Primidone Therapy for Essential Vocal Tremor

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Tremor is defined as a rhythmic and oscillatory movement with a relatively constant frequency and variable amplitude. Essential tremor (ET) is the most common neurologic disorder that causes action tremor, with an estimated prevalence worldwide of up to 5%. The incidence of ET increases with age, and it can be familial. Essential tremor can lead to substantial functional disability in up to 75% of patients. Manifestation of ET within the phonatory apparatus is known as essential vocal tremor (EVT). Essential vocal tremor typically presents as tremor associated with increased phonatory effort.

The 2005 American Academy of Neurology practice parameter gave a level A recommendation of efficacy for propranolol and the anticonvulsant primidone for the treatment of ET. It is estimated that 50% of patients with ET gain some benefit from primidone therapy. Essential vocal tremor is difficult to treat, and to date an effective pharmacologic treatment has not been established. Botulinum neurotoxin (BN) injection into 1 or both thyroarytenoid muscles has become a frequent mode of therapy. In a recent cohort study, BN injections for EVT were reported to help an estimated 56% of patients. Botulinum neurotoxin treatment necessitates repeated injections approximately every 3 months, and therefore a substantial sacrifice of time and money. An effective pharmacologic treatment could prevent the pain, time sacrificed, and money spent with repetitive BN injections, or at least potentially decrease the frequency or dosage needed. The purpose of this study was to roughly quantify the response rate of patients with EVT to primidone therapy.

IMPORTANCE Essential vocal tremor is difficult to treat. An effective pharmacologic treatment could allow patients to avoid or decrease the frequency or dosage of botulinum neurotoxin injections.

OBJECTIVE To evaluate the efficacy of primidone in the treatment of essential vocal tremor.

DESIGN, SETTING, AND PARTICIPANTS Medical records of all patients with a primary or secondary diagnosis of laryngeal spasm or essential tremor treated with primidone between June 1, 2012, and March 21, 2014, at a tertiary care medical center were reviewed. Data analysis occurred in April 2014.

MAIN OUTCOMES AND MEASURES Duration of therapy, improvement of symptoms, and whether the patient subsequently initiated botulinum neurotoxin therapy.

RESULTS All 30 patients were female (mean [SD] age, 71.9 [11.8] years). Mean (SD) therapy duration was 5.25 (7.22) months. Nine patients (30%) had other vocal conditions (4 had coexisting spasmodic dysphonia, 4 had laryngopharyngeal reflux disease, and 1 had muscle tension dysphonia). Twelve (40%) had previously undergone treatment. Fourteen of 26 patients (54%) reported an improvement in their vocal symptoms, and 16 of 29 (55%) did not discontinue primidone therapy. Twenty-two of 30 patients (73%) experienced adverse effects. Therapy was discontinued by 11 of 21 patients (52%) who experienced adverse effects and 2 of 8 patients (25%) who did not report adverse effects (P = .24) (1 patient who had adverse effects was missing data on discontinuation of therapy). Sixteen patients (53%) subsequently initiated botulinum toxin therapy, including 5 of 14 patients (36%) who reported clinical improvement with primidone therapy and 7 of 12 patients (58%) who did not report improvement (P = .43).

CONCLUSIONS AND RELEVANCE Primidone therapy was an effective pharmacologic treatment for essential vocal tremor in 14 of 26 patients in this case series, providing an alternative to botulinum neurotoxin therapy.


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Methods

Following University of Mississippi Medical Center Institutional Review Board review and approval, we performed a retrospective review of all patients seen in the clinic of the senior author (J.S.) with a primary or secondary diagnosis of laryngeal spasm (International Classification of Diseases, Ninth Revision, Clinical Modification code 478.75) or essential tremor (333.1) who were treated with primidone between June 1, 2012, and March 21, 2014. Informed consent was waived due to the retrospective nature of study. These diagnosis codes are used by the senior author for patients treated for EVT and spasmodic dysphonia. Patients’ medical records were reviewed and a specific diagnosis confirmed. Patient diagnosis was based on the history, physical examination, and endoscopic findings of the senior author alone or the senior author in conjunction with a single speech and language pathologist (J.A.).

