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# Benefits and Risks of Pharmacological Treatments for Essential Tremor

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## Abstract

Essential tremor can cause significant functional disability in some patients. The arms are the most common body part affected and cause the most functional disability. The treatment of essential tremor includes medications, surgical options and other forms of therapy. Presently there is no cure for essential tremor nor are there any medications that can slow the progression of tremor.

Treatment for essential tremor is recommended if the tremor causes functional disability. If the tremor is disabling only during periods of stress and anxiety, propranolol and benzodiazepines can be used during those periods when the tremor causes functional disability. The currently available medications can improve tremor in approximately 50% of the patients. If the tremor is disabling, treatment should be initiated with either primidone or propranolol. If either primidone or propranolol do not provide adequate control of the tremor, then the medications can be used in combination. If patients experience adverse effects with propranolol, occasionally other β-adrenoceptor antagonists (such as atenolol or metoprolol) can be used. If primidone and propranolol do not provide adequate control of tremor, occasionally the use of benzodiazepines (such as clonazepam) can provide benefit. Other medications that may be helpful include gabapentin or topiramate. If a patient has disabling head or voice tremor, botulinum toxin injections into the muscles may provide relief from the tremor. Botulinum toxin in the hand muscles for hand tremor can result in bothersome hand weakness and is not widely used. There are other medications that have been tried in essential tremor and have questionable efficacy. These drugs include carbonic anhydrase inhibitors (e.g. methazolamide), phenobarbital, calcium channel antagonists (e.g. nimodipine), isoniazid, clonidine, clozapine and mirtazapine.

If the patient still has disabling tremor after medication trials, surgical options are usually considered. Surgical options include thalamotomy and deep brain stimulation of the thalamus. These surgical options provide adequate tremor control in approximately 90% of the patients. Surgical morbidity and mortality for these procedures is low. Deep brain stimulation and thalamotomy have been shown to have comparable efficacy but fewer complications have been reported with deep brain stimulation. In patients undergoing bilateral procedures deep brain stimulation of the thalamus is the procedure of choice to avoid adverse effects seen with bilateral ablative procedures. The use of medication and/or surgery can provide adequate tremor control in the majority of the patients.

Essential tremor is one of the most common movement disorders and in some patients can cause significant disability. Clinically, essential tremor is characterised by a 4–12Hz postural and kinetic tremor.[1] The arms are the most common region affected by tremor and also cause the most functional disability. Other body parts like the head, face, voice, trunk and lower limbs can also be affected.[1] The reported prevalence of essential tremor varies greatly with estimates from 0.8 to 2200 per 10 000 population, with the majority of studies estimating the prevalence between 40 and 400 per 10 000 population.[2]

Tremor can begin at any age, but it typically begins in middle age. Essential tremor increases in prevalence with increasing age and it is estimated that 1 to 5 of every 100 persons aged ≥60 years are affected. Tremor usually progresses over time with an increase in severity and a wider distribution of tremor throughout the body. Essential tremor is diagnosed clinically as there are currently no diagnostic tests available. The majority of clinicians recognise essential tremor as a mono-symptomatic tremor disorder, with no other neurological signs or symptoms. The differential diagnoses of essential tremor include hyperthyroidism and hyperadrenergic conditions, dystonia, Parkinson's disease, cerebellar lesions, tremor due to peripheral neuropathy, psychogenic tremor and toxin or drug-induced tremor.[3-5]

Certain drugs can cause tremor that can be mistaken for essential tremor. These drugs include β-adrenoceptor agonists, valproic acid, thyroxine, tricyclic antidepressants, selective serotonin reuptake inhibitors, procainamide, methylxanthines, antipsychotics, and lithium. If a patient is experiencing tremor and taking any of these medications, the medications need to be discontinued or the doses should be reduced, if possible.

There are several different medications and modalities for the treatment of essential tremor, which will be summarised in this review. It should be noted that the biochemical basis of essential tremor is unknown. There is some evidence to suggest that the GABAergic system may be involved. However, drugs known to affect the GABAergic system have not consistently shown benefit in essential tremor. The drugs currently used in the treatment of essential tremor have been discovered by serendipity rather than on a biochemical basis.

The treatment for essential tremor can include pharmacological treatment, surgical treatment and the use of other modalities for treatment. Currently, there is no cure for essential tremor and there are no medications that are known to slow the progression of essential tremor. Unless there is functional disability with tremor, a patient does not necessarily need to take medications for the treatment of tremor. Essential tremor can worsen during periods of stress and anxiety. If a patient's tremor causes functional disability only during certain social circumstances like attending a party or a special event, the occasional use of β-adrenoceptor antagonists (β-blockers) and benzodiazepines may be considered. With the currently available medications, approximately 50% of patients can tolerate these medications and may have benefit. Patients who require medications on a daily basis should be started with β-blockers (such as propranolol) or primidone. If the tremor is inadequately controlled with either of these medications alone, a combination of these two drugs may be tried. If the patient continues to have bothersome tremor, medications like benzodiazepines, gabapentin, topiramate or botulinum toxin could be used. If a patient has disabling tremor that is not well controlled with medications, the use of surgical therapy especially deep brain stimulation of the thalamus should be considered. Over 80% of patients with disabling hand tremor can have significant relief from tremor with surgery. Each of these treatment options will now be discussed in detail.

