Efficacy and Tolerability of Pregabalin in Essential Tremor: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

Joseph Ferrara MD, Christopher Kenney MD, Anthony Davidson, Lina Shinawi, Abigail Kissel, Joseph Jankovic MD

Parkinson Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

Introduction

Essential tremor (ET) is a common neurological disorder characterized by action tremor, predominantly affecting the hands. Several medications, including propranolol, primidone, topiramate and gabapentin, have shown moderate tremorlytic effects in placebo-controlled trials;[1] however, current drug therapies are ineffective in approximately 25-55% of ET patients,[2] and treatment is often limited by adverse effects.

Pregabalin (PGB) is an amino acid derivative of GABA with antiepileptic, analgesic, and anxiolytic properties. PGB binds to the alpha-2-delta subunit of neuronal voltage-gated calcium channels, causing diminished release of excitatory neurotransmitters.[3] Preliminary studies suggest that PGB has tremorlytic effects,[4] and the drug has proven reasonably well-tolerated in elderly patients.[3] Accordingly, we assessed the tolerability and efficacy of PGB in patients with ET in this pilot placebo-controlled, cross-over design trial.

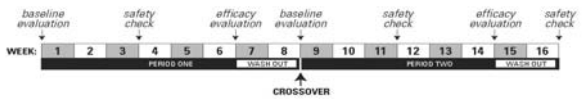
Methods

Participants:
Twenty patients with definite or probable ET, defined according to Tremor Investigational Group criteria,[5] were recruited from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic in Houston, TX. Exclusion criteria included: age <18 or >80 years; any ongoing cause of enhanced physiologic tremor; recent exposure to tremorgenic drugs; historical or clinical evidence of psychogenic tremor; prior surgical treatment for tremor; and use of other tremorlytic drugs, apart from stable dosing of a beta-blocker and an evening dose of a benzodiazepine hypnotic. The study protocol was approved by Baylor College of Medicine Internal Review Board for Human Research.

Evaluation Procedures:
A randomized, double-blind, placebo-controlled, crossover design study was used with Fahn-Tolosa-Marin Tremor Rating Scale (TRS) normalized total score serving as the primary endpoint.[6] Secondary endpoints were the Clinical Global Impression of Change (CGI-C), Quality of Life in Essential Tremor Questionnaire (QUEST),[7] Hamilton Anxiety Rating Scale (HAM-A),[8] and a health status questionnaire on sleep hygiene (HD-16).[9]

Patients were randomized to treatment with PGB or placebo, titrated over 6 weeks (figure). Identical assessments of the TRS (primary endpoint), CGI-C, QUEST, HAM-A, and HD-16 were made by a consistent rater at baseline, at the end of treatment periods for both drug and placebo, and following the 2-week washout period preceding crossover. Patients received the study drug at an initial dose of 75 mg twice daily, with upward titration to a target dose of 150 mg twice daily. Patients were given the option to increase the study drug as high as 300 mg twice daily if inadequate benefit was perceived after 3 weeks of treatment. Patients were permitted to return to a lower dose if side effects occurred during drug titration.

Study Design:



Data Analysis:
TRS raw scores were normalized prior to analysis using previously described methods,[10] and scored as per published guidelines.[7-9] Outcome on study completers was assessed via ANOVA models

Results

■ Demographics and clinical characteristics of participants at study initiation are listed in Table 1.

■ Analysis of variance revealed no treatment effect (P = 0.16), period effect (P = 0.67), or treatment-period interaction (P = 0.07). Although TRS measures were worse when patients were taking PGB, this difference did not reach statistical significance (Table 2). There was a statistically significant difference in QUEST scores between PGB and placebo, favoring placebo (P = 0.03).

■ One patient withdrew from the PGB period of the study due to postural instability and died of a malignant arrhythmia 6 days later. Other adverse effects were mild to moderate in severity (Table 3).

Table 1: Clinical Characteristics of Patients at Baseline

Sex, F/M		11/9
Age, mean years ± SD		62.2±12.7
ET duration, mean years ± SD		25.5±14.9
Family history of ET, N (%)		13 (65)
Adjunct beta-blocker use, N (%)		13 (65)
Number of failed tremorlytics before enrollment, mean ± SD		2.9±1.8
Normalized TRS, mean ± SD[1]	Part A:	18.3±6.0
	Part B:	50.8±16.4
	Part C:	43.1±15.3
	Total:	37.1±11.6
QUEST summary index, mean ± SD[2]		37.5±19.0
HAM-A, mean ± SD[3]		11.7±7.5
HD-16, mean ± SD[4]		87.8±160.7

1. TRS part A rates the severity of resting, postural and action tremor in upper and lower extremities, face, tongue, voice, head and trunk. Part B rates the severity of upper extremity tremor while writing, drawing, and pouring liquid. Part C rates functional disability of tremor while speaking, eating, drinking, maintaining hygiene, dressing, and working. 2. The QUEST rates patient perception of health status as influenced by tremor across 5 domains: physical, psychosocial, communication, hobbies/leisure, and work/finance. 3. The HAM-A rates the severity of anxiety symptomatology across 14 parameters. Scores of 14-17 correspond to mild anxiety, scores 18-24, moderate anxiety, and scores 25-30 severe anxiety. 4. The HD-16 rates insomnia-related quality of life across five domains: physical symptoms, energy and motivation, concentration, interpersonal relations, and psychological symptoms.

