inhibitory neurotransmitter.[6] When ingested orally, sodium oxybate is quickly absorbed, crosses the blood-brain barrier, and is converted into gamma-aminobutyric acid (GABA) within the brain.[7] Xyrem is US Food and Drug Administration approved for the treatment of cataplexy and excessive daytime sleepiness in narcoleptic patients.

From the School of Health and Rehabilitation Sciences, Speech Pathology (A.F.R.), University of Queensland, Brisbane, Queensland, Australia; Department of Neurology (A.B., S.J.F., K.S.), Icahn School of Medicine at Mount Sinai, New York, New York, U.S.A.; and the Head and Neck Surgical Group (A.B.), New York, New York, U.S.A.

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A.B. served on the scientific advisory boards for Allergan, Inc. and Revance Therapeutics; has received honoraria for activities with Myotech; has received research support from Allergan, Inc., Merz Pharma, and Revance Therapeutics; and has received royalty payments from Xomed/Medtronics, unrelated to this study. S.J.F. has received consulting fees from Merz Pharmaceutical and Impax Laboratories, Inc., unrelated to the research in this article. K.S. is a current member of the medical and scientific advisory council of the Dystonia Medical Research Foundation.

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Send correspondence to Kristina Simonyan, MD, Department of Neurology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1137, New York, NY 10029. E-mail: kristina.simonyan@mssm.edu

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The Xyrem REMS Program (https://www.xyrem.com/healthcare-professionals/xyrem-rems-program) coordinates and dispenses the drug through a central pharmacy that ensures that prescribers and patients are educated on and understand the risks and safe use conditions of Xyrem, including its very low risk of abuse/misuse.[8]

Recent trials of sodium oxybate in patients with alcohol-responsive movement disorders have established satisfactory tolerability and efficacy, with over 50% symptom improvement in alcohol-responsive movement disorders, such as essential tremor, myoclonus-dystonia, and posthypoxic myoclonus.[9–11] Sodium oxybate is a fast-acting drug, with its effects in movement disorders seen within 30 to 45 minutes of oral administration that are obvious to the patient and his/her family. Its effects are, however, short-lived, with each dose typically lasting 3.5 to 4 hours. Possible side effects include dose-dependent sedation and dizziness, with marked individual variability in susceptibility to side effects.[9–11]

In this study, we examined the use of sodium oxybate in alcohol-responsive SD patients with and without VT as well as in an independent smaller group of SD patients, for whom alcohol did not have explicit benefits on their voice symptoms. We assessed symptom improvement by conducting blinded, randomized analysis of recorded voice and speech samples before and after administration of the drug. In an exploratory manner, we examined self-assessment reports of the effects of sodium oxybate on overall voice symptoms in SD and SD/VT patients. We hypothesized that sodium oxybate would reduce both SD and VT symptoms in alcohol-responsive patients. As botulinum toxin injections into the affected laryngeal muscles are currently considered the gold standard treatment of SD, we conducted a follow-up study with a secondary goal to assess the effects of combined sodium oxybate and botulinum toxin treatment in SD and SD/VT.

MATERIALS AND METHODS

Patients

A total of 53 patients were recruited for this study, including 30 patients with isolated SD and 23 patients with combined SD/VT. In all patients, extensive history, physical, neurological, and fiberoptic laryngological evaluations were performed prior to the study participation to confirm the diagnosis of SD or SD/VT. Two SD patients and one SD/VT patient were excluded due to unconfirmed diagnosis of SD, with the remaining 28 SD patients (18 female/10 male; aged 50.7 $\pm$ 11.3 years) and 22 SD/VT patients (19 female/3 male; aged 58.0 $\pm$ 12.2 years) being included in the final cohorts (see detailed patient demographics in Table I). None of the patients had any past or present history of other forms of dystonia in other body regions, as well as no other neurological, psychiatric, or laryngological problems.

