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Review Article

Antiepileptic drugs in essential tremor

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CONTENTS

Abstract

Essential tremor (ET) is characterized by postural and kinetic tremor and is no longer considered to be a disease of single pathological origin. The Quality Standards Subcommittee of the American Academy of Neurology (AAN) recently published evidence-based recommendations for the treatment of ET, which included Level B recommendations for the use of gabapentin and topiramate. However, a number of other antiepileptic drugs, including two in phase III development for epilepsy, have more recently been evaluated in ET or in animal models of ET. Clinical studies with levetiracetam have not confirmed the promising efficacy in a single-dose study. However, these and other studies with zonisamide have involved very small numbers of patients. Larger studies are required to evaluate the efficacy of antiepileptic drugs in ET. Preclinical studies in animal models of ET have demonstrated early evidence of efficacy for brivaracetam and lacosamide. Recent advances in the characterization of the disease and in the development of genetic models may enable the development of targeted and more effective symptomatic therapies.

Introduction

Essential tremor (ET) is the most common tremor disorder in adults and is characterized by postural and kinetic tremor involving the arms and, less commonly, the head, lower limbs and voice. It is differentiated from other types of tremor such as Parkinsonian tremor and dystonic tremor. ET affects 1-6% of the population, and the typically progressive symptoms eventually result in disabilities associated with basic daily living activities such as eating, writing and driving. Although a prevalent hypothesis regarding the pathogenesis of ET implicates the abnormal function of a central oscillator located in the olivocerebellar system, recent advances in the characterization of this neurological disorder have highlighted the etiological, clinical and pathological heterogeneities of the disease. Epidemiological studies have also implicated putative environmental toxins, such as lead, as causative factors in its development (1, 2).

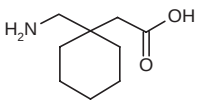
A number of methods of assessment for the symptoms of ET have been used in clinical studies, but no clinical rating scale has been consistently used. The most widely used scale has been the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (3). This scale evaluates tremor (at rest, postural and kinetic, as appropriate) in the face, tongue, voice, head, arms, legs and trunk. It also includes evaluation of handwriting, drawing and pouring, as well as various patient-reported activities of daily living. A variety of other methods have been used in individual studies, including accelerometry, spirography, assessment of daily living activities and global assessments of disability and improvement.

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) recently published evidence-based recommendations for the initiation of pharmacological and surgical therapies for patients with ET. The recommendations were based on a systematic literature review of clinical trials performed between 1966 and August 2004 (4). The mainstays of pharmacological treatment for ET are the antiepileptic primidone and propranolol. Propranolol is the only drug approved by the U.S. Food and Drug Administration for the management of ET. The two drugs are similarly effective as initial therapy in 50-70% of patients, both resulting in approximately 50% improvement in symptoms assessed by clinical rating scales and accelerometry. However, there tends to be a loss of benefit after 1 year, and patients also differ in their response to therapy. Thus, effective management of the syndrome may require combination therapy with these and other drugs. In drug-refractory ET, surgical procedures including thalamotomy and deep brain stimulation are considered. Limitations associated with the use of primidone and propranolol, including increased incidence of adverse reactions in the elderly, drug interactions and concurrent medical conditions precluding their use, have

led to the evaluation of alternative drug therapies. Several antiepileptic drugs have been investigated for the treatment of ET, including gabapentin, topiramate, levetiracetam, zonisamide, T-2000, lacosamide and brivaracetam. Gabapentin and topiramate have been recommended for the second-line treatment of ET with a Level B recommendation (4). This review summarizes recent data regarding the evaluation of these compounds in the treatment of ET.

Drugs in clinical trials for essential tremor

Gabapentin



The Level B recommendation for gabapentin was based on three controlled studies in a total of 61 patients. In a double-blind, crossover study, 20 patients with ET received gabapentin 1800 mg/day and placebo. After 2 weeks' treatment, the majority of patients either reported no change in their tremor or were worse following gabapentin or placebo treatment (5). The response to gabapentin (1200 mg/day) and propranolol was studied in a double-blind, placebo-controlled, 3-way crossover study in 16 patients. Both drugs resulted in a significant and comparable reduction in tremor measured by a clinical rating scale and by accelerometry, as compared with placebo (6). In a further double-blind, crossover study, two doses of gabapentin (1800 mg and 3600 mg daily) were evaluated in 25 patients. There were signficant improvements in patient global assessments, observed tremor scores, water pouring scores and activities of daily living, as compared with placebo. However, there was no difference in response between the doses and no improvements in accelerometry scores or investigator global impression scores (7). The results of these studies and the other clinical studies that follow are summarized in Table I.