It has been the senior author’s practice to use primidone as the first-line therapy for EVT. The drug is started at a low dose, typically 25 mg every night at bedtime, to avoid rapid, severe onset of adverse effects. The dose is then titrated in increments of 25 or 50 mg every month as tolerated. Ultimately, therapy is either kept at a dosage of satisfactory clinical response, discontinued as a result of adverse effect intolerance, continued with the addition of BN, or discontinued with initiation of BN therapy, with the patient responsible for determining how to proceed with treatment.

During our review, patient characteristics such as age, other vocal condition, previous treatment, primidone dosage, and the presence and type of adverse effects were collected. We also collected 3 outcome measures: whether the patient discontinued primidone therapy, self-reported improvement of symptoms, and whether they proceeded to BN therapy.

Our review identified 36 individuals. Six patients who had incomplete follow-up data or unrelated diagnoses (ie, focal extremity tremor) were excluded. Patients with missing data were excluded from the analysis of the characteristic for which data were unavailable. The Fisher exact test was used to compare the proportion of patients who proceeded to subsequent BN therapy with the proportion of patients who reported clinical improvement and to determine whether the relative proportion of patients who reported adverse effects was independent of the proportion of patients who discontinued primidone therapy. Two-sided P values less than .05 were considered statistically significant.

Results

Table 1 summarizes the characteristics of the study population. All 30 patients were female. Twenty-eight patients had a diagnosis of EVT, and 2 had a primary diagnosis of spasmodic dysphonia. The mean (SD) age was 71.9 (11.8) years, and therapy duration was 5.25 (7.22) months. At the time of diagnosis, 9 patients (30%) had other vocal conditions, and 12 (40%) had previously undergone treatment. Of the 9 patients with other vocal conditions, 4 had coexisting spasmodic dysphonia, 4 had laryngopharyngeal reflux disease, and 1 patient had muscle tension dysphonia.

Fourteen of 26 patients (54%) reported an improvement in their vocal symptoms, and 16 of 29 (55%) did not discontinue primidone therapy. Twenty-two of 30 patients (73%) experienced adverse effects (Table 2). Twenty-two patients (73%) ultimately reached a dosage of greater than 100 mg per day. The patients who discontinued therapy did so as a result of either adverse effects (n = 9 [31%]) or poor clinical response (n = 4 [14%]). Sixteen patients (53%) subsequently initiated botulinum toxin therapy, including 5 of 14 patients (36%) who reported improvement with primidone therapy, 7 of 12 patients (58%) who did not report improvement (P = .43), and 4 patients for whom data regarding improvement with primidone therapy were unavailable. However, 9 of 14 (64%) participants who exhibited clinical improvement were not subsequently treated with BN (Table 3). Therapy was discontinued by 11 of 21 patients (52%) who experienced adverse effects and 2 of 8 patients (25%) who did not report adverse effects (P = .24) (Table 4).

Discussion

Essential tremor is a heterogeneous disorder with variable clinical presentations. Whereas ET most often affects the hands and arms, it is estimated that the phonatory apparatus may be involved in 25% to 30% of patients with ET.12,17-19 A majority of prior studies have not demonstrated a sex predominance in ET, and those that have, demonstrated a male predominance.20
Essential tremor can affect voice through effects on intrinsic and extrinsic laryngeal muscles, pharyngeal and palatal muscles, and the muscles of articulatory structures, as well as muscles of the diaphragm, chest wall, and abdomen.21 When the voice is affected by ET, it is termed EVT. In contrast to the cited studies of ET, our study demonstrated female predominance and consisted exclusively of female patients. This is consistent with prior studies demonstrating a female predominance in head tremor, with a prior cohort study on EVT demonstrating a 93% female predominance.6 A possible explanation is that women are more likely than men to seek treatment, resulting in a selection bias.

Essential vocal tremor typically presents with tremor associated with increased phonatory effort. Vocal fatigue and muscular discomfort may result from attempts to stabilize the tremor and can result in complete arrest in phonation.12 Symptoms are typically present across all phonatory activity; however, the perception may be minimal while whispering. Therefore, many patients adopt whispering as their primary means of communication, with EVT and ET often indistinguishable in clinical presentation.22 Our findings showed that only 56% of patients benefited.6,12-16 Treatment may include pharmacologic therapies, such as propranolol and methazolamide, have not been noted to be effective in EVT.10,11 Previous investigations of primidone have not shown a substantial therapeutic effect on EVT. Chakrabarti and Pearce22 suggested that primidone therapy may benefit some patients with EVT. In a case series of 4 patients with vocal tremor, only 1 showed improvement of vocal symptoms; this patient discontinued primidone use as a result of adverse effects.23 Otherwise, to our knowledge, there are no other data specifically investigating the use of primidone in EVT.