## 1. First-Line Pharmacological Treatments

### 1.1 β-Adrenoceptor Antagonists

The β-blockers have been used for the treatment of tremor for over three decades.[6-8] The majority of the studies have reported the efficacy of propranolol in reducing postural hand tremor with subjective and objective scales.[9-13] Tolosa and Loewenson[10] conducted a double-blind trial of propranolol 120 mg/day in 11 patients. All patients improved and none of the patients experienced adverse effects. Murray,[11] in a double-blind crossover study with 12 patients treated with propranolol and placebo, reported that eight patients improved with propranolol and three with placebo; however, the degree of improvement with propranolol was greater than that with placebo. In the same paper he also reported that an additional 21 patients had a fair to excellent response when treated with propranolol after 2–4 years. Teräväinen et al.[13] conducted a double-blind crossover study assessing the effect of propranolol 120 mg/day in 21 essential tremor patients. Electrical recording of tremor amplitude and frequency showed that propranolol had no effect on the tremor frequency but reduced the amplitude in 15 patients.

Approximately 50% of essential tremor patients will have symptomatic benefit with propranolol, although some patients will have no response. Tremor can be reduced by as much as 50% to 60% in some patients. Some studies have reported a lack of benefit with propranolol,[14] however, inadequate doses, small sample size, or lack of objective measurements in these studies may be responsible for the lack of benefit. It is not known what factors distinguish those patients who respond to propranolol from those patients who do not respond.[12,13,15,16] Calzetti et al.[16] reported no significant relationship between changes in tremor amplitude or changes in disease duration with cardiac β-blockade or serum propranolol levels in patients who responded compared with patients who did not respond to propranolol.

In a dose response study of propranolol, Koller[17] studied the effect of propranolol using doses of 80–800 mg/day in 15 essential tremor patients. The dose was escalated weekly by 80mg. Although mean serum propranolol levels increased with increasing dosage, they did not correlate with tremor suppression. Five patients did not tolerate doses higher than 640 mg/day. Maximum tremor suppression occurred within a dose range between 160 and 320 mg/day. Doses above 320 mg/day produced no additional benefit.

A sustained release preparation of propranolol (once daily) has been reported to provide similar or, in some cases, greater tremor reduction than divided doses.[18,19] In a crossover study, Koller[18] compared long-acting propranolol (propranolol-LA) to propranolol in divided doses in 18 essential tremor patients. Three patients (16.7%) were unresponsive to both preparations and the remaining 83.3% of patients had some response to both preparations. Propranolol-LA was preferred by 87% of patients for ease of administration and by 67% for tremor control. Propranolol-LA provided similar or greater reductions in tremor amplitude (53 and 47% of patients, respectively) than divided dosing. Similarly, in a controlled study, Cleeves and Findley[19] reported that a propranolol-LA (at doses of 160, 240 and 320mg), was as effective as conventional propranolol (80mg three times daily) in reducing tremor amplitude.

Contraindications for the use of propranolol include moderate to severe bronchial asthma, significant sinus bradycardia, high grade or complete atrioventricular block, cardiogenic block and concurrent use of calcium channel antagonists. The majority of the adverse events with propranolol are mild, transient and rarely require discontinuation of therapy. The most common adverse effects are nausea, vomiting, diarrhea, bradycardia, hypotension,

drowsiness, paresthesias, light-headedness, weakness, fatigue and lethargy. Infrequent adverse effects include hallucinations, vivid dreams, insomnia, confusion, short-term memory loss, depression and abdominal pain. In divided-dose administration of propranolol, fatigue, lethargy and vivid dreams appear to be dose related. Agranulocytosis, alopecia, rashes, dry eyes, and impotence are rarely reported.[20]

The mechanism of action of propranolol in essential tremor is unknown. Young[21] proposed a central site of action because of the lack of effect of intravenous or intra-arterial propranolol and a delay in the effect of oral therapy. However, several controlled studies have shown that propranolol causes an immediate and sustained reduction in tremor.[15,22] Jefferson and colleagues[23] have proposed a peripheral site of action. Specific $\beta_2$ antagonists (ICI 118551 and LI 32-468), which act predominantly peripherally, are effective in decreasing tremor, providing support for a peripheral $\beta_2$ antagonistic mechanism of action.[23,24]

Other orally active β-blockers are available including metoprolol, nadolol, atenolol, timolol, and pindolol. The effectiveness of metoprolol, at divided doses of 100–200 mg/day, has been demonstrated in multiple case reports and a controlled study.[25-31] Calzetti et al.[30] in a single oral dose study of propranolol (120mg), metoprolol (150mg) and placebo reported that both agents were significantly more effective than placebo in reducing the magnitude of tremor. In a controlled study, nadolol, when administered once daily at doses of 120 and 240 mg/day, was found to significantly decrease tremor in essential tremor patients who also responded to propranolol.[32] Timolol was also reported to decrease tremor.[33] Atenolol and pindolol have been reported to have minimal or no effect on tremor.[23,34] Pindolol may actually cause or increase tremors due to its partial agonist activity.[35] Kuroda and coworkers[36] reported that arotinolol, a peripherally acting β-blocker, significantly reduced essential tremor in 15 patients at doses of 30 mg/day.