In another study, the efficacy of gabapentin 1200 mg/day was compared with propranolol 120 mg/day in 70 patients diagnosed with ET. Patients were treated for 4 weeks, and the improvement assessed by the Tremor Assessment Form was 43% in the gabapentin group compared with 47% in the propranolol group. There were no serious adverse events (8).

Table I: Studies evaluating the efficacy of antiepileptic drugs in the treatment of essential tremor (from Prous Science Integrity®).

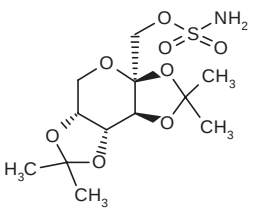
Drug	Design	Treatments	n	Conclusions	Ref.
Gabapentin	Randomized Double-blind Crossover	Gabapentin, 300 mg p.o. o.d x 1 d → 300 mg p.o. b.i.d. x 1 d → 300 mg p.o. t.i.d. x 1 d → 600 mg p.o. t.i.d. x 2 wks Placebo	20	Gabapentin was not effective in improving essential tremor scores. Only 2/18 patients who completed the study reported mild to marked improvement with gabapentin treatment	5
	Randomized Double-blind Crossover	Gabapentin, 400 mg p.o. t.i.d. x 15 d Propranolol, 40 mg p.o. t.i.d x 15 d Placebo	16	In all measurements gabapentin and propranolol showed significant and comparable efficacy in the reduction of tremor; accelerometry measures indicated that both gabapentin and propranolol reduced tremor potency	6
	Randomized Double-blind Crossover	Gabapentin, 300 mg p.o. t.i.d. x 1 wk → 600 mg p.o. t.i.d. x 2 wks → 900 mg p.o. t.i.d. x 1 wk → 1200 mg p.o. t.i.d. x 2 wks Placebo	25	Efficacy results (water pouring, activities of daily living and tremor amplitude scores) significantly improved with gabapentin treatment. The highest dose was not more effective than 1800 mg/d	7
	Open	Gabapentin, 1200 mg/d Propranolol, 120 mg/d	70	Gabapentin and propranolol were equally effective and well tolerated in patients with essential tremor	8
Topiramate	Randomized Double-blind Crossover	Topiramate, 25 mg/d x 1 wk → 25-50 mg/d 1x/1 wk up to 200 mg/d → 100 mg/d 1x/1 wk increased up to 400 mg/d or maximum tolerated dose x 2 wks Placebo	24	Topiramate treatment resulted in a significant reduction in normalized tremor rating scores, with a mean dose of 333 mg/d	9
	Randomized Double-blind Crossover	Topiramate, 400 mg/d or maximum tolerated dose [titration over 8 wks + maintenance period x 2 wks] Placebo	62	Treatment with topiramate significantly improved tremor severity, motor task performance and functional disability	10

