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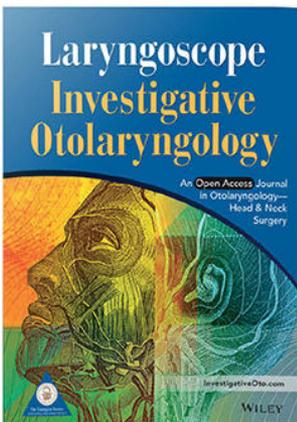


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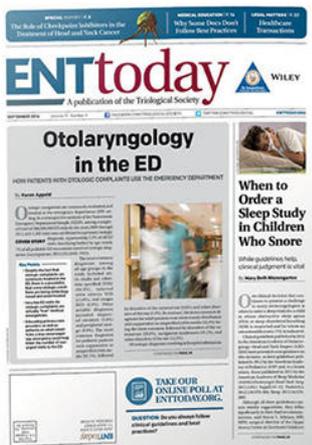
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# The Effect of Octanoic Acid on Essential Voice Tremor: A Double-Blind, Placebo-Controlled Study

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**Objectives/Hypothesis:** The purpose of this study was to determine the effects of octanoic acid on acoustic, perceptual, and functional aspects of essential voice tremor (EVT).

**Study Design:** Prospective, double-blind, placebo-controlled, crossover study.

**Methods:** Sixteen participants with a diagnosis of EVT were randomized to a 3-week dosing condition of octanoic acid or placebo, followed by a 2-week washout period and crossover to the other condition for an additional 3 weeks. Baseline and post-testing sessions were completed before and at the completion of each condition. Primary outcome measures were the magnitude of amplitude and frequency tremor, measured from the acoustic signal. Secondary outcomes were auditory-perceptual ratings of tremor severity and self-ratings of voice handicap.

**Results:** Magnitude of amplitude and frequency tremor were significantly lower after 3 weeks of octanoic acid dosing as compared to the placebo condition. Auditory-perceptual ratings of tremor severity did not show significant differences between conditions. A trend toward better voice was seen for the sustained vowel ratings, but not the sentence-level ratings. No significant differences between conditions were seen on self-reported voice disability as assessed on the Voice Handicap Index-10.

**Conclusions:** The results of this controlled investigation support the potential utility of octanoic acid for reducing the magnitude of tremor in people with EVT. Further research is needed to determine whether different dosing or treatment combinations can improve functional communication in EVT.

**Key Words:** Tremor, voice, essential tremor, octanoic acid, cross-over, placebo-controlled, randomized.

**Level of Evidence:** 1

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## INTRODUCTION

Essential tremor (ET) is a common neurological movement disorder that particularly affects people over the age of 65 years. The prevalence of ET is likely to increase considerably in upcoming years based on a projected increase of 9% in this age demographic by 2060, when nearly one-quarter of the population will be aged 65 years and older.<sup>1</sup> The voice is affected in 20% to 30% of people with ET,<sup>2,3</sup> producing involuntary oscillations of the respiratory,<sup>4</sup> laryngeal,<sup>5,6</sup> and oropharyngeal<sup>7,8</sup> muscles during speech production. People with essential voice tremor experience unstable, shaky, and hoarse voice quality, increased effort associated with speaking, decreased speech intelligibility, and pronounced voice-related disability.<sup>7</sup>

Additional Supporting Information may be found in the online version of this article.

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Treatment options are inadequate for improving voice in people with essential voice tremor (EVT).<sup>9,10</sup> The source of the oscillations in ET is thought to be within the olivocerebellar neural circuits<sup>11,12</sup> of the central nervous system, indicating that pharmacologic treatments, which have central versus solely peripheral effects, are more likely to impact tremor severity. Treatment-related research in EVT and clinical practice has primarily focused on botulinum toxin A (BTA), a treatment that can be helpful for approximately one-third of people with EVT,<sup>8,13,14</sup> but is considered less than optimal due to its variable efficacy,<sup>9,14</sup> invasiveness, and negative side effects. The long-chain alcohol 1-octanol and its derivative octanoic acid (OA) have been studied in ET of the limbs as a potential treatment for tremor, which may have similar mechanisms of action as ethanol, one of the most effective tremor-reducing agents.<sup>15,16</sup> Studies to date have shown that 1-octanol or OA can reduce the severity of tremor in the hands by as much as 41%, with minimal/mild side effects.<sup>17-20</sup> Treatment of EVT with OA may be advantageous to BTA due to its effect on the peripheral and central nervous system regions,<sup>21,22</sup> its potential diffuse effects on muscles across multiple speech sub-systems that are affected by EVT, and the reported positive effect of its related parent compound ethanol for improving voice tremor.<sup>7,23</sup>

Controlled investigations of alternative pharmacologic interventions for EVT are critical to improved clinical care and level of evidence for treatment decisions.