Divided-dosing propranolol and propranolol-LA are the most commonly prescribed β-blockers for the treatment of essential tremor. Propranolol, in divided doses, should be started from 10 mg/day up to 60 mg/day. The majority of patients will benefit from doses ≤120 mg/day. If the response is inadequate with 120 mg/day, the dose can be increased to 240–320 mg/day. An older patient should be started at 10 mg/day and the dose should be slowly increased to 80–100 mg/day. Propranolol-LA should be started at 60 mg/day and can be slowly increased to 120 mg/day or higher as needed and tolerated.

### 1.2 Primidone

O'Brien and coworkers[37] were the first to report that primidone was an effective treatment for essential tremor. They gave primidone to a patient for epilepsy and noticed an unexpected reduction in tremor. Subsequently, they gave 20 additional essential tremor patients primidone. Of these 20 patients, six could not tolerate the drug because of vertigo and nausea but 12 obtained a good response, which in some cases was dramatic. Several studies have demonstrated the efficacy of primidone in essential tremor.[38-40]

The mechanism of action of primidone for essential tremor is not known. Primidone is converted into phenylethylmalonamide and phenobarbital. Phenylethylmalonamide has a half-life of approximately 30 hours, while phenobarbital has a half-life of approximately 10 days. High doses of phenylethylmalonamide had no effect on tremor.[41] It is currently thought that primidone itself or a yet unrecognised metabolite appears to be responsible for the observed anti-tremor effect. Findley and Calzetti[42] suggested that both primidone and phenobarbital were responsible for the anti-tremor effects. However, Koller and Royse,[40] found that primidone resulted in a reduction in tremor when

there was no detectable serum phenobarbital. Furthermore, tremor control was lost when primidone was replaced by phenobarbital.[40]

Koller and Royse[40] (using objective recording techniques) found that primidone (50–1000 mg/day) significantly reduced the amplitude of hand tremor in both untreated and propranolol-treated patients. Low doses (i.e. 250 mg/day) were found to be as effective as high doses. A single oral dose of 250 mg/day of primidone decreased tremor by 60% one to seven hours after ingestion. Primidone decreased tremor more than propranolol. There were no correlations between therapeutic response and serum levels. Acute reactions to the initial dose, resulting in ataxia and confusion, led to drug discontinuation in three (9.4%) patients. Dose increases were not possible in nine (28.1%) patients due to excessive sedation and vertigo.

Findley et al.[39] in a double-blind trial, reported that primidone was significantly superior to placebo in reducing the magnitude of hand tremor. They reported an acute toxic reaction consisting of severe nausea, vomiting, ataxia and giddiness with an initial dose of primidone 62.5mg in five (22.7%) of 22 patients. These patients were withdrawn from the study and the effects lasted for a period of 12–72 hours. Less severe adverse effects of sedation, tiredness and depression occurred in 11 (50%) patients.

In a double-blind, randomised, crossover study, Gorman and coworkers[43] examined the effects of primidone, propranolol, and placebo in 14 essential tremor patients. Propranolol and primidone each significantly reduced tremor compared with placebo; however, there was no significant difference in tremor reduction between the two drugs. Studies have indicated that tolerance to primidone may develop,[44,45] however, Sasso et al.[46] reported that, in 11 patients treated with primidone (375–750 mg/day) for 12 months, the magnitude of tremor was still significantly reduced compared with the initial placebo period. Three patients discontinued the drug due to sedation.

Primidone should be started at 12.5mg (one quarter of a 50mg tablet) or 25mg (half of a 50mg tablet) at bedtime. After 1 week, this dose can be increased to 50mg at bedtime. The dose can be increased by 50mg per week up to a dose of 250 mg/day, or until adequate tremor control is achieved. Doses of up to 750 mg/day can be beneficial in some patients. Primidone can be given as a single dose at bedtime or in divided doses throughout the day. The most frequent adverse effects associated with primidone are ataxia and vertigo. These tend to occur at initial treatment and resolve with continued therapy or a reduction in dosage. Other adverse effects seen occasionally are nausea, vomiting, fatigue, emotional disturbances, impotence, diplopia, polyuria and skin rash.[20]

## 2. Second-Line Pharmacological Treatments

### 2.1 Benzodiazepines

GABA-agonist anxiolytic drugs such as clonazepam, diazepam, lorazepam, and alprazolam are frequently used in the treatment of essential tremor. These drugs are especially useful in patients with concomitant anxiety. In a double-blind crossover study in 12 essential tremor patients, five showed improvements with diazepam while four showed improvements with placebo.[11] The degree of improvement was less than that achieved with propranolol.