Table 2: Change in Measures of Efficacy

		Pregabalin	Placebo	P-value
Change in normalized TRS	Part A	2.4±4.7	-0.2±4.1	0.24
	Part B	6.7±12.3	3.6±6.6	0.24
	Part C	4.5±13.9	-1.5±12.8	0.13
	Total	5.1±9.7	0.3±4.6	0.16
CGI-C		3.9±1.3	3.8±0.5	0.16
Change in QUEST summary index		8.0±20.3	-9.7±14.5	0.03
Change in HAM-A		1.1±5.2	4.1±5.4	0.26
Change in HD-16		32.2±146.8	-38.6±99.3	0.14

For the TRS, HAM-A, QUEST and HD-16, higher scores represent increased symptom severity. CGI-C was scored as follows: 1=very much improved, 2=much improved, 3=mildly improved, 4=no change, 5=mildly worse, 6=much worse, 7=very much worse

Table 3: Adverse Events

Symptom	Frequency, N (%)	
	PGB (N=20)	Placebo (N=18)
Drowsiness	5 (25)	3 (17)
Dizziness	4 (20)	1 (6)
Fatigue	3 (15)	0
Instability	3 (15)	1 (6)
Insomnia	0	2 (11)
Headache	0	2 (11)
Confusion	1 (5)	1 (6)
Vivid dreams	1 (5)	1 (6)
Upper respiratory tract infection	2 (10)	1 (6)
Blurred vision	1 (5)	0
Burning tongue	1 (5)	0
Fatal arrhythmia	1 (5)	0
Possible jaw dislocation	1 (5)	0
Nausea	0	1 (6)
Night sweats	0	1 (6)
Weight gain	0	1 (6)

Discussion

■ In this randomized, double-blind, placebo-controlled, cross-over study, PGB failed to significantly reduce ET severity, as assessed by TRS.

■ It is possible that our study did not identify a change in tremor severity, which might have been apparent using accelerometry, a digitizing tablet or other kinematic techniques. Indeed, in a prior study of PGB for ET, there was a significant reduction in tremor amplitude as measured by accelerometry without a corresponding improvement in TRS subsection scores.[4]

■ We included the QUEST as a secondary endpoint in this study, as our interest was in demonstrating a reduction in tremor that improved quality of life and motor function. Unexpectedly, we found a statistically significant deterioration in QUEST scores during the PGB period versus placebo. The basis for this change is not clear, as TRS scores were similar for PGB and placebo, and patient-rated CGI-C was essentially unchanged from baseline in both groups.

■ Given its size, this trial cannot exclude the possibility that PGB has tremorlytic effects, but any effect is likely to be modest, and our results suggest that a larger study is unlikely to yield more favorable results in a similar ET population.

■ Overall, adverse events of PGB in our ET population were comparable to those previously reported in patients with epilepsy, anxiety and chronic pain conditions.[3,11]

■ In conclusion, we found PGB to be well tolerated in patients with moderately severe ET, but without a clinically meaningful tremorlytic effect.

References

1. Zesiewicz TA, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the AAN. Neurology 2005;64:2008-20.
2. Louis ED. Clinical practice. Essential tremor. N Engl J Med 2001;345:887-91.
3. Montgomery S, et al. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. Br J Psychiatry 2008;193:389-94.
4. Zesiewicz TA, et al. A pilot, double-blind, placebo-controlled trial of pregabalin (Lyrica) in the treatment of essential tremor. Mov Disord 2007;22:1660-3.
5. Findley LJ, Koller WC. Definitions and behavioural classification. In: Findley LJ, Koller WC, eds. Handbook of Tremor Disorders. New York: Marcel Dekker, 1995:1-5.
6. Fahn S, et al. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and Movement Disorders. Baltimore: Urban & Schwarzenberg, 1988:225-234.
7. Tröster AI, et al. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. Parkinsonism Relat Disord 2005;11:367-73.
8. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-55.
9. Leger D, et al. HD-16: a new quality of life instrument specifically designed for insomnia. Sleep Med 2005;6:191-8.
10. Ondo WG, et al; Topiramate Essential Tremor Study Investigators. Topiramate in essential tremor: a double-blind, placebo-controlled trial. Neurology 2006;66:672-7.
11. Lyrica [package insert]. New York, NY: Pfizer Inc.; Revised 6/2007.

Acknowledgment

This investigator-initiated study was supported by a grant from Pfizer, Inc.

The *Movement* Disorder Society