Continuation

Table I (cont.): Studies evaluating the efficacy of antiepileptic drugs in the treatment of essential tremor (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Topiramate	Randomized Double-blind Multicenter	Topiramate, 400 mg/d or maximum tolerated dose or dose at which tremor resolved [titration over 12 wks with 25 mg/d increases 1x/1 wk up to 100 mg/d,and then 50 mg/d] x 12 wks Placebo	223	Topiramate was effective in moderate to severe essential tremor. Mean Improvement on the Fahn-Tolosa-Maris Tremor Rating Scale was 29% for topiramate, with a mean dose of 292 mg/d, compared to 16% with placebo	11
	Randomized Double-blind	Topiramate, 252 mg [mean] [titration over 12 wks up to dose at which tremor resolved or maximum tolerated dose] x 3 mo Placebo	72	Tremor improved in most patients (25/36) treated with topiramate, compared with only 2 patients in the placebo group	12
	Randomized Double-blind Crossover	Topiramate, 25 mg/d p.o. o.d. [night] x 2 wks → 25 mg p.o. b.i.d x 2 wks → 50 mg p.o. b.i.d. x 2 wks Placebo	13	No outcome measure improved significantly in the active treatment period compared with the placebo-controlled period	13
Levetiracetam	Randomized Double-blind	Levetiracetam, 1000 mg p.o. s.d. Placebo	24	A single dose of levetiracetam improved tremor, as detemined by accelerometry and some functional tests	14
	Open	Levetiracetam, 250 mg p.o. b.i.d. x 1 wk → 500 mg p.o. b.i.d. x 1 wk → 1000 mg p.o. b.i.d. x 1 wk → 1500 mg p.o. b.i.d. x 1 wk	10	Levetiracetam was well tolerated but did not consistently improve essential tremor	15
	Randomized Double-blind Crossover	Levetiracetam, 250 mg/d x 2 d → 500 mg/d x 4 d → 3000 [max.] mg/d [escalated by 500 mg 1x/4 d] Placebo	12	Levetiracetam had no antitremor effects in patients with essential tremor	16
Zonisamide	Randomized Open Crossover	Zonisamide, 100 mg/d x 2 wks → up to 200 mg/d [if patient agreed] x 2 wks Arotinolol, 10 mg/d [20 mg/d in 2 patients previously treated with this dose]	14	Zonisamide improved tremor scores in patients with essential tremor similarly to arotinolol; however, zonisamide was more effective for tremors of cranial nerve areas (voice, face, tongue and head)	17
	Randomized Double-blind	Zonisamide, 100 mg/d x 2 wks → 200 mg/d x 2 wks Placebo	20	Zonisamide significantly reduced tremor as measured by accelerometry and was well tolerated; 50% of patients who took zonisamide reported at least mild tremor reduction at the study endpoint as measured by the Clinical Global Impression scale	18
T-2000	Randomized Double-blind Dose-finding	T-2000, 600 mg/d → 800 mg/d → 1000 mg/d [max] x 20 wks Placebo	24	This ongoing phase II study will assess the efficacy and safety of T-2000 in patients with essential tremor at various doses. Effect on tremor will be measured by a tremor scale and assessment of functional activity with specific tasks	19

Topiramate



Early anecdotal evidence indicated that topiramate could be effective in ET. It exhibits neurostabilizing effects as a result of activity at multiple receptors and ion channels, and is launched for the treatment of epilepsy and, more recently, migraine prophylaxis. A single-center, double-blind, placebo-controlled, crossover study was conducted in 24 patients. Following titration, patients received topiramate 400 mg/day either as monotherapy or as adjunctive therapy for 2 weeks. Fifteen patients completed both treatment periods. The primary efficacy parameter was the overall normalized tremor rating score based on the Fahn-Tolosa-Marin TRS. The reductions from baseline were significantly greater following topiramate treatment than after placebo. Topiramate was associated with significantly greater reductions from baseline for each of the normalized tremor scale subscores: tremor location/severity, specific motor tasks/functional disabilities and tremor-resultant functional disabilities (9).

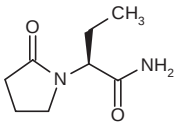
A randomized, double-blind, placebo-controlled, crossover trial of topiramate in ET was performed in 62 patients at three centers. Following an 8-week titration period to 400 mg/day topiramate or the maximum tolerated dose, patients were maintained at this dose for 2 weeks. Concomitant tremor medications could be continued. The primary efficacy parameter was mean normalized TRS score, and in 41 patients providing evaluable data in both periods, topiramate was associated with significant mean improvement in total TRS compared with placebo. The changes represented 18-23% median improvement in total TRS for topiramate-treated patients compared with 0-1% for placebo. Topiramate treatment was also associated with significant improvements in the TRS subscores, tremor severity, motor task performance and functional disability. Eighteen patients discontinued treatment due to adverse events. The most frequently reported adverse events in topiramate-treated patients were paresthesia, difficulty with concentration and anorexia (10).

A total of 223 patients aged 18-80 years with definite ET of the hands or forearms were randomized to either topiramate (target dose 400 mg/day) or placebo for 24 weeks in a phase III, multicenter, double-blind, parallel-group study. Topiramate was titrated during the first 12 weeks to the maximum tolerated dose or the dose at which tremor resolved. One antitremor medication was permitted if the dose had remained constant for at least 2 weeks before randomization and was unchanged throughout the study. The primary efficacy variable was the tremor score based on the Fahn-Tolosa-Marin TRS, and at the final visit this was significantly lower in the topiramate group compared with the placebo group. The mean percentage improvement in overall TRS was also significantly greater in the topiramate group (29% *vs.* 16% with placebo) and greater improvements in function and disability were observed. Adverse events were treatment-limiting in approximately one-third of topiramate-treated patients and included paresthesia, nausea, concentration/attention difficulty and somnolence (11).