The purpose of this study was to perform a randomized, double-blind, placebo-controlled investigation of the effects of OA on acoustic, perceptual, and functional aspects of voice. It was hypothesized that the following changes in tremor variables would occur after the OA condition when compared to the placebo condition: 1) the magnitude of amplitude tremor (Matr) would be lower, 2) the magnitude of frequency tremor (Mftr) would be lower, 3) auditory-perceptual ratings of perceived tremor severity would be better, and 4) participants would report less voice disorder disability/handicap.

## MATERIALS AND METHODS

### Participants

Seventeen participants with EVT were enrolled in the study after providing informed consent, with procedures completed for 16 participants (see Fig. 1 for study enrollment flow chart). An Investigational New Drug application was approved through the Food and Drug Administration (FDA) for the use of OA as a potential drug treatment for essential voice tremor. Participants were recruited from regional otolaryngologists, neurologists, and primary care physicians. OA had not been previously tested for people with EVT, but an initial power analysis was performed using an estimated effect size from a study that included similar acoustic outcome measures.<sup>24</sup> With an 80% power requirement, this analysis produced a required sample size of 16 participants; initial study targets included six additional participants (22 total) to adjust for possible attrition rates. Due to reaching the end of the funded study period, data collection was ended after enrollment of 17 participants. The analyzed sample size of 16 in this study generally exceeds that of other published prospective studies addressing treatment of people with EVT.<sup>6,14,24-26</sup>

Inclusion and exclusion criteria were determined through an initial nasoendoscopy evaluation performed by a laryngologist

and a voice evaluation with acoustic recordings performed by a speech-language pathologist (SLP), as well as through patient report. All participants were diagnosed with EVT by an otolaryngologist, with confirmation of essential tremor by a neurologist. Stringent inclusion and exclusion criteria were implemented (see Supporting Information, Appendix A, in the online version of this article).

A randomized, double-blind, crossover design was used to compare effects of OA to a placebo control. Total study duration was approximately 11 weeks for each participant, which included phases 1 and 2 for the active or placebo drugs (see Table I for study procedures and timeline). Each phase included baseline testing, 3 weeks of consecutive drug dosing, and post-testing at the end of each 3-week drug period, with a 2-week intervening washout. With an established elimination half-life of OA at 150 minutes,<sup>20</sup> this washout period well exceeds any potential for residual effects from phase 1 to phase 2. To control for possible order effects, a randomized, counterbalanced list (generated by an independent person) was used to assign drug order for each participant upon enrollment. Subjects were randomized to one of two sequences (placebo phase 1 then OA phase 2 or OA phase 1 then placebo phase 2). Participants and researchers were blinded to drug status (OA or placebo) throughout all study procedures, including data analysis and statistical testing.

### Baseline and Post-testing Assessment Procedures

Baseline and post-testing data were collected over 3 consecutive testing days at the start and end of each study phase, resulting in six data collection time points for each study phase. Post-testing (post-treatment) occurred on the final 3 days of each 3-week drug intake phase. Two acoustic measures of tremor magnitude served as the primary outcome measures, and two perceptual measures (listener ratings and patient self-impact ratings) served as the secondary outcome measures. During the initial testing of phase 1, additional procedures were performed to descriptively assess the extent of oropharyngeal and laryngeal