The effect of alprazolam on essential tremor was examined in a double-blind, placebo-controlled parallel study involving 24 patients.[47] Although alprazolam (0.75 mg/day to 2.75 mg/day) was shown to significantly reduce tremor as well as symptoms of anxiety, transient mild fatigue or sedation was seen in 50% of the patients. In another study, the effectiveness of alprazolam and acetazolamide as

symptomatic treatments for essential tremor were examined in a double-blind, crossover, placebo-controlled trial involving 22 patients with essential tremor.[48] Patients received, in random order, alprazolam, acetazolamide, primidone and placebo for 4 weeks, each separated by a 2-week washout period. The study demonstrated that alprazolam was superior to placebo and equipotent to primidone, whereas there was no statistically significant difference between acetazolamide and placebo. The mean effective daily dose of alprazolam was 0.75mg and the only reported adverse effect was mild sedation.

Clonazepam was shown to be ineffective in controlling essential tremor in a double-blind study.[49] However, in patients with kinetic predominant tremor, clonazepam (at a mean dose of 2.2 mg/day) improved kinetic tremor.[50] Clonazepam is also useful in patients with orthostatic tremor. In the original study of orthostatic tremor, Heilman[51] reported three patients who improved with clonazepam. In another study, 10 out of 18 patients with orthostatic tremor showed improvements with clonazepam at a dose of 1–6 mg/day.[52]

The exact mechanism of anti-tremor action of benzodiazepines is unknown. Benzodiazepines potentiate the neurotransmitter GABA by acting as agonists at $GABA_A$ receptors and it is possible that this may be responsible for the anti-tremor effect. Benzodiazepines, if used for prolonged periods in large dosages, pose a risk of habituation and addiction.[20] In addition, there is a risk of withdrawal symptoms if these drugs are stopped suddenly. In spite of these limitations, these drugs may be useful in patients with essential tremor who do not respond to other medications or have concomitant anxiety. Common adverse effects include somnolence (37%), dizziness (8%), depression (7%), fatigue (7%), loss of coordination (6%) and memory loss and confusion (4%).[20]

### 2.2 Gabapentin

Several open-label trials have supported the utility of gabapentin for essential tremor,[53-55] therefore, Gironell et al.[56] compared gabapentin (1200 mg/day), propranolol (120 mg/day) and placebo in a 3-way randomised trial involving 16 patients with essential tremor. Each arm was 15 days, separated by a 1-week washout period. Patients entering this trial were weaned off other tremor medications for 2 weeks prior to the study. Gabapentin was superior to placebo and equal to propranolol, as assessed by observational assessments, motor tasks, global impressions, and electrophysiological measures. Adverse events were mild during both treatment arms and all patients completed the study.

Ondo et al.[57] conducted a double-blind, placebo-controlled, crossover trial assessing gabapentin (1800 and 3600 mg/day) as adjunctive therapy to current anti-tremor medications in 25 essential tremor patients. Overall efficacy results were mixed, but largely supported the efficacy of gabapentin. Subjective global scores, activity of daily living scores, pouring tests, and objective tremor rating scores statistically improved, whereas observer global scores, spiral drawings, and accelerometry did not. Higher doses (3600 mg/day) were not superior to lower doses (1800 mg/day). No demographic or phenotypic factors predicted a more robust response. The drug was very well tolerated. Adverse effects included lethargy and drowsiness (20%), fatigue (16%), decreased libido (12%), dizziness (8%), nervousness (8%) and shortness of breath (4%).

In contrast to these mostly positive findings, Pahwa et al.[58] did not find any statistical differences between gabapentin 1800 mg/day adjunctive therapy and placebo in terms of objective ratings, functional ability, or activities of daily living measures of tremor. Twenty patients with essential tremor underwent a 2-week, crossover trial, which included a 1-week washout period between each

treatment arm. The drug was generally well tolerated; however, adverse events included dizziness (20%), nausea (10%) and sedation (5%).

There are several possible explanations for the contradictory results seen in the various gabapentin studies. In the study by Gironell et al.,[56] patients were not taking additional anti-tremor medications, whereas in the studies by Ondo et al.[57] and Pahwa et al.[58] studies, gabapentin was used as adjunctive therapy. In addition, patients included in the study by Pahwa et al.[58] had greater disability as a result of tremor at baseline than those patients in the study by Gironell et al.,[56] which may have made the patients more difficult to treat.

The mechanism of action of gabapentin with regards to tremor suppression is unclear. Gabapentin is a structural analogue of GABA. Although it has no affinity for the GABA receptor, it demonstrates multiple actions in the nervous system.[59-63] There is a lack of well-designed, multicentre trials investigating the use of gabapentin in the treatment of essential tremor. However, most initial studies indicate that there may be some benefit for tremor, that it is relatively well tolerated and that it has a good safety profile that includes primarily sedation or drowsiness, fatigue, dizziness, and nausea. Therefore, gabapentin may have a role in the treatment of essential tremor.

### 2.3 Topiramate

After reporting the efficacy of topiramate as a treatment for essential tremor in an open-label report,[64] Conner conducted a double-blind, placebo-controlled, crossover trial assessing the use of this agent in the treatment of 24 patients with essential tremor.[65] After an initial evaluation including objective measures of tremor, activities of daily living, and functional drawing assessments, patients gradually increased the dose of the drug, or placebo, over 8 weeks, then completed a further 2 weeks' treatment at a steady dose before their subsequent evaluation. A 2-week washout period separated each of the study arms. At a mean final dose of 333 mg/day, patients on topiramate demonstrated significant improvement in all assessment sub-scales (objective tremor scores, functional ability, and activities of daily living). Nine patients withdrew from the study. One patient (4.2%) withdrew because of dizziness, one (4.2%) because of disorientation and one (4.2%) with memory problems and ataxia. Of the remaining patients, three withdrew as a result of intercurrent illness, one was lost to follow-up, one was discontinued by another neurologist and one was removed for noncompliance. Tolerable adverse events with topiramate included weight loss, paraesthesia, confusion, and word-finding difficulty.