A double-blind, placebo-controlled study was also performed in 72 patients diagnosed with ET and who were resistant to previous therapy. Doses were titrated over 12 weeks to the maximum tolerated dose or the dose at which tremor resolved, and this dose (mean 252 mg/day) was then maintained for 3 months. A significant improvement was observed in the Fahn-Tolosa-Marin TRS from baseline to the end of study in 25 patients in the topiramate group compared with only 2 patients in the placebo group. Only a small number of patients discontinued therapy because of adverse effects (12).

Another double-blind, placebo-controlled, crossover trial evaluated increasing doses of topiramate to 100 mg daily after 4 weeks. However, of only 13 patients who received treatment, 3 withdrew within the first 4 weeks of the study. No outcome measure improved significantly in the active treatment period compared with the placebo control period, but the study was underpowered and the dose of topiramate was also much lower than in other studies in ET (13).

Levetiracetam

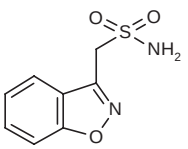


Levetiracetam is an N-type calcium channel blocker launched since 2000 for the treatment of epilepsy. It is currently in clinical evaluation for a range of disorders, including panic disorder, bipolar disorder, neuropathic pain in patients with spinal cord injury and alcohol dependence.

The effect of a single dose of levetiracetam 1000 mg was investigated in 24 patients (mean age 70 years) with ET in a double-blind, placebo-controlled trial. Tremor medications were tapered and discontinued at least 1 week prior to the study. Accelerometry and functional tests were performed at baseline and at intervals up to 130 min after administration of the study drug. The single dose of levetiracetam showed a significant antitremor effect. In the levetiracetam group, tremor amplitude negatively correlated with levetiracetam plasma levels, and significant benefits in favor of levetiracetam were observed for line drawing and spiral drawing. Tremor rating was also significantly lower in the levetiracetam group than in the placebo group at both 70 and 130 min post-dose (14).

However, two small clinical studies have not confirmed the efficacy of levetiracetam in ET. In an open-label pilot study in 10 patients diagnosed with ET, treatment with low-dose (500 mg b.i.d.) levetiracetam was evaluated after 2 weeks and high-dose (1500 mg b.i.d.) levetiracetam after a further 2 weeks. There was a modest but statistically significant improvement in the TRS observed tremor section, but no significant changes in other sections of the TRS including writing and activities of daily living (15). A pilot, randomized, double-blind, placebo-controlled, crossover study was also performed in 12 patients with ET. Levetiracetam was titrated over 4 weeks to a maximum of 3000 mg/day, administered for 2 weeks. The patients had a median tremor duration of 28 years. There were no statistically significant differences between the treatment groups on any tremor rating scale or accelerometry measure (16).

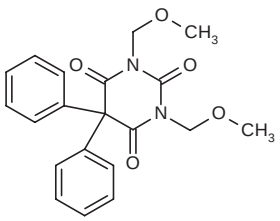
Zonisamide



Zonisamide is a sodium channel and T-type calcium channel blocker. It is also in development for the treatment of Parkinson´s disease and obesity. In addition to its neurostabilizing activities, zonisamide acts as a free radical scavenger, indicating a potential neuroprotective role for this compound.

An open-label, pilot, crossover study comparing zonisamide with arotinolol provided preliminary evidence that zonisamide might have therapeutic potential in the treatment of ET (17). Following this, a randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of zonisamide in 20 patients with ET. Zonisamide was initiated at a dose of 100 mg/day and titrated to 200 mg/day after 2 weeks. Treatment was continued for 2 more weeks. Patients were assessed by accelerometry, the Fahn-Tolosa-Marin TRS and the Clinical Global Impression (CGI) scale. The primary efficacy endpoint was tremor amplitude measured by accelerometry, and this was significantly improved from baseline to study endpoint in the zonisamide group compared with the placebo group. There were also improvements in the Fahn-Tolosa-Marin TRS part A scores, and 50% of patients who received zonisamide reported at least mild tremor improvement as measured by the CGI scale. Three patients in the zonisamide group withdrew due to somnolence (18).

T-2000

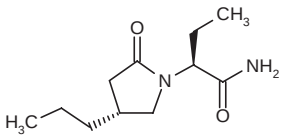


T-2000 is a long-acting, nonsedating barbiturate in phase II development for the treatment of epilepsy. A phase II study in ET was expected to start recruitment in May 2006 in Canada. This will be a randomized, double-blind, placebo-controlled, sequential-dose-escalation study (600, 800 and 1000 mg/day) with an expected enrollment of 24 patients. The total duration of treatment will be 20 weeks. Approval to conduct a phase III, randomized, double-blind, placebo-controlled study in patients with ET has also been granted in Canada (19, 20).