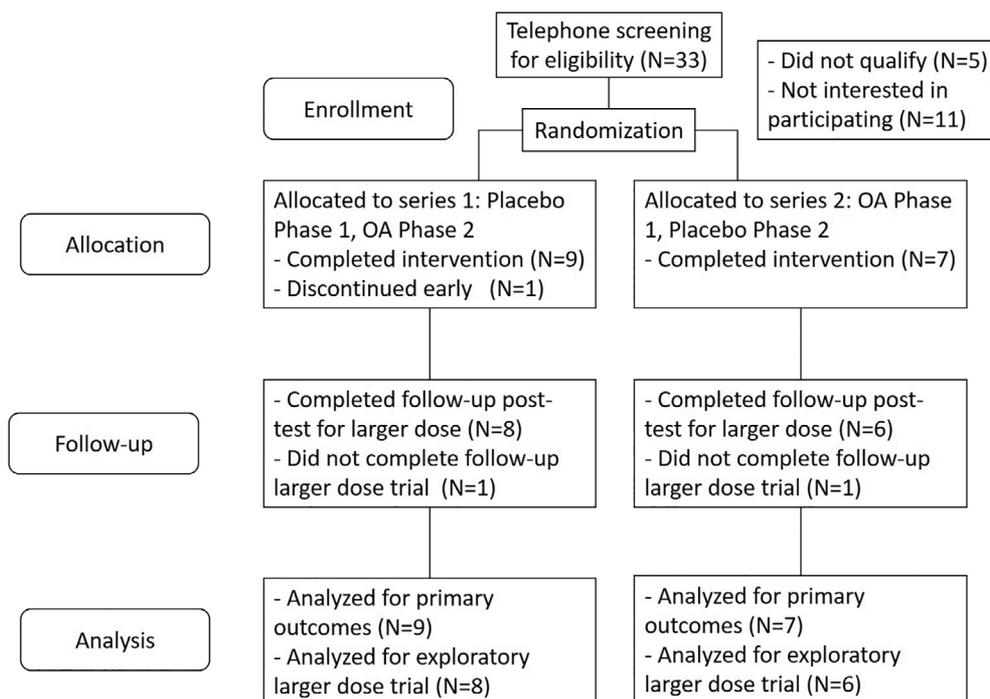


Fig. 1. Study enrollment and allocation flowchart. OA = octanoic acid.

TABLE I.  
Timeline and Study Procedures.

	Time					
	Week 1	Weeks 2–4	Weeks 5–6	Week 7	Weeks 8–10	Week 11
Procedures	Qualifying assessments	3 weeks at full drug dosing	Drug dosing lowered, then withdrawn		3 weeks at full drug dosing	Drug dosing lowered, then withdrawn
	Initial questionnaires		2-week drug washout period			
	Preintervention nurse visit (1/4)	Nurse visit in first week of full dosing, drug 1 (2/4)			Nurse visit in first week of full dosing, drug 2 (3/4)	Postintervention nurse visit (4/4)
	Baseline testing sessions 1, 2, and 3 for drug 1	Post-testing sessions 1 and 2 at 16 mg/kg dose		Baseline testing sessions 1, 2, and 3 for drug 2	Post-testing sessions 1 and 2 at 16 mg/kg dose	
	Drug step-up	Post-testing session 3 at 32 mg/kg dose		Drug step-up, then full dosing drug 2	Post-testing session 3 at 32 mg/kg dose	
Phase	Drug 1 at 16 mg/kg dose (placebo or octanoic acid)	Drug 1 (placebo or octanoic acid)		Crossover to drug 2 at 16 mg/kg dose (placebo or octanoic acid)	Drug 2 (placebo or octanoic acid)	

tremor and the extent of body tremor. A standardized nasoendoscopy examination was performed, which included all tasks required for the Vocal Tremor Scoring System (VTSS), a validated scale for the visual-perceptual rating of voice tremor affecting the laryngeal and oropharyngeal regions.<sup>8</sup> A digital video recording of the participant performing a range of functional tasks was obtained during initial testing, and later scored by a neurologist using a validated measure (Tremor Research Group Essential Tremor Rating Assessment Scale [TETRAS])<sup>27</sup> to determine the presence and severity of tremor across all body regions. As a self-assessment, the participant completed a rating scale (Quality of Life in Essential Tremor [QUEST])<sup>28</sup> to assess life impact of overall body tremor. The VTSS, TETRAS, and QUEST were included for descriptive purposes only to delineate tremor characteristics of this participant group.