Responsiveness of voice symptoms to alcohol intake was assessed by patients' self-reported evidence and further confirmed by a family member and/or a friend. Among all patients, 45 patients (23 SD and 22 SD/VT) reported voice symptom improvement following at least 1 drink (empirically defined as a standard 12-oz can of beer, 6-oz glass of wine, or 1-oz shot of hard alcohol). Five SD patients were either unsure about the effects of alcohol on their symptoms or stated that alcohol had an effect in the past but that effect was no longer present. We thus a priori stratified our cohort into two groups of alcohol-responsive and nonresponsive patients and separately examined the effects of sodium oxybate in each group.

Patients who received botulinum toxin injections for their voice symptom management participated in the main study at the end of their treatment cycle, which was at least 3 months following their last injection while being fully symptomatic. A smaller group of patients (N = 10) who received botulinum toxin injections and were able to return for the assessment of combined drug effects, participated in the second study at the peak of their botulinum toxin treatment, which was on average 1 to 1.5 months following the last injection. All botulinum toxin injections were given as part of the patient's standard care plan by their laryngologist outside of our research study.

All patients provided written informed consent prior to study participation, which was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

Study Procedures

Immediately before drug intake, all patients underwent baseline assessment of their vital signs, including blood pressure, pulse, height, and weight, as well as completed the Mini-Mental State Examination (MMSE) and Montreal Cognitive assessment (MoCa) to assess the level of their cognitive impairment, Columbia-Suicide Severity Rating Scale (C-SSRS) to assess the drug-induced suicidal potential, and Epworth Sleepiness Scale to assess the daytime sleepiness. In all patients, audio and video recordings of their voice and speech samples were performed using 20 sentences with high content of vowels to elicit ADSD symptoms (e.g., "Tom wants to be in the army.") and 20 sentences with high content of voiceless consonants to elicit ABSD symptoms (e.g., "He is hiding behind the house.").[12] In addition, we collected subjective responses about the overall effort during speaking in all patients (with an exception of one SD patient and three SD/VT patients due to technical reasons) using a visual analog scale from 0 to 10, with 0 corresponding to no effort and 10 corresponding to constant struggle.

A dose of 1 to 1.5 g of sodium oxybate was administered orally, and the above described testing was repeated immediately after the drug intake as well as 40 minutes following drug intake. The decision regarding the dosing was made based on the combination of our prior clinical experience in improving dystonic symptoms with alcohol and sodium oxybate,[9–11,13] as well as based on each patient's description of his or her alcohol tolerance. Patients who reported alcohol benefits on their voice symptoms after one drink were given 1.0 g of sodium oxybate, whereas patients who reported alcohol benefits from 2 or more drinks were given 1.5 g of sodium oxybate. Following drug intake, all patients remained in the clinic under constant supervised monitoring for a period of at least 5 hours to monitor the drug's effects and possible adverse reactions. At the end of this 5-hour period, the same assessment as described above was repeated (voice and speech testing was performed but not recorded) and, if there were no changes to the patient's baseline status, he/she was returned into the care of a family member and/or a friend. All patients were instructed not to drive for at least 12 hours after drug intake and not to engage in any activity requiring sustained attention and decision making, regardless of their tolerability. All patients were followed up by phone on the next day after study participation to assess their voice symptoms and possible adverse reactions. The same procedures were repeated for those patients who returned for the study of the combined botulinum toxin and sodium oxybate effects.

TABLE I.
Patient Demographics.

	Spasmodic Dysphonia	Spasmodic Dysphonia/Voice Tremor	*P* Value
No. of subjects	28	22	
Age, yr, mean ± SD	50.7 ± 11.3	58.0 ± 12.2	.15
Gender	18F/10M	19F/3M	.65
Dystonia subtype	16 ADSD, 12 ABSD	15 ADSD/VT, 7 ABSD/VT	N/A
Onset, yr, mean ± SD	37.7 ± 11.0	44.1 ± 14.2	.40
Duration, yr, mean ± SD	13.4 ± 11.5	14.7 ± 12.7	.55
Baseline spasmodic dysphonia severity (voice breaks, harshness, and breathiness), mean ± SD	25.6 ± 16.3	30.3 ± 16.8	.60
Baseline VT severity, mean ± SD	N/A	49.3 ± 24.7	N/A

Comparisons were made between each patient group and controls as well as between the two patient groups using two-sample *t*-test at a corrected $P \leq .05$.