The mechanism of action of the anti-tremor effects of topiramate is also unknown. Topiramate is a sulfamate substituted monosaccharide, which is structurally distinct from any other anti-epileptic medication.[66] It has multiple mechanisms of action including inhibiting voltage-gated sodium channels,[67] augmenting of the inhibitory chloride ion influx mediated by GABA,[68] inhibiting carbonic anhydrase in a manner similar to that of acetazolamide,[66] and antagonising the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor. It has no effect on the NMDA receptor subtype.[66]

### 2.4 Botulinum Toxin

Botulinum toxins are potent neurotoxins produced by *Clostridium botulinum*. Botulinum toxins bind to specific acceptors on nerve terminals and effectively denervate muscle by enzymatic cleavage of one of the proteins involved in vesicle fusion (SNARE proteins).[69,70] There are seven serotypes of botulinum toxin (A, B, C, D, E, F, and G), each with a unique presynaptic acceptor, and each cleaving one of the fusion proteins in a specific location.[70] In the US, the FDA has approved botulinum toxin A for treatment of blepharospasm, strabismus,

disorders of the VIIth cranial nerve and cervical dystonia. Botulinum toxin B has also been approved in the US for the treatment of cervical dystonia. Despite the limited areas of approval, botulinum toxin has been shown to have clinical application in a variety of disorders,[71] including tremor. The usefulness of botulinum toxin A has been assessed for tremor of the hand, head, and voice.[72] There is no information available for botulinum toxin B for tremor.

#### 2.4.1 Hand Tremor

Several studies have examined the usefulness of botulinum toxin A for the treatment of essential tremor of the hand. Jankovic et al.[73] randomised 25 essential tremor patients to receive either 50U of botulinum toxin A or placebo injections into the wrist flexors and extensors of the dominant limb. If patients failed to respond to the initial injection, they were eligible to receive another injection of 100U 4 weeks later. Tremor was assessed using tremor severity rating scales, accelerometry, and assessments of improvement and disability. There were no significant improvements in functional rating scales but postural accelerometry measurements showed reduction in amplitude in 9 out of 12 botulinum toxin A-treated subjects and in one out of nine placebo-treated subjects. All patients treated with botulinum toxin A reported some degree of finger weakness.

In a multicentre study, Brin et al.[74] assessed the safety and efficacy of botulinum toxin type A injection in 133 essential tremor patients. Patients were randomised to low-dose (50U) or high-dose (100U) botulinum toxin A or placebo treatment. At 16 weeks, both doses of botulinum toxin significantly reduced postural tremor. Functional disability scales did not show consistent improvement. All patients who received botulinum toxin type A experienced finger weakness as measured by a reduction in grip strength. However, on subjective patient reports, hand weakness was reported by 30% of patients in the low-dose group and almost 70% of patients in the high-dose group. Other adverse effects were uncommon and included pain at injection site (placebo 4.4%, low-dose 4.7%, high-dose 2.2%), rash (placebo 2.2%), stiffness (low-dose 2.3%), cramping (low-dose 2.3%), haematoma (low-dose 2.3%), and paresthesia (high-dose 6.7%).

The studies by Jankovic et al.[73] and Brin et al.[74] used fixed dosages of botulinum toxin A and required injection into four specified forearm muscles, the flexor carpi radialis and ulnaris and extensor carpi radialis and ulnaris, regardless of specific tremor movement and allowed injections without electromyography guidance. In contrast, three open-label studies, which allowed injections into variable muscles, depending on the tremor manifestations, showed significant improvements in patients' functional ability and mild-to-moderate improvement in patients' tremor amplitude.[75-77] In these studies, finger weakness was much less common and less severe due to the exclusion of the extensor carpi muscle and the adjustment of the dosage of botulinum toxin A. Botulinum toxin has limited efficacy for essential hand tremor and commonly causes hand and/or finger weakness.

#### 2.4.2 Head Tremor

Head tremor can be observed predominantly in the horizontal (No-No) or vertical plane (Yes-Yes). An open-label study that included both patients with essential tremor of the head (n = 14) and a combination cervical dystonia and tremor (n = 29), reported improvements in subjective measures and tremor amplitude measured using accelerometry.[78] Adverse events were mild and transient and included dysphagia, neck weakness and pain at the injection site in 40% of the patients in each group. Dysphagia occurred in five (35.7%) essential tremor patients and in two (6.9%) cervical dystonia and tremor patients. Post-injection pain occurred in four (28.6%) of the essential tremor patients and in two (6.9%) of the cervical dystonia and tremor patients.

