

REVIEW

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## Emerging Therapies for the Treatment of Essential Tremor

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**Abstract:** This article will review newer therapies for the treatment of essential tremor as well as cover potential therapies still in development. Drug pharmacology, specific dosing for ET and adverse effects will be reviewed. Finally, a rationale approach to treatment of ET will be discussed.

**Keywords:** gabapentin, topiramate, pregabalin, sodium oxybate, octanol

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## Introduction

Essential tremor (ET) is one of the most common neurological conditions and is disabling for most patients who suffer from it.<sup>1–3</sup> Despite the high prevalence and associated impact on quality of life, with the exception of thalamic deep brain stimulation (DBS), there has never been a therapy developed and approved specifically for this condition. This is largely due to the lack of good understanding of the underlying pathogenesis of ET. Recent studies suggest that loss of cerebellar purkinje cells and gabanergic dysfunction may explain most of ET<sup>4–6</sup> although how this ties in to known effective therapies still needs to be elucidated. Commonly, drugs like propranolol and primidone are used with substantial post-marketing data supporting their use (for review, see Koller, 2000).<sup>7</sup> Although these treatments are effective, their benefit is modest with most studies supporting, at best, a 50% reduction in tremor severity. Thalamic DBS is more effective but requires neurosurgery with its associated risks and is therefore reserved for the most disabled ET patients. There is a need for additional therapies that are not only efficacious but have good tolerability and safety in this often elderly population. In the last decade, there has been several therapeutics studied for ET, providing additional potential options for the clinician. These newer therapies are the purpose of this review.

## Gabapentin

Gabapentin has established efficacy in the treatment of epilepsy, as add on therapy, and neuropathic pain, particularly post-herpetic neuralgia. Several studies in ET have been published over the last decade and gabapentin can likely be regarded as an appropriate consideration in ET. Gabapentin is structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA) but it does not appear to act at GABA receptor or alter metabolism of GABA. There is no affinity at other known brain receptor sites such that the mechanism by which gabapentin works remains unknown. Gabapentin has differential bioavailability depending on dose so that doses of 900 mg/day given as divided doses have a bioavailability of 60% versus doses of 4800 mg/day have a bioavailability of 27%. Gabapentin is excreted unchanged in the urine with a half-life of 5–7 hours. Dosage adjustment for renal insufficiency/failure is necessary.

A total of 61 patients with ET have been studied in double blind placebo controlled studies.<sup>8–10</sup> The first study, published a decade ago, demonstrated little efficacy over placebo in 20 subjects using a cross-over design assessing clinical rating scale of tremor amplitude, handwriting and pouring water.<sup>8</sup> However, tolerability was fairly good using doses of 1800 mg/day and a suggestion was made to consider the drug in select patients. A second 3-month cross-over study of 25 subjects comparing doses of 1800 and 3600 mg with placebo showed significant improvement (absolute improvement of 30%–40% over baseline,  $p < 0.05$ ) in the subjects global impressions and activities of daily living scales, with other objective scales remaining unchanged.<sup>8</sup> There was no additional benefit in 3600 mg/day over 1800 mg/day. Again, tolerability was fairly good with only one subject withdrawing while on active treatment due to a presumed drug side effect (fatigue). A comparator study suggests that gabapentin 400 mg TID may have similar efficacy to propranolol given 40 mg TID.<sup>10</sup> The drug also has some study to support its use in neuropathic<sup>11</sup> and orthostatic tremor.<sup>12–14</sup> Side effects with gabapentin are typical of other anticonvulsants and include dizziness, somnolence and imbalance. In the placebo controlled gabapentin study of 25 subjects, side effects were drowsiness (5), fatigue (4), decreased libido (3), dizziness (2) and nervousness (2).<sup>8</sup> Fifty percent of subjects in the much larger post-herpetic neuralgia studies were over age 75 and the incidence of these side effects in these studies was only modestly higher than studies done in the younger epilepsy subjects. This fact, as well as the lack of significant drug interaction or major organ toxicity has made this drug a particularly appealing consideration in the often elderly ET population. The three times a day dosing regimen may present some problems with patient compliance.

