REVIEW ARTICLE

Drugs 2010; 70 (17): 2215-2228
0012-6667/10/0017-2215/$55.55/0

Pharmacological Management of Essential Tremor

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Contents

Abstract

Essential tremor (ET) is a common movement disorder with clinical features that manifest with both motor (tremor and balance disorders) and non-motor (such as mild cognitive deficits and hearing loss) symptoms. The diagnosis of ET is based on the presence of an action tremor of greater severity than enhanced physiological tremor, without other identifiable causes. Patients with ET experience a decrease in the performance of their motor skills and social activities, and a decline in their quality of life. The pathophysiology of ET is still not clear. Pharmacotherapy for ET is indicated if the disease interferes with the patient's quality of life. Propranolol, a nonselective β-adrenergic receptor antagonist, and primidone, an antiepileptic, remain the standard treatments for ET. However, studies show that several other agents, including topiramate, gabapentin and zonisamide, might also be beneficial. Local injections of botulinum toxins and surgical interventions such as thalamic deep brain stimulation play a role as alternative options when pharmacological treatment is not satisfactory. Several new agents including 1-octanol, pregabalin and sodium oxybate are currently under investigation.

With an estimated prevalence of 2–5%,[1,2] essential tremor (ET) is considered to be the most common pathological tremor.[3,4] The principal clinical characteristic of ET upon which diagnostic criteria are generally based is a 5–10 Hz kinetic and postural tremor that is almost always seen in the arms but is often recognizable in the head and voice.[5] Other anatomical sites such as the legs, trunk and face are less commonly affected.[6]

Although tremor remains the main feature of ET, several studies suggest that this disorder is not monosymptomatic, and is probably heterogeneous. An association with motor and sensory abnormalities such as parkinsonism, dystonia, cerebellar dysfunction, hearing impairment and restless legs syndrome have been reported.[7-9] Furthermore, non-motor manifestations including mild cognitive deficits such as deficits in verbal fluency, naming, recent memory, working memory, mental set-shifting and personality changes have been demonstrated in some patients with ET, although the effect size is modest.[10-14]

Significant predictive factors associated with increased tremor severity at the initial clinic visit include older age, longer disease duration, use of movement disorder drugs and the presence of voice tremor.[15] Tremor amplitude increases and frequency decreases over time. Greater amplitude is associated with functional worsening.[16] The aim of this article is to provide a summary of the treatment options to guide clinicians in the management of patients with ET.

1. Pathophysiology

The pathophysiological abnormalities of ET are complex and difficult to elucidate. The evidence from both experimental clinical data and animal models suggests that ET may be caused by disruption of the olivocerebellar circuit.[17] Disappearance of ET has been reported in cases with lesions to the cerebellum, pons or thalamus.[18-20] Positron emission tomography studies demonstrated cerebellar hyperactivity and possibly increased inferior olivary nucleus activity.[21]

Harmine, a compound from the β-carboline family, can induce synchronized rhythmic activity, which is similar to ET in both human and animal models. An animal model study revealed that rhythmic activity became synchronized in the inferior olivary nucleus and was conveyed through the cerebellum and the reticulospinal projections to the motor neurons.[22]

Pathological findings of ET in humans have been inconsistent. In one study, pathological findings, including purkinje cell loss in the cerebellum and the presence of brainstem Lewy bodies,

Table I. Medications for treatment of essential tremor

Treatment	Total daily dose [mg] (number of doses)	Comment	Adverse events
β-Adrenergic receptor antagonists (β-blockers): propranolol, nadolol	Propranolol 10–320 (bid–tid) Nadolol 20–160 (od)	Dose-dependent effect. Can be used as needed	Fatigue, hypotension, bradycardia, masked hypoglycaemia
Primidone	25–300 (bid–tid)	Adverse events usually occur with first dose. Pretreatment with 3 days of phenobarbitol 30 mg reduces these	Dizziness, nausea, ataxia
Topiramate	25–400 daily	Dose-dependent effect	Cognitive worsening, tingling, altered taste, weight loss, kidney stones, acute vision change
Gabapentin, pregabalin	Gabapentin 300–3200 (tid) Pregabalin 75–300 (bid)	Variable efficacy	Weight gain, oedema, dizziness, sleepiness
Zonisamide	50–200 (bid)	Variable efficacy. Also helps PD tremor	Similar to topiramate, but usually milder
Benzodiazepines	As tolerated	May help with anxiety and essential tremor	Sedation, cognitive slowing, dizziness, dependency
Levetiracetam	500–2000 (bid)	Mild efficacy	Minimal
Botulinum toxin	Variable	Injected into muscles for tremor of distal arm, head and jaw	With training, very safe. Local weakness, bruise
Ventral intermediate deep brain stimulation	NA	Reserved for severe tremor; best for hand tremor	Any CNS surgical complication, dysarthria, balance

bid = twice daily; **NA** = not applicable; **od** = once daily; **PD** = Parkinson's disease; **tid** = three times daily.