ABSD = abductor spasmodic dysphonia; ADSD = adductor spasmodic dysphonia; F = female; M = male; N/A = not applicable; SD = standard deviation; VT = voice tremor.

Data Analysis

All patients' voice and speech recordings were anonymized, randomized for pre- and postdrug assessments, and blindly rated by an experienced speech-language pathologist (A.F.R.) as reported previously.[13–18] SD symptoms were assessed by counting the number of SD-characteristic voice breaks in each sentence. Voice harshness in ADSD, breathiness in ABSD, and VT symptoms were evaluated using a visual analog scale of severity (0 for none, 100 for most severe/profound) that used three gradation indicators along a 100-mm line (normal, modulates voice, offsets voice), with distance in millimeters used to describe the degree of deviancy from normal. "Modulates voice" corresponded to a symptom severity that was present throughout the voice but did not offset the natural rhythm of speech. "Offsets voice" was used to represent the most severe form of a symptom that offset the natural rhythm of speech. Patients' subjective assessment of their overall voice effort during speaking before and after drug intake was rated based on a visual analog scale of severity from 0 (no effort) to 10 (constant struggle). Qualitative changes in symptom measures based on voice and speech recordings as well as patients' self-assessment reports were assessed as follows: ((baseline-drug intake)/baseline) × 100%.

Shapiro-Wilk tests found that data were normally distributed ($W \leq 0.97$, $P \geq .06$); therefore, two-sample paired *t* tests were used to examine the effect of sodium oxybate on SD and SD/VT symptoms at a Bonferroni-corrected $P \leq .05$.

RESULTS

All patients were within the normal limits on all baseline measurements, including the scores for MMSE ≥26, MoCa ≥26, C-SSRS = 0, and Epworth Sleepiness Scale ≤7. These measurements remained unchanged when the assessments were repeated immediately after drug intake as well as at 40 minutes and 5 hours after drug intake. No significant differences were found between the examined SD and SD/VT groups with respect to their age, gender, disorder age of onset, symptom duration, or severity (Table I; all $P \geq .15$).

Across all alcohol-responsive SD and SD/VT patients, sodium oxybate had a significant effect on their voice symptoms (speech recordings: $t_{44} = 3.67$, $P = .001$; self-assessment: $t_{41} = 9.81$, $P = 3.3 \times 10^{-12}$), which was observed approximately 30 to 40 minutes after drug intake, lasting on average 3.5 hours, and gradually wearing off by the end of the fifth hour of the patient's visit. One patient experienced an unusually prolonged benefit from sodium oxybate that lasted 9 months following a single dose of 1.0 g.[13] All patients tolerated the drug well without major adverse effects at the dose of 1 to 1.5 g. Transient minor side effects were observed in 14 SD and 11 SD/VT patients and included slight lightheadedness, drowsiness, dizziness, or headache. All side effects resolved within 45 to 60 minutes following drug intake. There was no significant relationship between the symptom severity and treatment response (SD: all $r \leq 0.16$, all $P \geq .46$; SD/VT: all $r \leq 0.21$, all $P \geq .35$).

Effects of Sodium Oxybate in Patients With Isolated SD

The alcohol-responsive SD group (N = 23) included patients who had reported positive effects of at least one alcohol drink on their voice symptoms; their reports were verified by a family member/friend. Six out of 23 SD patients who reported a measurable effect of alcohol did not experience improvement of their voice symptoms with sodium oxybate. Among these, two ABSD patients stated that their voice symptoms were typically ameliorated by one alcohol drink, whereas two ABSD and two ADSD patients stated that their voice was improved following two to three drinks.