## Topiramate

Topiramate is approved for use in epilepsy and migraine. However, there has been significant study with respect to its efficacy in ET and based on these studies, can be regarded as an established treatment consideration in ET. Biochemical and physiology studies of its mechanism of action support blocking of voltage dependent sodium channels, augmentation of gamma-aminobutyrate (GABA), antagonism at the AMPA/kainate glutamate receptor and inhibition of



carbonic anhydrase. The precise mechanism by which it works in ET is unknown. Pharmacokinetic studies support rapid oral absorption with a T<sub>max</sub> in 2 hours, 80% oral bioavailability, linear pharmacokinetics over the typical dose ranges and an elimination half-life of 21 hours. Two of three double-blind placebo controlled trials of topiramate in ET in a total of 245 subjects were positive.<sup>15–17</sup> The largest study of 208 subjects showed significant improvement in subjective and objective measurements of tremor corresponding to 20%–30% improvement over baseline with a mean final dose of 292 mg/day.<sup>15</sup> Topiramate appears to be efficacious at doses lower than those used to treat approved conditions with studies suggesting benefit below 100 mg/day.<sup>15,18</sup> Dose limiting side effects include paresthesias, nausea, and cognitive issues. In epilepsy studies, the incidence of cognitive issues is 40%–50% and, in migraine studies with slower titrations, 20%. In the large, double blind study in ET,<sup>15</sup> titration was over 12 weeks and the average age of subjects was 61. Dose limiting side effects were seen in 31.9% of subjects with the frequency of cognitive side effects being 13%. Therefore, those ET patients with advanced age and/or baseline cognitive impairment may not be appropriate for topiramate. The 10%–22% frequency of appetite suppression and weight loss seen in most topiramate studies might be useful in some overweight patients but could be a serious concern in more frail patients. Patients should be cautioned about kidney stones, seen in about 2% of subjects across studies.

## Zonisamide

Zonisamide is approved as adjunctive treatment for epilepsy. Pharmacological studies support that zonisamide has activity at sodium and calcium channels. There is also dopaminergic and serotonergic neurotransmitter facilitation. A single study in a rodent tremor model supports suppression of tremor independent of dopaminergic mechanisms (relevant to parkinsonian tremor).<sup>19</sup> Zonisamide has a T<sub>max</sub> of 2–6 hours, delayed slightly with food. Elimination half life is 63 hours. Standard doses for epilepsy are 100–400 mg/day. A small double blind placebo control study in 20 subjects showed no significant benefit in clinical rating scales for tremor but improvement on accelerometry at a mean dose of 160 mg/day.<sup>20</sup> Two open-label studies in a total of 47 subjects suggested modest benefit at 100–200 mg/day<sup>21,22</sup> and there is

another study supporting that zonisamide may be more effective than propranolol in isolated head tremor.<sup>23</sup> Adverse events in ET seem quite common and include somnolence, decreased concentration, imbalance and GI side effects; in the above open label studies, 25%–50% dropped out due to lack of efficacy and/or adverse events. At this point, cautious trial in refractory patients could be considered however, further study is likely warranted.