distinguished 10 cases of ET from 12 control cases. Torpedoes, a nonspecific cytoplasmic marker of cell distress, are also seen in some cases.[23] Some patients have no identifiable pathology.[24]

2. Diagnosis

No gold standard test or biological marker is currently available for diagnosis of ET. Core and secondary criteria for probable ET, derived from the *Consensus Statement of the Movement Disorder Society on Tremor*, require the presence of an action tremor of greater severity than enhanced physiological tremor, without other identifiable causes.[5]

3. Treatment

Treatment options for ET are still limited and sometimes only partially effective. In this section, we discuss pharmacological therapies and briefly discuss surgical treatment. Comparisons among studies are limited by the lack of uniform and validated assessment measures and varied inclusion criteria. No drug is thought to offer more than symptomatic improvement; therefore, the functional benefit must be compared against the adverse effects. Table I shows a summary of medications used in the treatment of ET.

3.1 Alcohol

3.1.1 Ethyl Alcohol

Many patients with ET experience a transient improvement after consuming a small amount of ethyl alcohol (ethanol).[25] This effect is seen with the equivalent of one drink, typically takes 10–15 minutes for onset and lasts for 3–4 hours.[26] There may be a rebound tremor after this transient effect. One study also demonstrated that orally administered ethanol improves gait ataxia in patients with ET.[27] The mechanism of action of ethanol in reducing tremor in ET is unclear. It is suggested that ethanol may act via an influence on the inferior olivary nucleus or directly on ethanol-sensitive GABA receptors within the cerebellum.[27] The possible relationship between

the risk of developing ET and the alcohol dehydrogenase 1B, β-polypeptide (ADH2) genotype and its allelic variants has been investigated but has not revealed any associations.[28]

The evidence for the risk of alcoholism in patients with ET, and whether ET can be a cause of secondary alcoholism, is meagre. In one chart review of 36 patients with ET, a significantly higher frequency of alcohol dependence and abuse than in control subjects was reported.[29] However, in another study the frequency and amount of alcohol intake of ET patients were found to be largely similar to the drinking habits of a control sample from the general population.[30]

3.1.2 Octanol

Octanol (8-C alcohol) is a US FDA-approved food additive that is naturally derived from citrus oils. The recommended daily intake is 1 mg/kg/day. The lethal dose of octanol is of 3500–20 000 mg/kg. Octanol metabolism is similar to ethanol via alcohol dehydrogenase.[31] In a rat study, octanol at a dose of 0.26 mg/kg (compared with 100 mg/kg of ethanol) was shown to reduce harmaline-induced tremor by 50% without affecting the animal's physical activity.[32] This signifies octanol as a potential treatment for ET without reaching a toxic dose.[32,33]

In an open-label dose-escalation study, single oral doses of 1-octanol were given to 21 patients with ET. The drug was well tolerated up to 64 mg/kg/dose. The main adverse effect was an unusual taste. No overt intoxication was seen. There was evidence for efficacy, with a significant reduction in tremor amplitude, as measured by accelerometry and handwriting, that was maximal at 2 hours. It was suggested that higher doses may produce more sustained benefit.[34] In a randomized, placebo-controlled pilot trial of a single oral dose of 1 mg/kg of 1-octanol in 12 patients with ET, no significant adverse effects or signs of intoxication were observed. 1-Octanol significantly decreased tremor amplitude for up to 90 minutes. The study suggested 1-octanol as a well tolerated and safe potential treatment for ET, and further trials are warranted.[33] The short duration of benefit of this medication (1–3 hours) is a drawback.

3.2 β-Adrenergic Receptor Antagonists (β-Blockers)

β-Adrenergic receptor antagonists (β-blockers) have been used for many years to treat tremor. Several clinical trials have shown that β-blockers, particularly propranolol, reduce tremor amplitude by 50–60%. However, only 50% of patients will respond satisfactorily to β-blockers, and severe tremor seldom responds.[35,36] It was proposed that the tremorolytic activity of β-blockers in essential, physiological and isoprenaline-induced tremor is exerted via the same β_2-adrenergic receptors located in a deep peripheral compartment, which is thought to be in the muscle spindles.[37]