The benefits of a single-dose sodium oxybate in drug-responding SD patients (N = 17) included on average 32.7% reduction of the number of voice breaks (pre- vs. post-treatment: 3.6 ± 1.6 vs. 2.6 ± 1.8; $t_{22} = 2.79$; $P = .011$) but not the severity of harshness (pre- vs. post-treatment: 48.0 ± 25.3 vs. 42.8 ± 23.6; $t_{22} = 1.09$; $P = .29$) or breathiness (pre- vs. post-treatment: 24.0 ± 18.1 vs. 20.0 ± 19.5; $t_{22} = 1.30$; $P = .21$) (Fig. 1, I.A–C). No significant differences in sodium oxybate effects were found on ADSD and ABSD symptoms (all $P \geq .23$). Similar findings were observed based on patients' self-assessment reports, which showed on average 40.2% reduction of the overall effort during speaking following a single-dose drug intake.

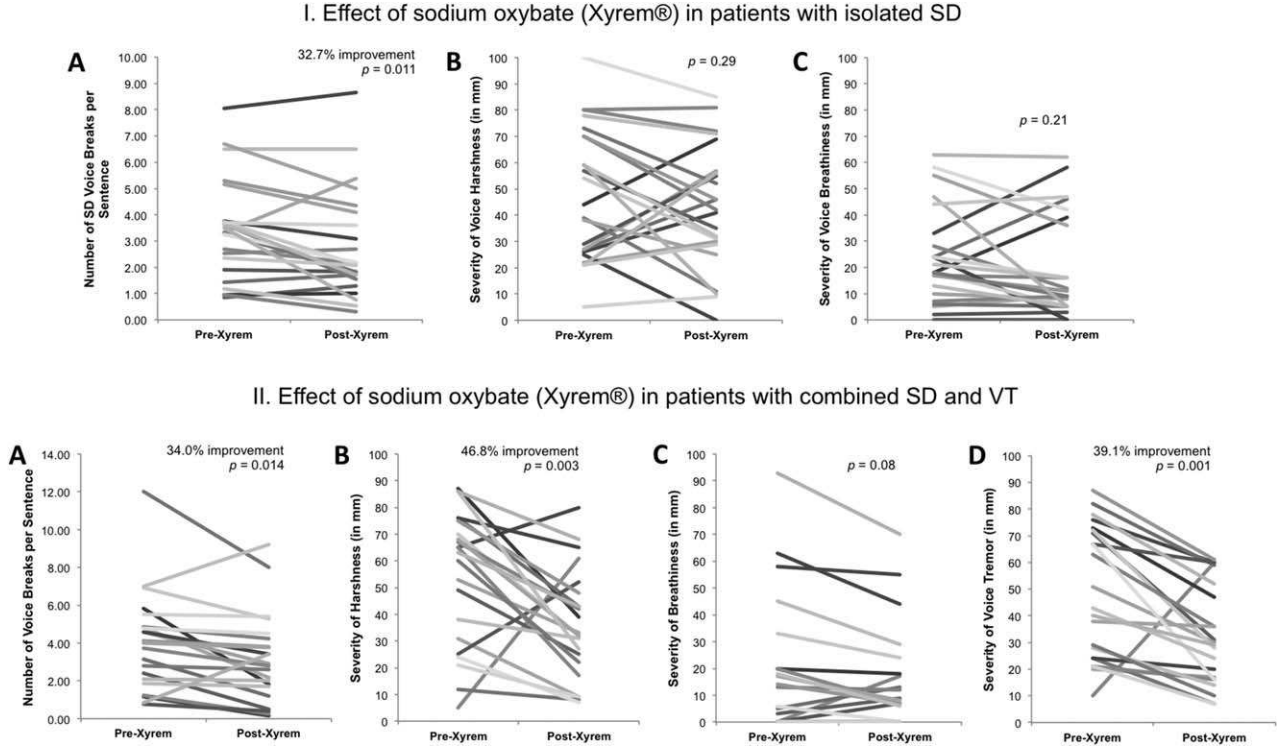

Fig. 1. Effects of sodium oxybate (Xyrem) on voice symptoms in patients with isolated spasmodic dysphonia (SD) (I, A–C) and in patients with combined SD and voice tremor (VT) (II, A–D). Voice and speech recordings were examined for the quantitative assessment of the number of voice breaks, severity of harshness, and breathiness as characteristics of SD, and the severity of VT as an additional characteristic feature of SD/VT before and 40 minutes after the drug intake.

In an explorative study of a smaller independent group of SD patients (N = 5) who were either unsure of the effects of alcohol on their voice symptoms or were alcohol-responsive in the past but not in the present, none had any significant effects of sodium oxybate on any of their voice symptoms (all $P \geq .12$).

Effects of Sodium Oxybate in Patients With Combined SD and VT

The alcohol-responsive SD/VT group (N = 22) included patients who had reported positive effects of at least one alcohol drink on their voice symptoms. Sodium oxybate showed no effects on SD symptoms in two out of 22 alcohol-responsive patients (one ADSD/VT and one ABSD/VT), whose symptoms typically responded to one alcohol drink; one of these patients (ADSD/VT) also had no improvement of VT.