## Pregabalin

Pregabalin is indicated for use in painful diabetic neuropathy, fibromyalgia, post-herpetic neuralgia and as adjunctive therapy for adults with partial complex seizures. Typical daily dosing for these conditions ranges from 150–600 mg/day. Pregabalin has activity at the alpha2-delta subunit of voltage gated calcium channels. Despite its structural similarity to the inhibitory neurotransmitter GABA, it does not seem to have direct effect at these receptors, although study has shown that prolonged application increases the density of the GABA transporter protein. It is inactive at opioid, dopamine, noradrenaline and serotonin receptors and does not modulate activity of these transmitters or produce changes in cyclooxygenase enzyme activity. T<sub>max</sub> for pregabalin is 1.5 hours with linear pharmacokinetics and an elimination half-life of 6.3 hours with dose adjustment needed for renal insufficiency/failure. There are 2 open label case reports of patients with tremor responding to pregabalin.<sup>24,25</sup> There is a single double-blind placebo controlled study of 22 subjects showing significant ( $p = 0.05$ ) benefit in reduction of tremor amplitude (measured by accelerometry and tremor rating scale) at a mean daily dose of 286.8 mg/day.<sup>26</sup> Side effects leading to drop out occurred in a third of ET subjects ( $N = 1$  for flu, dizziness and malaise). Typical side effects with pregabalin across studies include dizziness, sleepiness, dry mouth and peripheral edema. Less common side effects include weight gain, blurred vision and decreased visual acuity. There are rare reports of angioedema occurring. It is reasonable to consider using pregabalin in those refractory patients, although additional data regarding efficacy in ET is needed.

## Sodium Oxybate

Gamma hydroxybutyrate when produced as the sodium salt is termed sodium oxybate. Gamma hydroxybutyrate

**Table 1.** Summary of studies.

Authors	Study type	Therapy	Number subjects	Results
Pawha <sup>9</sup>	Cross over with placebo	Gabapentin 1800 mg/day vs. placebo	20	No significant impact on subjective and objective tremor measures
Ondo <sup>8</sup>	Placebo controlled	Placebo, Gabapentin 1800 and 3600 mg/day	25	30%–40% improvement in subjective measures
Gironell <sup>10</sup>	Comparator, cross over	Gabapentin 1200 mg/day vs. propranolol 120 mg/day	16	Similar efficacy of gabapentin and propranolol on tremor amplitude and subjective assessments
Connor <sup>16</sup>	Cross over with placebo	Topiramate 333 mg/day	24	Improvement in tremor amplitude and ADLs compared with placebo
Frima <sup>17</sup>	Cross over with placebo	Topiramate up to 100 mg/day	10	Marginal benefit of topiramate, not significant
Ondo <sup>15</sup>	Placebo-controlled	Topiramate 292 mg/day	208	29% improvement in tremor rating score over baseline. Improvement in ADLs
Zesiewicz <sup>20</sup>	Placebo-controlled	Zonisamide 160 mg/day	20	Significant improvement in accelerometry, insignificant improvement in clinical rating scales
Handforth <sup>22</sup>	Evaluator blinded open label	Zonisamide up to 300 mg/day	25	Improvement on videotaped tremor scales, subjective improvement on functional disability. 300 mg no better than 200 mg but more adverse effects.
Ondo <sup>21</sup>	Open-label	Zonisamide up to 200 mg/day	22	Modest improvement in tremor rating scales, large dropout rate and adverse events
Zesiewicz <sup>24</sup>	Placebo-controlled	Pregabalin 286.8 mg/day	22	Reduction in tremor amplitude by clinical scale and accelerometry, drop outs due to adverse events in 1/3
Frucht <sup>28</sup>	Open label, blinded rater	Sodium oxybate up to 3 mg/day	2	Greater than 50% reduction in tremor amplitude, mild sedation
Frucht <sup>29</sup>	Open label, blinded rater	Sodium oxybate 4.3 mg/day	9	40%–50% reduction in tremor amplitude
Bushara <sup>33</sup>	Placebo controlled	1-octanol 1 mg/kg single dose	12	Significant improvement in tremor amplitude for up to 90 minutes
Shill <sup>34</sup>	Open label dose finding study	1 octanol 1–64 mg/kg single dose	21	2–3 hour tremor improvement, tendency for dose response
Wissel <sup>41</sup>	Open label, head tremor	400 Units botulinum toxin type A (Dysport)	14	Improvement in tremor scores and mean amplitude of tremor by accelerometry
Pacchetti <sup>38</sup>	Open label	Botulinum toxin type A (Dysport) 95.5 Units guided by pattern of active muscles	20	3 months significant tremor improvement over baseline using EMG, accelerometry and ADL scales. Minimal finger weakness as a side effect
Brin <sup>40</sup>	Placebo controlled	50 or 100 Units botulinum toxin (Botox) into wrist flexors and extensors	133	Improved postural tremor but not kinetic tremor or functional disability. Hand weakness as a side effect
Adler <sup>43</sup>	Open-label, dose ranging study of vocal tremor	1.5, 2.5 and 3.75 Units botulinum toxin into each vocal cord	13	Functional disability and acoustical measures improved during the 6 weeks of study