Additional data were collected at each of the three baseline and post-testing sessions. Voice recordings were performed in a sound-attenuated booth with a head-mounted condenser microphone (AKG C550; Harman International Industries, Stamford, CT) positioned 9 cm from the mouth. The Computerized Speech Lab (CSL 4500; KayPENTAX, Montvale, NJ) was used for audio recordings, with a sampling rate of 50 kHz. Speaking tasks included three repetitions of sustained /a/ vowels, standardized sentences,<sup>29</sup> and an all-voiced sentence,<sup>30</sup> all at a comfortable pitch and loudness. Participants also completed several questionnaires at each visit, including the Voice Handicap Index-10<sup>31</sup> (VHI-10) and a suicide risk screening<sup>32,33</sup> per FDA requirements for clinical trials. For all baseline and post-testing, participants were instructed to avoid alcohol (48 hours prior) and caffeine (testing day), and to fast the morning of post-testing. Testing was performed 3 hours after drug intake for all post-testing visits, based on prior OA studies addressing timing of effects.<sup>17,19</sup>

### Drug Trials

OA was formulated in softgel capsules with dosing sizes of 400 and 200 mg (Best Formulations, City of Industry, CA). Dosing of 16 mg/kg was chosen for the main drug-dosing period (20 days), based on prior studies showing that dosing at 64 mg/kg of 1-octanol produced significant reduction in dominant hand

tremor in a 90-minute period,<sup>18</sup> with few and mild side adverse effects up to 128 mg/kg,<sup>18,20</sup> whereas 4 mg/kg dosing of OA did not significantly improve hand tremor until 300 minutes after intake.<sup>17</sup> A higher dosing of 32 mg/kg was implemented on the final day of the drug phase (day 21) to obtain preliminary data on possible dose-dependent effects. Soybean oil was formulated in identical softgel capsules and sizes for the placebo dosing, with identical procedures and dosing used for the placebo phase. Participants were instructed to take each dose in the morning with a meal, with intake time logged daily.

### Safety Monitoring

Four independent nurse monitoring visits occurred over the course of the study, and results were reviewed regularly by the study physician. Visits occurred at baseline, within week 1 of each drug phase, and upon study completion. Vital signs and a patient questionnaire that addressed adverse effects and their severity were assessed at each visit. The questionnaire included 30 symptoms assessed/reported in prior OA studies<sup>17,18</sup> (see Supporting Information, Appendix B, in the online version of this article). An electrocardiogram (ECG) and hepatic function panel (HFP) were collected at baseline (prior to any drug intake) and upon study end.

### Outcome Measures and Data Analysis

All data analysis for the dependent variables was performed by a researcher who was not involved with data collection and was blind to subject identity, drug condition, and time point. The objective acoustic measures of magnitude of amplitude (Matr) and frequency tremor (Mftr) reflected the extent of tremor in the acoustic signal and served as the primary outcome measures. Auditory-perceptual tremor severity ratings and self-reported voice disability (VHI-10) served as secondary outcome measures. The sustained vowel /a/ provided the necessary steady-state context for extracting Matr and Mftr measures, which were computed for a 4-second interval of each vowel token, 1.0 second after onset to avoid any onset effects. Matr and Mftr

TABLE II.  
Demographics of the 16 Participants Who Completed the Study.

	Value	Additional Information
Age, yr, mean (SD)	70.3 (8.7)	
Sex	14 F, 2 M	
Presence of other body tremor	Yes: 10, no: 6	Affected body areas: head: 4, jaw: 1, face (lips): 1, upper extremities: 8, lower extremities: 1
Positive family history for tremor	Yes: 10, no: 6	
Self-reported voice improvement with alcohol	Unknown: 6, yes: 3, no: 7	
Auditory-perceptual tremor severity (sustained vowel)	Mild: 1, mild-moderate: 4, moderate: 5, moderate-severe: 2, severe: 4	
Years post-EVT onset, mean (SD)	9.34 (7.12)	Range: 1.00–25.00
Initial VHI-10 score, baseline 1, phase 1 (10 items, 40 points possible), mean (SD)	19.38 (8.50)	Range: 2.00–34.00, points possible = 48.45%
VTSS (6 items, 18 points possible), mean (SD)	10.80 (3.99)	Range: 4.00–17.00, points possible = 60.00%
TETRAS total score (21 items, 112 points possible), mean (SD)	17.22 (14.12)	Range: 7.00–62.00, points possible = 15.38%
Activities of Daily Living subscale (12 items, 48 points possible), mean (SD)	10.00 (7.03)	Range: 4.00–34.00, points possible = 20.83%
Performance subscale (9 items, 64 points possible), mean (SD)	7.22 (7.47)	Range: 1.00–28.00, points possible = 11.28%
QUEST total score (30 items, 120 points possible), mean (SD)	29.75 (20.11)	Range: 7.00–74.00, points possible = 24.79%
QUEST, Voice Impact subanalysis (4 questions, 16 points possible) questions 3, 19, 20, and 21 relate to tremor interfering with telephone use, communication, and speech intelligibility, mean (SD)	8.06 (4.30)	Range: 0.00–15.00, points possible = 50.38%