There are little comparative data among β-blockers. In a double-blind, comparative study, a long-acting formulation of propranolol was shown to be as effective as conventional propranolol in reducing the amplitude of ET.[38] The effect of a single dose of propranolol (120 mg), metoprolol (150 mg) and placebo in 23 patients with ET was compared in a randomized, double-blind trial and both β-blockers were significantly more effective than placebo in reducing the magnitude of tremor (metoprolol and propranolol decreased the tremor by 47% and 55%, respectively). There was no significant difference between propranolol and metoprolol in tremor reduction.[39] In another comparative study of the effect of tremor reduction between metoprolol and propranolol in 23 patients with ET, metoprolol decreased tremor in 13 of 23 patients with ET and 10 of 20 patients had tremor reduction with propranolol. Metoprolol also reduced tremor in three patients with asthma in whom propranolol had caused respiratory distress. This study also showed that patients generally responded to both propranolol and metoprolol or to neither drug, and patient age, duration of tremor, tremor frequency, family history or response to intravenous ethanol did not distinguish responders from nonresponders.[40]

In a double-blinded crossover trial of 24 patients with ET comparing the effect of propranolol 120 mg and pindolol 15 mg daily, tremor amplitude improved more with propranolol.[41]

In a crossover, multiple-dose comparative trial of arotinolol and propranolol (arotinolol 10 mg/day

and propranolol 40 mg/day, arotinolol 20 mg/day and propranolol 80 mg/day, and arotinolol 30 mg/day and propranolol 160 mg/day, with each course of treatment lasting 6 weeks) in 161 patients with ET, arotinolol was found to be as effective as propranolol in reducing tremor, and motor task performance scores showed that arotinolol had a more significant effect than propranolol.[42] In general, propranolol and nadolol are the most studied β-blockers.[34] The absence of cardiac (β1) selectivity is probably preferable when treating tremor. β-Blockers, especially short-acting drugs such as propranolol, can be used on an as-needed dosing schedule. The benefit of β-blockers appears to be dose responsive. Adverse effects include hypotension, fatigue, bradycardia, erectile dysfunction and the possible exacerbation of reactive airway disease, and are also dose dependent.

3.3 Antiepileptics

3.3.1 Primidone

Primidone has been used to treat ET for decades. It is metabolized into two main compounds: phenobarbital and phenylethylmalonamide (PEMA). Nagaki et al.[43] studied the blood and cerebrospinal fluid (CSF) pharmacokinetics of primidone and showed that primidone rapidly appeared in both serum (time to maximum concentration [t_{max}] mean range 1.5–2.5 hours) and CSF (t_{max} mean range 2.0–3.5 hours), suggesting ready penetration of the blood-brain barrier. The pharmacokinetics and metabolism of primidone in elderly patients aged 70–81 years is similar to that of younger populations, aged 18–26 years. Aging is associated with a greater accumulation of PEMA; however, this is unlikely to have a major clinical significance.[44]

The definite mechanism of action of primidone is not clearly understood. It was proposed that the mechanism of action of primidone in ET is similar to that in epilepsy, in which the drug alters transmembrane sodium and calcium channel ion fluxes.[45]

In a study that showed that primidone has a similar effect in both untreated and propranolol-treated ET patients, a single oral dose (250 mg) of primidone decreased tremor by 60% 1–7 hours after ingestion; however, no difference was noted with high doses compared with low doses and there was no correlation between therapeutic response and serum concentration.[46] Anecdotally, the benefit of primidone is not thought to be dose dependent, in contrast with β-blockers.

The effect of primidone in a suspension versus tablet-based form as initiation schedules for treating ET was compared in 40 patients with ET in a double-blind, double-dummy, randomized trial. The study showed no significant difference between the suspension and the tablet group in quality of life or tremor amplitude. Tremor severity had subjectively reduced to 71% (SD 34%) of baseline tremor severity. However, the study reported 30% withdrawals, mainly due to adverse effects. Early adverse effects are common in the treatment of ET with primidone, especially nausea, dizziness and sedation. O'Suilleabhain and Dewey[47] suggested that lower doses (25 mg at night) can be prescribed initially, with gradual titration to a higher dose (100 mg twice daily). Another strategy is to pre-treat with 3 days of low-dose phenobarbital (30 mg), which increases the metabolism of primidone, resulting in even lower initial serum concentrations. In our clinic, we usually begin with 25 mg at night and titrate to 100 mg twice daily.[45]

Overall, primidone and propranolol have comparable efficacy. Short- and long-term effects of propranolol (80–160 mg/day) and primidone (50–250 mg/day) were studied in the treatment of 50 patients with ET. Acute adverse reactions occurred more commonly in primidone (32%) than with propranolol (8%); however, significant chronic adverse effects occurred in 17% of patients taking propranolol compared with 0% taking primidone. The tolerance rate to drug effects was similar in both treatment groups (13%) with long-term treatment. As a result, the acute adverse reactions of primidone and adverse effects with long-term use of propranolol limit the effect of these medications for the treatment of patients with ET.[48]