In the group of drug-responding SD/VT patients (N = 20), sodium oxybate significantly reduced the number of voice breaks on average by 34.0% (pre- vs. post-treatment: 4.1 ± 2.5 vs. 2.8 ± 2.0; $t_{21} = 2.67$; $P = .014$), the severity of harshness on average by 46.8% (pre- vs. post-treatment: 58.3 ± 23.1 vs. 31.6 ± 17.8; $t_{21} = 3.38$; $P = .003$), and the severity of voice tremor on average by 39.1% (pre- vs. post-treatment: 51.2 ± 23.6 vs. 31.4 ± 18.5; $t_{21} = 3.94$; $P = .001$). The severity of breathiness remained unchanged (pre- vs. post-treatment: 18.6 ± 25.2 vs. 14.8 ± 19.2; $t_{21} = 1.86$; $P = .08$) (Fig. 1, II.A–D). These effects were independent of SD type; that is, there were no significant differences in symptom improvement between ADSD/VT and ABSD/VT patients (all $P \geq .46$). Similarly, patients' self-reported assessment of voice symptoms before and after drug intake found on average 43.8% reduction of the overall effort during speaking.

Combined Effects of Sodium Oxybate and Botulinum Toxin in SD and SD/VT

Ten patients (three ADSD, four ADSD/VT, and three ABSD/VT) returned at the peak of their botulinum toxin treatment (1–1.5 months following the last injection) for the follow-up secondary study that examined the combined effects of sodium oxybate and botulinum toxin on voice symptoms. Compared to their baseline assessments, botulinum toxin improved SD symptoms on average by 44.1%, whereas voice tremor was improved only by an average of 11.8%. Sodium oxybate was not found to be effective in further improving SD-specific voice breaks, harshness, or breathiness ($t_9 \leq 0.90$, $P \geq .24$). However, a trend toward significance was found for the effect of sodium oxybate on VT ($t_6 = 2.23$, $P = .03$).

DISCUSSION

Our study demonstrated that sodium oxybate significantly reduced voice symptoms in the majority of alcohol-responsive SD patients both with and without co-occurring VT. Specifically, the effects of sodium oxybate were observed on the frequency of SD-characteristic voice breaks in both ADSD and ABSD patients. Voice breaks are one of