EVT = essential voice tremor; F = female; M = male; QUEST = Quality of Life in Essential Tremor questionnaire; SD = standard deviation; TETRAS = Tremor Research Group Essential Tremor Rating Assessment Scale; VHI-10 = Voice Handicap Index-10; VTSS = Vocal Tremor Scoring System.

were computed from the amplitude and frequency contours, respectively, using higher-order perturbation functions over an analysis window, and expressed as a percent of the mean overall signal to normalize each measure<sup>34</sup> (Motor Speech Profile; KayPENTAX). Perturbation measures follow guidelines established by the National Center for Voice and Speech.<sup>35</sup> Mean values of the three /a/ tokens per testing session were computed for each tremor magnitude variable.<sup>36</sup>

Three raters with experience in voice disorders performed paired-sample ratings of tremor severity for the first sustained /a/ utterance and the all-voiced sentence for each respective baseline to post-test session. The sustained vowel provided a context in which tremor is known to be more perceptually salient,<sup>37</sup> whereas the all-voiced sentence provided a context more representative of everyday speaking. Paired samples were counterbalanced for baseline/post-test order, and then randomized for blinded analysis. Sound-pressure level was balanced for each token of the paired sample to avoid listener bias based on SLP disparities. Listeners rated samples independently in a quiet environment using the audio signal only, with immediate repetition of each sample as needed.

### Statistical Analyses

An independent statistician who was blinded to drug condition performed all statistical analyses using SAS (SAS Institute Inc., Cary, NC) and R codes (The R Foundation for Statistical Computing, Vienna, Austria). Statistical testing was performed on each of the primary outcome measures (Matr and Mftr) as well as the secondary outcome measures (auditory-perceptual ratings and VHI-10). Mixed effect statistical modeling was used to

determine post-treatment drug differences, with testing session as a repeated factor and baseline averages as covariates. An additional statistical model was run to assess post-treatment differences without the inclusion of baseline covariance, based on statistical recommendations for two-period crossover treatment studies.<sup>38</sup> Analysis of outcome measures for the 3-week, daily 16 mg/kg was determined from mean values for each variable from baseline 1 and 2 and post-test 1 and 2, and exploratory analyses of the 1-day dosing effects at 32 mg/kg were determined from the comparison of baseline 3 to post-test 3. Intrarater reliability for the auditory-perceptual ratings was assessed with Cohen's  $\kappa$  for 16% of the samples for each speaking context, which were included as repeated samples in the overall randomized samples that were rated. Inter-rater reliability across the three raters was assessed using Fleiss'  $\kappa$  for all samples within each speaking context.

### RESULTS

The average age for the 16 participants was 70.3 years (standard deviation [SD] = 8.7 years), with two males and 14 females, consistent with prior reported demographics<sup>7,24,36</sup> (see Table II for full participant characteristics). Group means, standard deviations, and statistical results for the primary and secondary outcome measures are summarized in Tables III, IV and V. Period and sequence effects were not significant for any of the primary outcome measures, indicating that there was no influence of drug order. Reliability of  $\kappa$  for the auditory-perceptual ratings of the sustained vowel ranged from

TABLE III.  
Magnitude of Amplitude Tremor and Frequency Tremor.