was previously mainly known and used as the recreational street drug known as Liquid Ecstasy, Liquid G or simply GHB. It has now been approved for use medicinally in the treatment of cataplexy and excessive daytime sleepiness with narcolepsy under very controlled distributing. GHB has activity at GABA-B receptor, producing an inhibitory effect, and also has excitatory activity at a now known GHB receptor.<sup>27</sup> The mechanism by which it might work in ET is unknown. Sodium oxybate is rapidly absorbed in a liquid formulation with peak concentrations in 0.5–1.25 hours. High fat meals delay and decrease absorption. Pharmacokinetics are non-linear with a 3.7 fold increase in blood levels following a doubling of typical clinical doses from 4.5 to 9 grams. Elimination is primarily through metabolism by the drug entering the Krebs cycle to produce carbon dioxide and water. Elimination half-life is 0.5 to 1 hour. No significant pharmacokinetic drug interactions are known but pharmacodynamic interactions are likely, particularly with sedative hypnotics and ethanol. These agents are specifically contraindicated with the medicinal use of sodium oxybate. Given the high sodium content of this liquid formulation (546 mg per 3 gm sodium oxybate), caution should be used in patients with hypertension, heart failure or renal disease. For treatment of narcolepsy, patients are dosed at bedtime and then again 2.5–4 hours later beginning with a dose of 2.25 gm. An open label pilot study of 5 subjects with alcohol responsive movement disorders, including 2 with ET, demonstrated greater than 50% improvement in an open label, blinded videotape review of tremor amplitude.<sup>28</sup> The two subjects with ET were titrated to doses of 1.5 gm given BID. Higher doses produced sedation or emotional lability. Subjects in the study reported wearing off at 4 hours, similar to what they noted when drinking ethanol. A follow-up to this study included 9 subjects with ET and 11 subjects with myoclonus.<sup>29</sup> Subjects were started at 1 gm TID and increased every 2 weeks as tolerated, until efficacious dose or 3 gm TID. The average total daily dose for ET at the end of the study was 4.3 gm/day. Transient dizziness (35%), headache (20%), emotionality (20%) and nausea (10%) were seen. 2 subjects stopped titration due to adverse events. Fourteen out of 20 subjects opted to continue the drug following the study.

Sodium oxybate appears promising in the treatment of ET. Further studies are warranted, particularly

placebo-controlled studies and comparators with ethanol. Limitations at this point seem to be the short duration, the potential emotional changes and the restricted access.

## **T2000**

T2000 is a non-sedating barbiturate being developed for the treatment of epilepsy and ET. Mechanism of action in ET is not yet known or not yet published but it has known activity at GABA-evoked chloride channels.<sup>30</sup> Half life is 18–20 hours and roughly 13 and 30 hours for its major active metabolites, monomethoxymethyl-5,5-diphenylbarbituric acid and 5,5-diphenylbarbituric acid respectively. There is a single publication of two series of 12 and 22 subject short duration (less than 20 days) placebo controlled studies using tremor rating score as a primary outcome measure which supports further evaluation of this therapy in ET.<sup>30</sup> Indeed, there is an ongoing Phase II long duration open-label study of doses from 600–1000 mg/day which should be completing soon.