3.3.2 Topiramate

Topiramate is an antiepilepsy medication that is also frequently used to treat headache. It is a complex medication with multiple mechanisms of

action including GABAergic, sodium channel blockade and carbonic anhydrase inhibition.[49]

Two clinical trials have investigated the effectiveness and safety of topiramate in patients with ET. A single-centre crossover trial of topiramate (400 mg/day or the maximum tolerated dose) as monotherapy or adjunctive treatment was performed in 24 patients with ET. The study showed significantly reduced tremor in normalized overall tremor rating scores (p-value 0.015); however, the study had high withdrawal rate, with only 15 patients completing the study. Decreased appetite, weight loss and paraesthesias were the most common adverse events.[50] In another large multicentre trial of patients with moderate to severe ET in the upper limbs, topiramate showed tremor reduction as well as functional improvements including motor tasks, writing and speaking. However, the study reported a withdrawal rate of 32% in the topiramate group compared with 9.5% in the placebo group. The most common treatment-limiting adverse events in topiramate-treated patients were paraesthesia (5%), nausea (3%), concentration/attention difficulty (3%) and somnolence (3%).[51]

In general, topiramate is probably as effective as primidone and β-blockers; however, it is possibly less well tolerated, mostly due to cognitive worsening, especially in the elderly. The risk of kidney stones also modestly increases. The improvement seems to be dose dependent up to 400 mg/day. In our clinic, we usually start at 12.5 mg twice daily and titrate to 100 mg twice daily or occasionally higher.

3.3.3 Gabapentin

Gabapentin is an antiepilepsy medication mostly used for a variety of painful conditions, especially neuropathic pain. Controlled trials of this medication for ET have been associated with mixed results.

In a double-blind, crossover, placebo-controlled trial of 16 patients with ET, monotherapy with gabapentin (400 mg three times daily) demonstrated significant and comparable efficacy with propranolol (40 mg three times daily) in reducing tremor from baseline. Gabapentin and propranolol treatment reduced the score more than placebo (-3.10 ± 1.10 [$p = 0.01$] and -4.50 ± 1.10 [$p = 0.001$], respectively), and significant differences were not observed between gabapentin and propranolol.[52] In another double-blind, placebo-controlled, crossover trial, two different doses of gabapentin (1800 and 3600 mg/day), either as a monotherapy or in addition to another tremorolytic agent, were compared in 25 patients with ET. The results showed overall significant improvement in patient global assessments ($p < 0.05$), observed tremor scores ($p < 0.005$), water pouring scores ($p < 0.05$) and activities of daily living scores ($p < 0.005$). The results were similar for high and low doses.[53] Another double-blind crossover trial used gabapentin 1800 mg/day. Of 20 patients, 18 completed the study and 2 patients withdrew as a result of adverse effects. The study showed no significant difference in total tremor scores, hand tremor scores, handwriting scores or pouring scores.[54] Overall, gabapentin is well tolerated. The main adverse events are dizziness, sedation, oedema and weight gain. Results for tremor are probably more modest than with primidone or topiramate, although no formal comparative studies are available.

3.3.4 Levetiracetam

The effectiveness and safety of levetiracetam in patients with ET have been investigated in several studies. Overall, levetiracetam showed modest or no efficacy.

The effect of levetiracetam in 24 patients with ET was assessed in a double-blind, placebo-controlled trial and showed a significant antitremor effect in ET patients with hand tremor for at least 2 hours after taking a single dose of levetiracetam (1000 mg), as measured by accelerometry and functional tests, with no significant adverse effects. However, the study could not address the long-term tolerability and efficacy of levetiracetam.[55] In a double-blind, placebo-controlled, crossover trial of levetiracetam (titrated from 500 to 3000 mg/day during a 5-week titration phase) in patients with ET, the planned enrollment of 45 was stopped when an interim analysis of the first 15 patients revealed no efficacy with levetiracetam.[56] In an open-label, 11-week pilot study of levetiracetam (maximum dose 3000 mg/day) in 14 patients with ET who were

either unresponsive to treatment with β-blockers or primidone, or had intolerable adverse effects or contraindications for being treated with these medications, levetiracetam did not produce any statistically significant modifications in any of the monitored variables.[57] In another small open-label pilot study of the effect of levetiracetam (500 mg twice daily for 2 weeks and 1500 mg twice daily for 4 weeks) in ten patients with ET, levetiracetam failed to improve tremor consistently, although it was well tolerated. Adverse events included dizziness, sedation and nervousness.[58]