In a crossover study in ten patients with no-no head tremor without dystonia, Pahwa et al.[79] found that, overall, bilateral injections of botulinum toxin were no more effective than placebo. However, three patients did show marked responses with botulinum toxin type A. Adverse effects were frequent with botulinum toxin and included neck weakness (70%), swallowing difficulty (30%), headache (20%), dizziness (10%), neck soreness (10%) and dry skin (10%), all of which resolved without treatment.

#### *2.4.3 Voice Tremor*

The efficacy of botulinum toxin in the treatment of patients with voice tremor has not been completely established. Open-label studies suggest that botulinum toxin A may be of benefit in voice tremor.[80] In a study by Hertegard et al.,[81] 15 patients with essential tremor of the voice were treated with botulinum toxin A injections to the thyroarytenoid muscles, and in some cases, to the cricothyroid or thyrohyoid muscles. Subjective improvements in voice tremor were reported by 67% of patients, while objective improvements in voice tremor were observed in 50% of patients. The most frequent adverse effect was a temporary breathy quality to the voice, which lasted 1–2 weeks in 12 (80%) patients and up to 4 weeks in three (20%) patients. Three patients (20%) also reported slight dysphagia after injection. One patient showed an improvement in essential voice tremor following injection that lasted for greater than 10 weeks.[82] Patients with vocal tremor may have satisfactory improvement if injections are administered unilaterally.[83] The efficacy of botulinum toxin for treatment of tremor in unusual sites, such as the palate and chin, is anecdotal.[84,85]

The treatment of tremor using botulinum toxin has had variable success. The reduction in tremor amplitude following injection may be offset by weakness when both agonist and antagonist muscles are injected. However, in selected patients with functionally disabling tremor who have not responded to oral pharmacological treatments, a careful trial of botulinum toxin administered into the appropriate muscles may be warranted.[86]

## 3. Treatments with Undetermined Efficacy

### 3.1 Carbonic Anhydrase Inhibitors

There have been several open-label[87-89]studies that have examined the efficacy of carbonic anhydrase inhibitors in essential tremor. Muenter and coworkers[87] treated 28 essential tremor patients with methazolamide (mean dose 200 mg/day) and reported marked improvements in tremor in 12 patients, moderate improvements in four patients, mild improvements in four patients, and no benefits in eight patients. The greatest improvement occurred in head and voice tremor.

The most common adverse effect observed with carbonic anhydrase inhibitors was various degrees of somnolence occurring in 14 (50%) patients.[87] The combination of nausea, epigastric distress and anorexia occurred in eight (28.6%) patients, paraesthesias and numbness occurred in five (17.9%) patients, depression was reported in two (7.1%) patients and imbalance was reported in two (7.1%) patients. Emotional lability, impotence, diarrhoea, constipation, nasal congestion, heart palpitations, dyspnoea, tinnitus, rash, insomnia and nervousness each occurred in one patient.

Busenbark and colleagues[88] assessed the use of acetazolamide in 24 essential tremor patients and found significant reductions in tremor severity, but no significant changes in patient functional measures.

Placebo-controlled studies have failed to find any benefits with carbonic anhydrase inhibitors in the treatment of essential tremor. In a double-blind, study in 25 essential tremor patients, no significant differences were observed between methazolamide

and placebo in terms of patient self-reporting of functional disability, clinical ratings of motor tasks, tremor severity, and accelerometric measurements.[89] Adverse effects were common and generally mild, including paraesthesias (56%), drowsiness (48%), headache (32%), anorexia (28%), nausea (28%), depression (24%), abdominal cramping (20%), confusion (16%), dyspnoea (8%), irritability (8%), elevated creatine (4%), altered taste (4%) and diarrhoea (4%). Ten patients discontinued methazolamide because of intolerable adverse effects, including paraesthesias (2 patients), drowsiness (4), headache (1), elevated creatine (1), altered taste (1) and diarrhoea (1).

In a double-blind, randomised, crossover, placebo-controlled study, conducted by Gunal et al.,[48] 22 patients with essential tremor received, in random order, alprazolam, acetazolamide, primidone and placebo. There were no significant differences between acetazolamide and placebo. The adverse effects of acetazolamide were mild, with 10% (3) of the patients reporting tolerable paresthesias. No other adverse effects were reported.

Double-blind, placebo-controlled studies have failed to demonstrate that either of the carbonic anhydrase inhibitors, acetazolamide or methazolamide, are superior to placebo in the treatment of essential tremor. Adverse effects with these drugs are problematic in many patients. While there are anecdotal reports of benefit in individual patients, the use of these agents should be limited.

### 3.2 Phenobarbital

Although phenobarbital has been used for the treatment of essential tremor for many years, it has minimal clinical benefits. In a double-blind controlled study, 12 essential tremor patients received phenobarbital, propranolol, or placebo administered orally for 1 month.[90] Propranolol appeared to be significantly more effective than placebo. Significant improvements in patients' subjective evaluations and tremor amplitude measurements were observed with both propranolol and phenobarbital compared with placebo. Adverse effects were mild for both propranolol and phenobarbital. Five of the 12 patients experienced adverse effects while taking propranolol including dizziness (3), heartburn (1) and insomnia (1). Similarly, five of the 12 patients experienced adverse effects while taking phenobarbital including drowsiness (2), hypotonia (1), constipation (1) and dizziness (1).