## **1-Octanol**

1-octanol is an interesting drug which has long been used in chemistry labs to determine an agent's lipid solubility and in the food/perfume industry in very small amounts as a flavoring agent, but is not yet approved for any therapeutic uses. Animal studies done some years ago provided evidence that it might have efficacy in ET<sup>31</sup> with recent studies supporting that its mechanism of action in ET may very well be through gap junction blockade.<sup>32</sup> An open-label dose escalation study (1 to 64 mg/kg) and double-blind placebo controlled study (1 mg/kg) suggest efficacy in ET with similar pharmacokinetics as ethanol.<sup>33,34</sup> Side effects so far seem limited to its unusual strong taste/smell. These preliminary studies were done using single doses in a controlled setting so further multiple dosing studies are needed to determine both safety and continued efficacy with long term use. Rebound tremor is a concern given its relationship to ethanol. Further consideration to other drugs with a similar mechanism of action is warranted.

## **Lacosamide**

Lacosamide is a new drug approved for use in adults with partial onset seizures.<sup>35</sup> The drug has activity at voltage gated sodium channel as well as collapsing





response mediator protein-2 (CRMP-2). T<sub>max</sub> occurs within 4 hours and elimination half-life is 13 hours. Dose adjustment for severe renal impairment is necessary. Typical daily dose is up to 400 mg/day, divided into twice daily dosing beginning at 50 mg BID. Side effects include dizziness, diplopia, nausea and fatigue. PR interval prolongation has been seen in clinical studies and the drug should be used in caution in patients with known conduction block. There is a single animal study supporting benefit over standard therapies for tremor. Further clinical trials in ET are warranted.

## Botulinum Toxin

While not necessarily new, botulinum toxin injection deserves mentioning given that it may not be among that standard treatment armamentarium of many clinicians and therefore, may not be routinely considered in a typical clinical setting. Botulinum toxin, which works by temporarily chemodenervating the neuromuscular junction, has been studied in ET and, is among the movement disorders which may be amenable to toxin injection.<sup>36</sup> An initial small open label study of 14 subjects with ET demonstrated 5 had moderate to marked improvement supporting the need for additional clinical study.<sup>37</sup> An open label study of 20 refractory limb tremor patients showed improvement over baseline in activities of daily living, tremor rating scores and accelerometry.<sup>38</sup> Therapy was tailored to each subject based on the pattern of muscle activity with a mean total dose of  $95.5 \pm 40.5$  Units of botulinum toxin type A (Dysport). Subjects had persistent significant ( $p < 0.05$ ) tremor benefit at 3 months which had worn off by 5 months. Three subjects had mild fingers weakness as an adverse event. A placebo controlled study of 25 hand tremor subjects reported at least mild to moderate improvement in tremor in 75% with active treatment vs. 27% with placebo.<sup>39</sup> However, this study allowed for booster injections of 100 Units (Botox) after failing to respond to the initial 50 Units, making this study difficult to translate into practice since booster injection are rarely, if ever, used any longer. A second study of 133 subjects using fixed doses of 50 or 100 Units botulinum toxin (Botox) compared with placebo into forearm wrist flexors and extensors showed significant (generally 30% across time and doses,  $p < 0.0005$ ), improvement in postural tremor

from 4–16 weeks after treatment as measured by clinical rating scale.<sup>40</sup> However, kinetic tremor was only modestly improved (only significant at week 6) and functional disability was inconsistently improved. This decreased relevant efficacy (kinetic tremor), tempored by hand weakness as a side effect, makes consideration of botulinum toxin in the limb a consideration only for more refractory and disabled subjects.