Preclinical studies in animal models of ET

Two animal models have been developed which exhibit tremor characteristic of ET and these have been used to evaluate established and novel therapies for the disorder. Harmaline is a γ-aminobutyric acidA ($GABA_A$) receptor inverse agonist and induces a temporary tremor in animals due to its action at the inferior olivary nucleus. The GABAergic system is postulated to be involved in the etiology of ET and tremor induction by harmaline is attributed to inhibition of $GABA_A$ receptors, resulting in enhanced electrical coupling of cerebellar afferents in the inferior olivary nucleus.

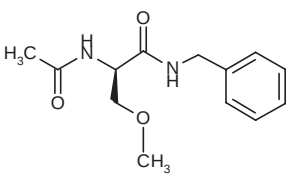
Two compounds in phase III development for epilepsy have been evaluated for their potential activity in ET using the rat model of harmaline-induced tremor. Brivaracetam (UCB-34714) is a new pyrrolidone derivative with high affinity for the levetiracetam binding site (the synaptic vesicle protein SV2A). Behavioral effects were assessed following intraperitoneal injection of brivaracetam, propranolol and primidone. Drugs were administered 30 min prior to harmaline injection. Brivaracetam dose-dependently (21-70 mg/kg) reduced both elicited tremor index and spontaneous tremor index (by 53% and 43%, respectively) without significantly altering sedation index. Propranolol and primidone also attenuated spontaneous tremor index and increased sedation index. The results indicated that brivaracetam demonstrated the most significant efficacy in this model at doses that did not enhance harmaline-induced sedation and without adverse effects (21).



Brivaracetam

The antitremorigenic effects of brivaracetam and propranolol were studied *in vitro* in a population of inferior olivary neurons from rat brainstem slices which display spontaneous oscillations. Perfusion of either brivaracetam 10 μM or propranolol 30 μM prevented the harmaline-induced hyperpolarization of the resting membrane potential and the increase in the amplitude of oscillations. Harmaline reduced the initial frequency of the oscillations by 47%, and brivaracetam and propranolol further reduced the oscillations to approximately 20% of their initial frequency (22).

Lacosamide (SPM-929) is a functionalized amino acid with broad anticonvulsant activity. In rats, lacosamide (0.3-30 mg/kg i.p.) reduced the intensity of harmaline-induced tremors in a dose-dependent manner. At the highest doses tested, the maximum efficacy was improved compared with propranolol and comparable to primidone. The latency of tremor onset was increased at the highest dose of lacosamide but was not altered following either propranolol or primidone (23).



Lacosamide

There are some limitations associated with the harmaline-induced model of ET, including development of rapid tolerance to harmaline, enhanced physiological tremor and locomotor deficits due to Purkinje cell degeneration. A recently developed genetic model of ET involves the deletion of $GABA_A$ receptor α1 subunits in mice, resulting in the loss of 50% of all $GABA_A$ receptors in the brain. In these mice, tremor and motor incoordination mimic human ET. In this model, primidone, propra-

nolol and gabapentin reduced the amplitude of the pathological tremor. Such models may enhance the prediction of new therapeutical targets and further elucidate the etiology of the disorder (24).

Conclusions

A number of antiepileptic drugs show promise in the treatment of ET. Gabapentin and topiramate are recommended (Level B) for second-line treatment according to the Quality Standards Subcommittee of the AAN based on published studies, while primidone and propranolol remain first-line therapy in patients with this disorder. The studies of antiepileptic drugs have generally been conducted in small numbers of patients, and larger studies are required to confirm the efficacy of these compounds. The precise etiology of ET is unknown, and as this is further elucidated, targeted therapies may result in drugs with greater efficacy.

References

1. Louis, E.D. *Essential tremor*. Lancet Neurol 2005, 4(2): 100-10.

2. Sullivan, K.L., Hauser, R.A., Zesiewicz, T.A. *Essential tremor: Epidemiology, diagnosis, and treatment*. Neurologist 2004, 10(5): 250-8.

3. Fahn, S.E., Tolosa, E., Marin, C. In: *Parkinson's Disease and Movement Disorders, 2nd Ed*. Jankovic, J., Tolosa, E. (Eds.). Williams & Wilkins, Baltimore, 1988, 225-34.

4. Zesiewicz, T.A., Elble, R., Louis, E.D. et al. *Practice parameter: Therapies for essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology*. Neurology 2005, 64(12): 2008-20.