Adverse effects with primidone therapy are common and frequently dose limiting.24 Common adverse effects include fatigue, lightheadedness, and disequilibrium. An acute toxic reaction to the first dose consisting of various combinations of nausea, sedation, malaise, ataxia, and confusion has also been reported. Our findings also showed a high frequency of fatigue, nausea, and general malaise.

Injections of BN into 1 or both thyroarytenoid muscles appear to be a promising treatment for EVT, although 1 report found that only 56% of patients benefited.5,12-16 Treatment may be individualized on the basis of the muscle groups involved (ie, extrinsic vs intrinsic laryngeal musculature).15 The brief duration of response to BN injection necessitates a substantial sacrifice of time and money; the need for repeated needle sticks also causes distress in some patients.16 Therefore, an effective pharmacologic treatment that would allow patients to avoid or decrease the frequency of BN injections would be advantageous.

Our data demonstrated a more favorable clinical response to primidone than had been previously reported by Hartman and Vishwanat23 and Chakrabarti and Pearce.22 Our finding that 54% of patients had a favorable clinical response is in line with the 50% response rate of ET to primidone therapy reported by Deuschl et al.9 The majority of patients continued primidone therapy (55%) and proceeded to BN therapy (53%). As mentioned, 64% of the participants who exhibited clinical improvement were not subsequently treated with BN.
Proceeding to BN therapy could indicate multiple scenarios, including intolerance of adverse effects or suboptimal clinical response either in magnitude or rapidity. Proceeding to BN therapy, however, did not always indicate discontinuation of primidone therapy as 5 patients continued using primidone even after initiating BN therapy and 1 of those patients reported improvement with primidone therapy. Concurrent treatment with primidone and BN may be indicated in certain situations. A patient may continue primidone during a trial of BN therapy, or a patient may be experiencing primidone benefit in treating coexisting nonlaryngeal tremor or laryngeal spasm. Additionally, primidone continuation allows the clinician to focus BN therapy to intrinsic laryngeal musculature while avoiding BN adverse effects such as dysphagia when treating extrinsic laryngeal musculature or the base of the tongue.

This study is limited by its retrospective nature, short follow-up, small sample size, lack of objective voice outcome measures, and by a lack of a control group. We were unable to investigate patients treated with primidone for EVT prior to June 1, 2012, as a result of changes in medical record keeping at University of Mississippi Medical Center. Some patients included in our review had just recently begun therapy and therefore had limited follow-up; more long-term follow-up is necessary in future study. Categorical, subjective vocal outcomes were used because the patients were ultimately responsible for making decisions regarding continuation of therapy. This study did not have a control group, which limits our ability to more accurately assess the effect of primidone therapy. Additionally, we were unable to control for possible placebo effect. Nevertheless, this study provides evidence that primidone is effective in a substantial proportion of patients. There is a need for prospective investigation of primidone efficacy in EVT using pretreatment and posttreatment standardized outcome measures.

Given the aging United States population, the number of patients seen in otolaryngology clinics for EVT will continue to increase. An effective pharmacologic treatment is needed because of the substantial financial cost and time associated with BN treatment. Primidone appears to be a promising pharmacologic treatment for EVT and requires further study.

Conclusions

On the basis of the limited results of this study, EVT may be responsive to pharmacotherapy. Further investigation into the expected improvement and long-term risks and benefits are under way at our institution.

| Discontinuation of Therapy | Reported Adverse Effects, No. (%) | P Value*
|---------------------------|----------------------------------|-------
| No (n = 16)               |                                  |       |
|                           | No (13, 75)                      | 10 (48) | .24 |
|                           | Yes (n = 13)                     | 2 (25)  | 11 (52) |
| Total                     |                                  | 8 (100) | 21 (100) |

* Two-sided Fisher exact test.