Botulinum toxin may be particularly useful for subjects with intractable head and/or voice tremor as these symptoms typically result from fewer overactive muscles and be appropriate for the very focal therapy that the neurotoxin provides. Forty three subjects with head tremor of which 29 had concomitant cervical dystonia underwent open label injection with botulinum toxin type A (Dysport) into the bilateral splenius capitis muscles.<sup>41</sup> All subjects with isolated head tremor without dystonia ( $N = 14$ ) improved over baseline in terms of clinical rating scales and accelerometry. Tolerability is generally good, making this a reasonable option for disabling head tremor.

An initial pilot study of vocal cord botulinum toxin was done in 10 subjects with a randomization of unilateral injection with 15 Units botulinum toxin (Botox) vs bilateral injection of 2.5 Units in a cross over design. 2/10 with unilateral and 3/10 with bilateral responded with objective scales and 8/10 wished to continue with injections following the study.<sup>42</sup> In an open label study of voice tremor, 13 subjects were injected with varying doses of botulinum toxin type A (Botox) into the vocal cords and followed for 6 weeks.<sup>43</sup> Significant improvement was seen at all doses of 1.25, 2.5 and 3.75 Units per side in terms of tremor severity scales, disability and acoustical measures. Main adverse effects were breathiness (11/13) and dysphagia (3/13). Dose response in either efficacy or adverse effects could not be assessed due to small numbers however, it is prudent to recommend starting with lower doses and increasing as needed based on both these outcomes.

## Other Therapies

Tiagabine, a centrally acting GABA reuptake inhibitor, has been reported to exacerbate ET<sup>44</sup> and a follow-up letter to the editor in response to the report suggests lack of benefit and high adverse events in an open label study of 5 ET subjects.<sup>45</sup>



Levetiracetam, an antiepileptic, has been considered for treatment of ET. Indeed, a placebo controlled study of 20 subjects showed benefit at 2 hours in terms of tremor amplitude as measured by accelerometry and clinical rating scales.<sup>46</sup> However, an open label study of 10 subjects showed 5 of them worsened with treatment.<sup>47</sup> A ten subject placebo controlled study designed to showed a 30% or more reduction in tremor severity by clinical rating showed no benefit.<sup>48</sup> These studies have been followed by a larger placebo controlled study which was terminated early when a planned interim analysis revealed lack of efficacy (and perhaps worsening) in the 15/45 subjects completing to study.<sup>49</sup>

## Conclusion

ET is a condition that is common and often disabling for those affected. Despite this fact, there is not a single pharmaceutical agent that has been developed or approved specifically for ET. There are likely many reasons for this including the lack of perceived morbidity with ET, the often older target population with many other pressing health issues, the lack of understanding of the underlying pathogenesis of ET and finally, the lack of a well-defined animal model of ET. Despite all these limitations, the last several years have seen an increase in the number of therapies studied for ET. Most of these agents are primarily approved for epilepsy, although it is likely that we will see an expansion of more targeted therapies with time as we elucidate the pathogenesis of ET.

For the clinician seeing patients with ET, the following recommendations are made. First line therapy should still be considered with propranolol or mysoline. For those patients maximized on either or both of these therapies, topiramate might be considered next as long as the patient has good cognitive functioning and has family members who can observe for worsening of memory. Gabapentin is a reasonable consideration for those patients who might be more prone to side effects. Zonisamide and pregabalin could be considered in refractory patients. Sodium oxybate is reasonable to consider in alcohol responsive ET but currently difficult to use in clinical practice. Octanol and T2000 remain promising but as yet, unproven and unavailable. Botulinum toxin might be considered in those patients who simply do not tolerate medication, have a more severe tremor

phenotype or have problematic voice or head tremor but only should be done by a clinician with experience in toxin injection. Monotherapy for ET should be attempted whenever possible. Using polypharmacy to treat ET should only be done when there is a clear additive effect with additional drugs that is not attainable with each drug by itself. Generally speaking, using two drugs with a similar mechanism of action should be avoided.

Further research into the underlying pathogenesis of ET continues and hopefully, will one day broaden the availability of safe and effective therapies for ET.

## Disclosure

The author reports no conflicts of interest.

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