Findley and Cleeves[91] reported that, in 12 patients with essential tremor, phenobarbital (120 mg/day) was better than placebo on accelerometric measurement and clinical assessment. However, these benefits of phenobarbital were not reflected in patients' self-assessments of tremor. Adverse effects seen with phenobarbital were drowsiness resolving after one week (16.7%), mild fatigue (41.7%) and intolerable sedation (8.3%).

Koller and Royse,[40] using objective measures, found no effect of phenobarbital (90 mg/day) in essential tremor patients. In a double-blind comparison of primidone and phenobarbital, Sasso and colleagues[92] found primidone superior to both placebo and phenobarbital in reducing tremor in 13 patients. Two patients dropped out of the study due to asthenia from phenobarbital in one case and primidone in the other. Of the 13 patients who completed, adverse effects were reported by ten while on primidone, 11 while on phenobarbital and five during placebo. The most common adverse events were drowsiness and fatigability, which occurred equally in the primidone and phenobarbital arms, ataxia, which occurred most with phenobarbital and nausea and vertigo, which occurred primarily with primidone. From the results of these studies, it appears that phenobarbital has a minimal if any role in the treatment of essential tremor.

### 3.3 Calcium Channel Antagonists

Calcium channel antagonists have been shown to have a limited and variable effect in essential tremor. In a study in eight essential tremor patients, nifedipine worsened tremor and verapamil had no effect on tremor.[93] In a placebo controlled trial of 11 essential tremor patients, nicardipine decreased tremor significantly after the initial dose, but the effect was not sustained at 1 month.[94] In a crossover study with nicardipine (1 mg/kg/day) and propranolol (160 mg/day), both drugs improved tremor.[95] In a double-blind crossover study, nimodipine (120 mg/day) was studied in 16 essential tremor patients.[96] Fifteen patients completed the study and of these, eight showed improvements in tremor. Headache and heartburn was reported by one patient (6.3%) who withdrew from the study. No other adverse events were reported. Due to their limited and variable effect, calcium channel antagonists are not routinely used in the treatment of essential tremor.

### 3.4 Isoniazid

In a double-blind trial of isoniazid in 11 essential tremor patients only two patients with essential tremor appeared to experiences short-term improvements, while only one patient experienced sustained benefits.[97] The use of isoniazid is not recommended in essential tremor due to potential toxicity. Four patients withdrew from the study due to adverse events which included increased liver enzymes in two patients (18.2%), dizziness in one patient (9.1%) and hepatotoxicity in one patient (9.1%). No other adverse events were reported.

In general, the most common adverse effects of isoniazid affect the liver and the nervous system.[20] Severe and potentially fatal hepatitis may develop with isoniazid therapy. This is an age-related effect and can affect 8/1000 persons over the age of 65 years. Mild and transient elevations in serum transaminases occur in 10–20% of patients. The most common adverse effect is peripheral neuropathy, which is typically preceded by paraesthesias of the hands and feet. Other common adverse effects are nausea, vomiting, fatigue, weakness, fever, rash and pyridoxine deficiency. Less common adverse effects include convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and psychosis.[20]

### 3.5 Clonidine

Clonidine, an imidazole derivative, is mainly an $\alpha_2$-adrenoceptor agonist but also acts as an agonist at imidazole receptors in the rostroventrolateral medulla. The $\alpha_2$-adrenoceptor agonist mechanism of action was reported to be beneficial in the treatment of essential tremor.[98] In an open-label trial in ten essential tremor patients, a good response to a single dose of clonidine was demonstrated.[98] In contrast, however, clonidine did not result in significant improvements in tremor control, according to the results from both a placebo-controlled, double-blind trial in ten essential tremor patients using an oral dose of 0.4 mg/day[99] and a double-blind, crossover trial in 25 essential tremor patients using intravenous clonidine.[100] Clonidine is not recommended for use in essential tremor.

### 3.6 Clozapine

Clozapine has been reported to be effective in the treatment of essential tremor. In an open-label trial, 12 essential tremor patients and 13 patients with other types of tremor were treated with clozapine (18–75 mg/day). Nine essential tremor patients reported reduction in their tremor. Sedation was the only adverse event reported, which occurred in 21 of the 25 patients. However, in the majority of these patients, sedation decreased or resolved within 1–2 weeks of treatment.[101]

In a randomised, double-blind, crossover study, 13 out of 15 medication-resistant essential tremor

patients, experienced a significant reduction in tremor with clozapine.[102] Sedation was reported by all patients and was markedly decreased after 6–7 weeks in all but one patient who withdrew from the study due to severe intolerable sedation.

The potentially life-threatening risk of agranulocytosis is reported to occur in 1.3% of patients taking clozapine. Due to this potential risk, patients on clozapine must have white blood cell counts prior to drug initiation, at regular intervals throughout treatment and 4 weeks after discontinuation. Other adverse effects associated with clozapine use include drowsiness/sedation (39%), salivation (31%), tachycardia (25%), dizziness/vertigo (19%), constipation (14%), hypotension (9%), headache (7%), sweating (6%), dry mouth (6%), syncope (6%), nausea (5%), fever (5%), visual disturbances (5%), weight gain (4%), hypertension (4%), and seizures (3%). Rarely (<0.01%), clozapine is associated with fatal myocarditis.[20] Clozapine may be effective in the treatment of essential tremor, however, the risk agranulocytosis and myocarditis limit the use of this drug.