5. Pahwa, R., Lyons, K., Hubble, J.P., Busenbark, K., Rienerth, J.D., Pahwa, A., Koller, W.C. *Double-blind controlled trial of gabapentin in essential tremor*. Mov Disord 1998, 13(3): 465-7.

6. Gironell, A., Kulisevsky, J., Barbanoj, M. *A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor*. Arch Neurol 1999, 56(4): 475-80.

7. Ondo, W., Hunter, C., Vuong, K.D., Schwartz, K., Jankovic, J. *Gabapentin for essential tremor: A multiple-dose, double-blind, placebo-controlled trial*. Mov Disord 2000, 15(4): 678-82.

8. Unal, Z., Gozke, E., Boylu, E., Dortcan, N., Orhan, S. *Can gabapentin be an alternative of propranolol in the treatment of essential tremor?* 8th Congr Eur Fed Neurological Soc (EFNS) (Sept 4-7, Paris) 2004, Abst P2267.

9. Connor, G.S. *A double-blind placebo-controlled trial of topiramate treatment for essential tremor*. Neurology 2002, 59(1): 132-4.

10. Hulihan, J., Connor, G.S., Wu, S.C., Edwards, K., Tarsy, D., Kraut, L. *Topiramate in essential tremor: Pooled data from a double-blind, placebo-controlled, crossover trial*. Neurology 2003, 60(5, Suppl. 1): Abst P04.068.

11. Ondo, W.G., Jankovic, J., Connor, G.S. et al. *Topiramate in essential tremor: A double-blind, placebo-controlled trial*. Neurology 2006, 66(5): 672-7.

12. Kapisyzi, M., Kruja, J. *The effectiveness and tolerability of topiramate for treatment of essential tremor*. Mov Disord 2005, 20(Suppl. 10): Abst P581.

13. Frima, N., Grunewald, R.A. *A double-blind, placebo-controlled, crossover trial of topiramate in essential tremor*. Clin Neuropharmacol 2006, 29(2): 94-6.

14. Bushara, K.O., Malik, T., Exconde, R.E. *The effect of levetiracetam on essential tremor*. Neurology 2005, 64(6): 1078-80.

15. Ondo, W.G., Jimenez, J.E., Vuong, K.D., Jankovic, J. *An open-label pilot study of levetiracetam for essential tremor*. Clin Neuropharmacol 2004, 27(6): 274-7.

16. Handforth, A., Martin, F.C. *Pilot efficacy and tolerability: A randomized, placebo-controlled trial of levetiracetam for essential tremor*. Mov Disord 2004, 19(10): 1215-21.

17. Morita, S., Miwa, H., Kondo, T. *Effect of zonisamide on essential tremor: A pilot crossover study in comparison with arotinolol*. Parkinson Relat Disord 2005, 11(2): 101-3.

18. Zesiewicz, T.A., Ward, C.L., Staffetti, J.F., Dunne, P.B., Sullivan, K.L. *A double-blind, placebo-controlled trial of zonisamide (Zonegran) in the treatment of essential tremor*. Neurology 2006, 66(5, Suppl. 2): Abst S33.004.

19. *Placebo-controlled, dose escalation study of T-2000 in essential tremor (NCT00321087)*. ClinicalTrials.gov Web Site 2006.

20. *Taro to begin dose escalation study of T-2000 in Canada to evaluate efficacy in essential tremor*. Taro Pharmaceutical Press Release May 15, 2006.

21. De Ryck, M., Matagne, A., Kenda, B., Michel, P., Klitgaard, H. *Contrasting effects of ucb34714 and drugs for essential tremor on harmaline-induced elicited versus spontaneous tremor and sedation in rats*. Mov Disord 2004, 19(Suppl. 9): Abst P1296.

22. Niespodziany, I., Klitgaard, H., Margineanu, D. *Effects of brivaracetam (ucb 34714) on harmaline-induced electrophysiological changes in rat inferior olivary neurons*. 35th Annu Meet Soc Neurosci (SFN) (Nov 12-16, Washington D.C.) 2005, Abst 971.1.

23. Stoehr, T. *Lacosamide has potent anti-tremor effects in a rat model for essential tremor*. Neurology 2006, 66(5, Suppl. 2): Abst S33.005.

24. Kralic, J.E., Criswell, H.E., Osterman, J.L. et al. *Genetic essential tremor in γ-aminobutyric acid receptor α_1 subunit knockout mice*. J Clin Invest 2005, 115(3): 774-9.