the most frequent features of SD symptomatology, causing chopped, cut-off voice quality during speaking.[2,12] SD is currently managed with botulinum toxin injections,[2] which reduce voice symptoms by about 90% in 90% of ADSD patients but only by about 70% in 10% of ABSD patients.[5] Over the years, this treatment may, however, become burdensome for patients both psychologically and financially due to the fact that injections need to be repeated every 3 to 4 months for life, whereas the treatment-related benefits usually last for only about 30% of each injection cycle and are often accompanied by side effects in over 50% of patients.[5] Our findings demonstrate that sodium oxybate improves SD voice breaks comparable to the effects of botulinum toxin in alcohol-responsive patients. Its short-lived (on average 3.5–4 hours) but fast-acting (within 30–40 minutes of intake) mechanisms may pose both benefits and drawbacks for the patients, as one would need to have repeated oral intakes of the drug. On the other hand, administration of sodium oxybate may be done on demand when needed to manage voice symptoms in a particular setting compared to botulinum toxin injections, which have a longer-lasting effect (on average 3–4 months) and cannot be taken on a daily on-off basis. As sodium oxybate was found to act similarly in both ADSD and ABSD patients, this drug may potentially be beneficial for those alcohol-responsive patients who either do not benefit from botulinum toxin injections or choose to forgo injections due to personal or medical reasons. Furthermore, sodium oxybate showed a potential for improvement of VT symptoms, even in patients who underwent successful botulinum toxin injections for their SD symptoms. This finding points to another possible application of this drug, that is the management of VT co-occurring with SD, which is known to respond less well to botulinum toxin treatment.[12,19]

Our findings suggest that the effect of sodium oxybate on voice symptoms in alcohol-responsive SD and SD/VT patients parallels the effects of alcohol. Based on the patient's history, the best effect of the drug was observed in patients who reported symptom improvement following one to two alcohol drinks. On the other hand, patients, who required over three alcohol drinks or who were equivocal about experiencing any benefits from alcohol ingestion, did not benefit from sodium oxybate at the administered doses of 1.0 to 1.5 g. Although it is possible to increase the drug's dose above 1.5 g, the side effects associated with the use of higher doses would likely limit the practical use of sodium oxybate in this disorder.[9–11,20]

A minority of alcohol-responsive patients (six out of 23 SD and two out of 22 SD/VT) had either no effect from sodium oxybate or their voice symptoms somewhat worsened following drug intake. Considering the involuntary character of laryngeal spasms and diurnal variability of SD symptoms, further studies are necessary to detail whether sodium oxybate indeed worsened the voice symptoms in the minority of alcohol-responsive SD and SD/VT patients.

A limitation of this study was that we relied on patients' self-reports of alcohol response. However, to overcome this subjective self-assessment, we verified that the patients' family members or friends also noticed improvement of voice symptoms followign the alcohol intake. As in any open-label study, the placebo effects of the drug cannot be ruled out, and future double-blinded, placebo-controlled, randomized clinical trials are warranted. Nevertheless, the observed and reliably reproducible kinetics of the drug's action in the majority of patients may argue against an explanation dependent solely on the placebo benefit. Our current state of knowledge further suggests that the therapeutic benefits from sodium oxybate might not be exclusively placebo driven and likely to be rooted in dystonia pathophysiology because 1) the effects of sodium oxybate were similar to those of alcohol in SD and SD/VT patients; 2) alcohol modulates the inhibitory neurotransmitter GABA[21,22]; 3) sodium oxybate is structurally similar to GABA, converts into GABA within the brain,[7] and increases the dopamine level mediated by $GABA_B$ receptors[23–25]; and 4) both GABAergic and dopaminergic neurotransmission are abnormally reduced in SD and other dystonias, contributing to the loss of inhibition and abnormal plasticity that and potentially underlying the generation of dystonic movements.[15,26–28] Conversion of sodium oxybate into GABA in our patient cohort might have thus directly increased GABA levels and stabilized the balance between excitation and inhibition within the dystonic neural network, leading to the reduction of voice symptoms.

CONCLUSION

Collectively, our findings suggest that the mechanisms of sodium oxybate in SD and SD/VT may be similar to those of alcohol in these disorders, potentially representing a novel oral agent for alcohol-responsive SD and SD/VT patients.

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