3.3.5 Phenobarbital

In a double-blind controlled clinical trial, the effect of phenobarbital (1.3 mg/kg) was compared with propranolol (1.7 mg/kg) and placebo in 12 patients with ET. After 1 month of therapy, only propranolol showed a more significant effect than placebo at clinical evaluation. However, patients' subjective evaluation and tremor amplitude measurement (by accelerometer) showed a significantly better effect with both propranolol and phenobarbital than with placebo.[59] In another double-blind crossover trial that compared primidone with phenobarbital in 13 patients with ET, primidone was superior to both placebo and phenobarbital in reducing tremor. It was also noted that primidone has an effect in ET independent from that of its metabolite phenobarbital.[60]

3.3.6 Pregabalin

There is conflicting evidence for pregabalin in the treatment of patients with ET. The tolerability and efficacy of pregabalin in 20 patients with ET has been assessed in a double-blind, crossover design over 6 weeks. The study reported no improvement in Tremor Rating Scale measures and statistically significant worsening of Quality of Life in Essential Tremor Questionnaire (QUEST) scores while patients were taking pregabalin. The most common adverse effects were drowsiness and dizziness.[61] Results and adverse events of pregabalin are probably similar to gabapentin. In a case report, two patients with ET experienced marked improvement in upper extremity tremor with the use of pregabalin.[62] The same authors reported significant improvements in accelerometry and action tremor limb scores on the Fahn-Tolosa-Marin Essential Tremor Rating Scale in a pilot study of escalating doses of pregabalin (maximum 600 mg/day); however, about one-third of patients withdrew from the study because of adverse events.[63]

3.3.7 Zonisamide

The efficacy and tolerability of zonisamide in treating ET was assessed in a double-blind, placebo-controlled, randomized trial of zonisamide (initiated at a dosage of 100 mg/day and escalated to 200 mg/day at day 14) in 20 patients with ET. The study showed significant improvement in tremor amplitude, as assessed by accelerometry, in the zonisamide group compared with the placebo group at endpoint ($p = 0.03$). Thirty percent of patients ($n = 3$) taking zonisamide discontinued the study due to adverse effects, including fatigue, headache and paraesthesia.[64]

A single-blind open-label trial of zonisamide as monotherapy or as adjunct to a stable antitremor medication in 25 patients with moderate/severe upper limb ET showed reduced tremor scores. The study indicated that 200 mg/day was superior to 100 mg/day, whereas 300 mg/day produced no additional benefit and was associated with more adverse symptoms, most commonly somnolence, poor energy, imbalance and altered taste.[65] The efficacy and tolerability of zonisamide in the treatment of ET was assessed in a retrospective study of 13 patients refractory to an average of 2.8 drugs. Data showed that zonisamide was effective and well tolerated in the treatment of tremor and the authors suggested that placebo-controlled and larger studies are warranted to confirm these results.[66]

In another open-label pilot trial of zonisamide in 22 patients with ET, only 14 patients completed the study. The study reported significant (albeit modestly) improvement of the Tremor Study Group rating scale (TSGRS) scores in this small group of medically refractory patients who completed the evaluation. However, clinical impressions did not improve, and the study was complicated by a large withdrawal rate caused by a subjective lack of efficacy and adverse effects,

including decreased concentration/cognition, constipation, nocturia, abdominal pain/diarrhoea and sedation.[67] A pilot crossover trial of zonisamide versus arotinolol was performed in patients with ET for 2 weeks. The result showed a significant improvement after zonisamide and arotinolol administration compared with baseline. There was no significant difference in the antitremor effect between the drugs; however, zonisamide was more effective for tremors of cranial nerve areas.[68]

Overall, the existing data for zonisamide is mixed. The drug has some similarities to topiramate but may be better tolerated. In our practice, we usually start at a dose of 50 mg at night and titrate to 100 mg twice daily.

3.3.8 Oxcarbazepine

A case of ET responding to oxcarbazepine in a patient with suboptimal response to propranolol has been reported. This patient showed a significant and sustained improvement in the tremor following the initiation of oxcarbazepine.[69] There are no trials to support its use.