	% Modulation	SD	F Value (With BL Covariance)	P Value (With BL Covariance)	F Value (Without BL Covariance)	P Value (Without BL Covariance)
Magnitude of amplitude tremor						
Octanoic acid						
Baseline	13.49	6.48				
Post-test	9.35	5.42				
Placebo						
Baseline	12.91	6.46				
Post-test	12.43	7.37				
Statistical results			4.69	.0499*	6.68	.0216*
Magnitude of frequency tremor						
Octanoic acid						
Baseline	5.19	3.58				
Post-test	3.98	2.94				
Placebo						
Baseline	5.57	4.29				
Post-test	5.35	3.76				
Statistical results			4.85	.0450*	5.53	.0339*

Data are presented as group means, standard deviations (SD), *F* statistics, and *P* values with and without baseline (BL) covariance adjustment ( $\alpha < .05$ ). Means include data from baseline 1 and 2 and post-test 1 and 2 for each drug phase.

\*Statistically significant.

0.604 to 0.636, whereas reliability for the sentence-level speaking context ranged from 0.497 to 0.515 (Table VI). These levels are considered substantial and moderate, respectively, as described by Landis and Koch.<sup>39</sup>

A significantly lower Matr was seen after the OA condition as compared to the placebo condition, supporting the first hypothesis (Table III). Mean values for the OA condition showed a baseline to post-test reduction of 4.14 in Matr, as compared with a 0.48 reduction for the placebo condition, with a Cohen's *d* effect size of 0.645. Eleven of the 16 participants (69%) showed a reduction of >10% of their baseline mean in Matr upon post-testing. Likewise, Mftr was significantly lower after the OA condition as compared to the placebo condition, supporting the

second hypothesis. Mean values for the OA condition showed a baseline to post-test reduction of 1.21 in Mftr, as compared with a 0.22 reduction for the placebo condition, with a Cohen's *d* effect size of 0.588. Ten of the 16 participants (63%) showed a reduction of >10% of their baseline mean in Mftr upon post-testing.

Auditory-perceptual paired comparison ratings of differences in tremor severity between baseline and post-treatment voice recordings were not significantly different after the OA condition as compared to the placebo condition, not supporting the third hypothesis (Table IV). Ratings for the sustained vowel showed trends toward better for the OA condition, but not for the all-voiced sentence ratings. Self-perceived voice handicap as measured

TABLE IV.  
Paired Comparison of Baseline to Post-treatment Auditory-Perceptual Ratings.

	Auditory-Perceptual Ratings (BL-PT)	SD	F Value (Main Effect, Drug)	P Value (Main Effect, Drug)	F Value (Main Effect, Task)	P Value (Main Effect, Task)	F Value (Interaction Effect, Drug*Task)	P Value (Interaction Effect, Drug*Task)
Octanoic acid								
Sustained vowel	1.53	1.13						
All-voiced sentence	1.19	0.87						
Placebo								
Sustained vowel	1.25	1.13						
All-voiced sentence	1.63	1.12						
Statistical Results			0.14	.7172	0.00	.9602	2.02	.1699

1 = post-test better than baseline, points possible = 0-3 (sum of three raters' scores). Data are presented as group means for summed scores, standard deviations (SD), *F* test statistics, and *P* values ( $\alpha < .05$ ).

BL-PT = baseline to post-treatment.

TABLE V.  
Voice Handicap Index-10.

	VHI-10 Mean	SD	F Value (With BL Covariance)	P Value (With BL Covariance)	F Value (Without BL Covariance)	P Value (Without BL Covariance)
Octanoic acid						
Baseline	16.75	6.88				
Post-test	15.16	7.51				
Placebo						
Baseline	18.38	8.59				
Post-test	16.56	7.62				
Statistical results			0.00	.9831	2.05	.1739

Data are presented as group means, standard deviations (SD), *F* statistics, and *P* values with and without baseline (BL) covariance ( $\alpha < .05$ ). Means include data from baseline 1 and 2 and post-test 1 and 2 for each drug phase.

VHI-10 = Voice Handicap Index-10.

by the VHI-10 was also not significantly different after the OA condition as compared to the placebo condition, not supporting the fourth hypothesis (Table V).

Due to participant logistics and traveling distance, the data for the exploratory analysis for the higher, 32 mg/kg dosing were completed for only 14 participants. None of these comparisons showed significant differences for the primary or secondary outcome measures, although trends toward lower tremor magnitude on the acoustic measures and lower ratings of tremor severity on the sustained vowel were evidenced after the OA condition (Table VII).