3.4 Calcium Channel Antagonists

3.4.1 Flunarizine

Flunarizine is a selective calcium channel antagonist that was used for migraine prophylaxis and the treatment of vertigo and peripheral vascular disease. Biary et al.[70] studied the effect of long-term treatment of ET with flunarizine in subjects who had a favourable response after 1 month of treatment. After 30 months, 41% (7 of 17) of patients felt there was continued benefit; however, adverse effects (dystonia, parkinsonism, weight gain and depression) occurred in about 30% of patients, leading to drug discontinuation. In a double-blind placebo-controlled trial of the effect of flunarizine treatment (10 mg/day) in 17 patients with ET, significant improvement was reported in 13 of the 15 subjects who completed the study.[71] In another study, the effects of flunarizine (initial dose of 5 mg/day, titrated to 10 mg/day) in 12 patients with moderate to severe ET were studied and showed that flunarizine was an ineffective drug and might worsen the symptoms in some patients. The results of the study discouraged the use of flunarizine in the treatment of ET, especially in patients over the age of 60 years.[72] The same result was reported in another study where flunarizine was tested in ten patients with moderate to severe ET, in which flunarizine was shown to be ineffective and to possibly worsen the symptoms in some patients.[73]

Efficacy results for flunarizine are mixed. In addition, this medication blocks dopamine receptors, which can lead to a variety of extrapyramidal side effects; therefore, its use, especially in the elderly, is discouraged. This medication is not available in the US.

3.4.2 Nimodipine

Very little data supports the use of nimodipine for ET. In one small double-blind placebo-controlled study, nimodipine at a dose of 30 mg four times daily was effective in 8 of 15 patients with ET who completed the study.[74] The study reported that nimodipine significantly reduced the mean value of tremor amplitude from baseline (55 with nimodipine vs 118 at baseline; $p = 0.00141$) compared with placebo (108 with placebo vs 118 at baseline; $p = 0.0755$). The authors concluded that nimodipine is effective in some patients with tremor.

3.4.3 Nicardipine, Nifedipine and Verapamil

In a placebo-controlled study of nicardipine for ET, a single oral dose of 30 mg was administered, followed by 1 month of sustained treatment (60 mg/day) in 11 patients with ET. The study showed that a single oral dose of nicardipine reduced the tremor amplitude versus baseline ($p = 0.003$). However, after 1 month of treatment, nicardipine failed to sustain the initial statistical improvement.[75] In another study, the acute effects of two calcium channel antagonists, nifedipine and verapamil, on tremor were investigated in eight patients with ET and were compared with those of propranolol and placebo. Tremor intensity increased following a single oral dose of nifedipine 10 mg. Nifedipine also increased physiological tremor in six healthy volunteers. This effect of nifedipine was not correlated with an increase in heart rate or decrease in systemic blood pressure. Verapamil (80 mg) did not substantially alter the patients' tremor activity.[76] Overall, the benefits of calcium

channel antagonists are contradictory. In our experience, they are seldom effective.

3.5 Botulinum Toxins

Botulinum toxins inhibit the release of acetylcholine by cleaving proteins in the SNARE (Soluble NSF Attachment Protein REceptor) complex, which shepherds the neurotransmitter to the neuromuscular junction. Therefore, the signal for muscle contraction is focally minimized and the muscle weakens. This effect typically lasts for 3–4 months. In a double-blind, randomized, placebo-controlled trial, both low-dose (50 U) and high-dose (100 U) botulinum toxin type A (Botox®) were significantly effective in reducing postural tremor on the clinical rating scales of ET of the hands after 4 and 16 weeks. However, kinetic tremor was significantly reduced only at the 6-week examination. Adverse reactions consisted mainly of dose-dependent hand weakness.[77] Numerous smaller studies have generally shown benefit for hand tremor. Head tremor improved by 50% in one double-blind, placebo-controlled study of botulinum toxin. Adverse effects consisted of neck or jaw weakness, headache, difficulty swallowing and dizziness, and were mild and transient.[78]

In one study, patients with a clinical diagnosis of essential voice tremor were treated with botulinum injections to the thyroarytenoid muscles and, in some cases, to the cricothyroid or thyrohyoid muscles. The study showed a beneficial effect in 67% of patients by subjective evaluation. The results of perceptual evaluations and acoustic analysis also showed a significant improvement in voice tremor. Hertegard et al.[79] concluded that the treatment was successful in 50–65% of the patients, depending on the method of evaluation. In a report of a 21-year-old man with essential palatal tremor, injection of 5 U of botulinum toxin type A into each tensor veli palatini resulted in complete resolution of all the symptoms.[80]

The administration of botulinum toxin type A for tremor is dependent upon the anatomy of the tremor and skill of the injector. In general, head tremor has the most robust response. Oscillation around the wrist responds well, but tremor involving the elbow, shoulder or fingers is more refractory. Cost limits its use in the US.

3.6 Benzodiazepines

Benzodiazepines have also been used to treat tremor for decades. Alprazolam is the only benzodiazepine that has been studied in a double-blind, crossover, placebo-controlled trial. The effectiveness of alprazolam, a triazole analogue of the benzodiazapine class, acetazolamide, a carbonic anhydrase inhibitor, and primidone were investigated as symptomatic treatments for ET in 22 patients. The study demonstrated that alprazolam was superior to placebo and equipotent to primidone. The mean effective daily dose of alprazolam was 0.75 mg and there were minimal adverse effects.[81] In another double-blind, placebo-controlled parallel study of 24 patients, alprazolam significantly improved tremor, with transient mild fatigue or sedation in 50% of the patients being the primary adverse effect. It was suggested that alprazolam may provide therapeutic benefit, especially in patients who require only intermittent therapy.[82] In one study, clonazepam provided tremor suppression in all 14 patients with kinetic tremor without cerebellar signs (a subtype of ET).[83] However, the efficacy of clonazepam (up to 4 mg/day) was evaluated in a double-blind placebo-controlled study, and using a variety of objective measures, was not found to be an effective treatment.[84]

Benzodiazepines can certainly improve tremor, especially tremor that is exacerbated by anxiety. Well known adverse events, including sedation and falls, and the propensity for addiction and dependency, relegate benzodiazepines to a tertiary role in most cases.

3.7 Antidepressants

3.7.1 Mirtazapine

One open-label report of 30 ET patients who completed 1 month of treatment with mirtazapine 30 mg/day found improvement in 85% of patients, with a marked reduction of tremor; the benefit was maintained during the 12-month follow up. Mirtazapine had limited adverse effects

and excellent overall tolerability, and could be used as daily monotherapy.[85] However, another randomized, double-blind, placebo-controlled, crossover study of 17 ET patients showed no significant improvement with mirtazapine over placebo as measured by the Tremor Rating Scale. All secondary measures, including tremor questions, pouring questions, drawing questions, activities of daily living scores and the Parkinson's disease questionnaire, were also negative. Adverse effects were more common in the mirtazapine group and included drowsiness, confusion, dry mouth, weight gain, polyuria, itching, nausea, gait and balance problems, blurred vision and a bad taste.[86] Anecdotally, we have seen little benefit of mirtazapine; however, traditional serotonergic reuptake inhibitors often exacerbate ET and, therefore, mirtazapine can be considered when antidepressant therapy is justified.

3.7.2 Trazodone

Analysis of the results of a double-blinded crossover study comparing propranolol, clonidine, urapidil, trazodone and placebo in patients with tremor showed that propranolol and clonidine significantly reduced the power spectrum of postural tremor, but rest and intention tremors were unchanged. No significant effects on the tremor power spectrum were observed after placebo, urapidil or trazodone administration.[87] Despite some use in ET, we have never seen any benefit with trazodone in our practice.

3.8 Atypical Antipsychotics

3.8.1 Clozapine

The effects of a single dose of clozapine 12.5 mg and placebo were evaluated in a randomized, double-blind, crossover study in 15 drug-resistant patients with ET. Tremor was effectively reduced by a single dose of clozapine in 13 of 15 patients. Sedation was the only adverse effect reported during the clozapine test; however, the time course of sedation and of the antitremor effect were not coincident. A significant reduction of tremor was reported with long-term clozapine treatment with no tolerance to the drug antitremor effect developing, while sedation markedly decreased after 6–7 weeks of therapy. No clozapine-induced haematological adverse effects were observed in the cohort of patients during long-term treatment.[88]

Clozapine probably does improve ET, but sedation, weight gain and the risk of agranulocytosis, which initially require weekly blood tests, lessens its appeal.

3.8.2 Quetiapine

The safety and tolerability of quetiapine (up to 75 mg/day) as monotherapy for ET were investigated in an open-label study in ten patients, but only three patients showed some benefit (improvement >20%). Adverse effects included a paradoxical psychiatric reaction in one patient and anger in another, and in both cases quetiapine was discontinued.[89]

3.9 Miscellaneous

3.9.1 Clonidine

Clonidine is an old medication most often used for hypertension. The absence of peripheral α-adrenergic receptors for tremor suggest that the drug acts centrally, consistent with the theory that ET originates in a central oscillating pacemaker.[90] The efficacy of clonidine versus propranolol in the control of ET was compared in a double-blind, randomized controlled trial with a 1-year follow-up in 186 patients with ET. Both propranolol ($p \geq 0.005$) and clonidine ($p \geq 0.0005$) proved to be statistically efficacious. Propranolol was not more efficacious than clonidine ($p \geq 0.4$) but withdrawals were significantly higher in the clonidine group (22 patients; $p \geq 0.006$).[91] A single double-blind, placebo-controlled study of clonidine (average dose 0.4 mg/day) did not show any benefit in ten subjects.[92] In one study, ten cases of ET were evaluated before and after administration of clonidine using clinical tests and electrophysiological recordings. Improvement due to the desynchronizing effect of clonidine on tremor was observed in all cases. The author suggested both a central and peripheral nervous system effect of clonidine as the possible mechanism of action.[93]

Clonidine can be considered for ET, but results are mixed and hypotension and sedation can be problematic. Clonidine along with β-blockers

is a good choice in the setting of baseline hypertension.