Drug safety and side effects were assessed in the nurse visits throughout the study for each participant. No participants showed any indication of adverse medical effects when comparing baseline to end-of-study ECG and HFP results. One adverse event (nonserious) resulted in early study termination for a participant. Deblinding and follow-up by the study physician indicated that the participant's symptoms were related to a preexisting medical condition, with end-of-study deblinding showing the event occurred during the placebo phase (phase 1). Mean number of reported adverse effects was similar for the placebo (3.4) and OA conditions (3.7), and were similar to the baseline symptom frequency (before any intervention) for both conditions. Mean severity of symptoms was between the levels of minimal to mild for both the placebo (1.35) and OA (1.53) conditions (see Supporting Information, Appendix B, in the online version of this article for symptom summary information).

## DISCUSSION

Whereas several pharmacologic options with level A or B evidence are available for the treatment of ET that affects the limbs, few such options are available for treating EVT. Efficacy studies for EVT primarily address BTA treatment,<sup>14,40</sup> or have implemented open-label designs or retrospective analyses to study pharmacological alternatives such as propranolol<sup>26</sup> or primidone.<sup>41</sup> Prospective studies that include strong experimental controls and objective measures of voice tremor are needed to determine the potential benefit of drug alternatives in EVT. Well-controlled, open-label,<sup>18,42</sup> and double-blind trials<sup>17</sup> of 1-octanol and OA have provided preliminary support for its ability to reduce magnitude of tremor in the limbs, but voice tremor was not addressed. The current study investigated the effects of OA on acoustic, perceptual, and functional aspects of EVT. To our knowledge, this is the first double-blind, placebo-controlled pharmacological trial for people with EVT. In contrast to prior OA studies for ET, which limited the inclusion of participants to those who showed alcohol-responsive tremor reduction, participants meeting stringent criteria for EVT were included regardless of whether their voice tremor was alcohol responsive.

Significantly lower magnitudes of amplitude and frequency tremor were measured after the OA condition as compared to the placebo condition, with moderate to large effect sizes<sup>43</sup> for each of the primary outcome variables. In limb tremor, tremor amplitude rather than tremor frequency typically responds to pharmacological treatment,<sup>44</sup> and is the primary outcome measure in many treatment efficacy studies as assessed with accelerometry.<sup>17,18,42,44–46</sup>

EVT is characterized by modulations in the amplitude and frequency of the acoustic signal,<sup>36,47</sup> and changes to pitch and loudness can differentially affect these two parameters.<sup>36</sup> The results of the current study are consistent with prior studies showing that pharmacologic intervention (BTA) can improve the extent of frequency or amplitude tremor,<sup>14,24</sup> and that differential levels of change for each variable may occur after treatment.<sup>14</sup>

These objective Matr and Mftr measures are derived from sustained vowel utterances, which are characterized by normally invariant frequency and amplitude characteristics

TABLE VI.  
Intrarater and Inter-rater Reliability for Auditory-Perceptual Ratings of Tremor Severity.

Task	Intrarater Reliability (Computed With Cohen's $\kappa$ )		Inter-rater Reliability (Computed With Fleiss' $\kappa$ )	
	Mean	Range	Mean	Range
Sustained vowel	0.604	0.402–0.778	0.636	N/A
All-voiced sentence	0.515	0.359–0.664	0.497	N/A

N/A = not applicable.

TABLE VII.  
Exploratory Higher Dose (32 mg/kg) Results for Magnitude of Amplitude and Frequency Tremor, Voice Handicap Index-10, and Auditory-Perceptual Tremor Severity Ratings.