3.9.2 Amantadine

Although several preliminary reports suggested that amantadine might be effective in the treatment of ET,[94-96] it did not demonstrate any significant efficacy in a double-blind, crossover, placebo-controlled trial. In fact, an increase in postural tremor as an adverse effect of amantadine was reported by 37.5% of patients.[97]

3.9.3 Barbiturates

In a small randomized placebo-controlled trial, the effect of the barbiturate T2000 (1,3-dimethoxymethyl-5,5-diphenyl-barbituric acid; DMMDPB), given in twice-daily doses of 400 and 300 mg, on ET was assessed in two parallel groups. The effect of T2000 at a dose of 400 mg twice daily was significantly different from that of the placebo group. The group with 300 mg twice daily did not demonstrate a significant treatment effect; however, some treated patients experienced marked improvement compared with the placebo group. The authors suggested that the results support further evaluation of T2000 in the treatment of ET.[98]

3.9.4 Sodium Oxybate

Sodium oxybate is a powerful hypnotic that is currently used to treat narcolepsy/cataplexy. The efficacy of sodium oxybate for the treatment of ET was assessed in an open-label, rater-blinded, add-on study of sodium oxybate in 11 patients with ethanol-responsive myoclonus and 9 patients with ET. Patients were started at dose of 1 g three times daily (taken before meals), with titration of the dose at 2-week intervals repeated until the maximum dose of 3 g three times daily was reached; patients were pleased with the results of treatment or they developed adverse effects. The severity of mean postural and kinetic tremor scores decreased with maximal improvement in these measures and occurred at doses just below the highest dose employed in the trial (1.5 g for ET). The average final daily dose of sodium oxybate for patients with ET was 4.3 g (range 1.5–7.5 g). Mild transient adverse effects included dizziness (35%), headache (20%), emotionality (20%) and nausea (10%). Tolerability was 'acceptable', and more than half of the patients chose to continue treatment after the trial.[99]

3.9.5 Isoniazid

A double-blind 4-week trial of isoniazid (up to 1200 mg with 100 mg of pyridoxine) in 11 patients with ET who were refractory to treatment with β-blockers or primidone showed benefit only in two patients and only one has benefited from its long-term use. The author suggested that isoniazid may be useful in rare cases of tremor but must be monitored carefully because of its toxicity.[100]

3.9.6 Methazolamide

Methazolamide improved tremor in 10 of 28 ET patients in an open-label trial. Four patients had marked improvement and two had moderate improvement but discontinued use of the drug as a result of adverse effects. These effects consisted primarily of somnolence, nausea, epigastric discomfort, anorexia, paraesthesia and numbness. Methazolamide may be an effective drug in the treatment of some patients with ET, particularly those with head and voice tremor;[101] however, two placebo-controlled clinical trials failed to show any efficacy.[102,103]

3.10 Deep Brain Stimulation

Deep brain stimulation (DBS) of the ventral intermediate thalamus is not a pharmacological treatment of ET; however, any review would be incomplete without its mention. Surgery is reserved for severe and refractory cases as there is predictable perioperative morbidity. Although there are no comparative studies, DBS almost surely improves tremor more than any pharmacological agent. Results are often dramatic and distal arm tremor responds best. Midline and proximal tremors and very low frequency tremors respond inconsistently. The main chronic adverse events are dysphagia and balance difficulties.[104]

4. Conclusions

Numerous therapeutic options exist for ET. β-Blockers and primidone are generally considered to be the first-line therapies. Topiramate,

alprazolam and botulinum toxins are probably the next most beneficial drugs. However, individual patients may respond unpredictably to any of the agents discussed here. Polypharmacy, with the exception of propranolol and primidone, is rarely studied but often used. In all cases, symptomatic benefit and patient disability must be weighed against adverse events and the cost of treatment. In refractory cases, DBS of the ventral intermediate thalamus is probably the most robust treatment for ET.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Ondo reports receiving honoraria from GlaxoSmithKline, Boehringer Ingelheim, TEVA, Ipsen and Lundbeck, and grants from Takeda, Allergan, Ipsen, Novartis, TEVA and Bayer, with grants pending from Lundbeck. Dr Sadeghi has no conflicts of interest that are directly relevant to the content of this review.

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