	Mean	SD	F Value (With BL Covariance)	P Value (With BL Covariance)	F Value (Without BL Covariance)	P Value (Without BL Covariance)
Magnitude of amplitude tremor						
Octanoic acid						
Baseline	12.73	6.74				
Post-test	9.79	5.28				
Placebo						
Baseline	13.07	6.75				
Post-test	12.98	8.24				
Statistical results			1.90	.1934	3.69	.0787
Magnitude of frequency tremor						
Octanoic acid						
Baseline	5.68	3.90				
Post-test	5.14	3.19				
Placebo						
Baseline	5.74	4.24				
Post-test	5.64	3.73				
Statistical results			0.37	.5530	0.28	.6094
VHI-10						
Octanoic acid						
Baseline	16.33	7.44				
Post-test	14.29	8.13				
Placebo						
Baseline	19.21	8.60				
Post-test	15.79	7.64				
Statistical results			0.00	.9831	0.01	.9323
A-P tremor severity						
			F Value	P Value		
Octanoic acid						
Sustained vowel	1.79	1.31				
All-voiced sentence	1.29	1.33				
Placebo						
Sustained vowel	1.57	1.45				
All-voiced sentence	1.36	1.01				
Statistical results						
Drug, main effect			0.03	.8670		
Task, main effect			1.84	.1921		
Drug*task			0.20	.6587		

Data are presented as group means, standard deviations (SD), *F* statistics, and *P* values with and without baseline (BL) covariance adjustment ( $\alpha < .05$ ). Means are for data from baseline 3 and post-test 3 for each drug phase.

A-P = auditory-perceptual; VHI-10 = Voice Handicap Index-10.

that enable the reliable measurement of signal modulation, and this task is important in differential diagnosis and characterization of voice tremor.<sup>48</sup> Tremor is perceived to be significantly more severe during sustained vowels as compared to connected speech,<sup>37</sup> a context in which frequency and amplitude modulation cannot be appropriately measured because high modulation is expected. Other acoustic measures also may not reflect tremor characteristics well in conversational (connected) speech.<sup>48</sup> The mixture of voiced and unvoiced sounds, rapid speaking rate, and natural variations in pitch and loudness can mask tremor in connected speech, making tremor less perceptible.

In the current study, auditory-perceptual ratings of tremor severity in sustained vowels showed trends toward lower severity for the OA condition relative to the placebo. It is likely that this speaking context allowed the greatest sensitivity to small changes in tremor severity. In contrast, the ratings of the connected speech sentence did not show concordant trends and may have been more difficult for listeners to consistently rate. Reliability of listener ratings supports this; although intrarater and inter-rater  $\kappa$  reliability levels for both speaking contexts fell in the range of moderate agreement,<sup>39</sup> only the  $\kappa$  values for the sustained vowel reached  $\geq 60\%$ , with values up to 14% higher for the vowel

versus the connected speech sentence (Table VI). A recent open-label study<sup>26</sup> included auditory-perceptual ratings of tremor severity to assess the efficacy of BTA and propranolol, and also found low inter-rater  $\kappa$  reliability (0.25) for sentence-level ratings among experienced listeners. Auditory-perceptual tremor severity did not show significant change after either form of treatment, leading the authors to suggest that objective tremor measures may be important to determine EVT treatment outcome.<sup>26</sup> In the current study, the lack of self-perceived voice disability difference on the VHI-10 for the OA condition is consistent with the auditory-perceptual findings. Because perceptual saliency of tremor is lower in connected speech, larger amounts of change may be necessary in EVT to functionally improve communication. Additionally, although baseline means for the VHI-10 in this study were 2.5 to 3 standard deviations greater than means previously reported for a non-voice-disordered control group,<sup>31</sup> it is possible that higher initial scores on this impact measure would have allowed for a greater degree of post-treatment change.

Although the objective reduction in tremor magnitude from the acoustic analysis of sustained vowels in this study provides some support for the efficacy of OA, future studies are needed to determine whether differences in the amount and timing of dosing, combined modality treatment, or other factors could produce functionally meaningful voice improvement in people with EVT. Our exploratory analysis of a higher OA dose did not support a dose-dependent effect, as these results showed trends but no statistically significant benefit of OA. However, these data had far fewer data points than the regular dosing, and dosing at 32 mg/kg occurred on only 1 day as compared to 20 days for the 16-mg/kg dose. It is possible that higher dosing for a longer time would be needed for better OA efficacy. The significant reductions in tremor magnitude after 3 weeks of OA intake are promising due to their potential applicability to the overall population of people with EVT (not just those who are alcohol responsive), as well as the high percentages of participants who showed at least some acoustically measurable reduction in tremor. However, further investigation of multiple OA variables in larger study samples is needed to determine its potential for meaningful improvement in communication for people with EVT.

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