### 3.7 Mirtazapine

Mirtazapine is a novel antidepressant that acts centrally as a presynaptic $\alpha_2$-adrenoceptor antagonist. Pact and Giduz[103] reported a series of five patients with tremor (three had parkinsonian tremor and two had action tremor) who were treated with mirtazapine. Mirtazapine 30 mg/day significantly reduced tremor in all five patients. Ertan et al.[104] also reported that essential tremor was controlled with mirtazapine. In 20 patients with essential tremor, 18 (90%) showed a decrease in their total tremor rating scale score and eight (40%) showed a substantial reduction. Adverse events were reported by nine (50%) patients and included sedation, headache and weight gain.

In a double-blind, placebo-controlled study in 17 essential tremor patients, Lyons and Pahwa[105] reported no significant improvements with mirtazapine (45 mg/day) or placebo compared with baseline, as measured by the Tremor Rating Scale. Adverse events were more common in the mirtazapine group and included drowsiness (23.1%), confusion (7.7%), dry mouth (7.7%), weight gain (15.4%) and polyuria (15.4%), whereas in the placebo group the only adverse effects were dry mouth (7.7%) and drowsiness (7.7%). Three patients discontinued the study due to adverse effects; one patient had balance and gait difficulty, nausea and polyuria, one had excessive drowsiness and blurred vision and one patient had drowsiness, dry mouth and a bad taste in their mouth. Due to its lack of efficacy and significant adverse effects, mirtazapine is not recommended for the routine treatment for essential tremor.

## 4. Surgical Treatment

### 4.1 Thalamotomy

There are multiple reports regarding the efficacy of thalamotomy for essential tremor.[106-114] These reports have consistently shown that over 90% of patients have experienced improvements in tremor contralateral to the side of the thalamotomy. Long-term follow-up studies have indicated that the benefits of thalamotomy can continue for up to 20 years.

Mohadjer et al.[112] reported that, at a mean follow-up of 8.6 years after thalamotomy, 80% of the 65 patients with essential tremor showed an improvement in tremor. That is, 69% of patients experienced complete or substantial reductions in tremor, while 11% experienced moderate improvement. Temporary adverse effects were reported in 33% of patients and included bradykinesia, hypotonia, gait disturbances and facial weakness. Twenty-five percent of the patients reported minor speech difficulties and 17% reported fine movement disturbances, dysdiadochokinesia and disequilibrium. At the follow-up evaluations, only 5% reported

continued hypotonia and gait disturbances, 1% reported continued speech difficulties and 3% reported continuation of dysdiadochokinesia and disequilibrium.

Tasker reported a lifetime mortality experience with thalamotomy of <0.5%.[115] Variations in morbidity and mortality rates can be related to different techniques of the procedure (e.g. radio-frequency lesioning is less hazardous than leukotomy or chemothalamotomy), different diagnoses (essential tremor, Parkinson's disease or other tremor), the presence of associated medical conditions and the number of lesions. Bilateral thalamotomies are not recommended due to increased morbidity and mortality. One of the main concerns is the risk of speech difficulty associated with bilateral thalamotomy.

### 4.2 Deep Brain Stimulation of the Thalamus

Due to morbidity rates associated with ablative surgery, especially bilateral lesions, deep brain stimulation of the ventral intermediate nucleus of the thalamus is increasingly used for the surgical treatment of tremor. The Activa Tremor Control Therapy®[1] system consists of a deep brain stimulation electrode and an extension wire that connects the electrode to an implantable pulse generator (the power source for the system). The intracranial end of the deep brain stimulation electrode has four platinum-iridium contacts. The implantable pulse generator is implanted subcutaneously in the infraclavicular area of the chest. Any one of the stimulating contacts can be used for monopolar stimulation or any two or more can be used in combination for bipolar stimulation.[116] The implantable pulse generator is adjusted using an external programming device. The patient can turn the stimulator on or off with a hand held magnet or an Access Review® device that also allows the patient to determine if the system is on or off and monitor battery usage. Adjustable stimulation parameters include pulse width, amplitude, frequency and the choice of active contacts. The typical stimulation parameters are: a frequency of 135–185 Hz; a pulse width of 60–120 microseconds; and an amplitude of 1–3V.

There have been a number of studies that have reported the safety and efficacy of chronic thalamic stimulation in essential tremor.[116-124] Benabid and colleagues[121] were among the first to report the efficacy of thalamic stimulation. In 1993, they observed significant tremor reduction in 68% of 13 patients with essential tremor who underwent thalamic deep brain stimulation.

In a multicentre study of 29 patients with essential tremor and 24 patients with parkinsonian tremor, Koller et al.[123] showed that 3 months after unilateral thalamic stimulation, 23 essential tremor patients reported marked improvements in tremor, three patients reported moderate improvements, one reported mild improvements and two patients were unchanged. There were also significant improvements in activities of daily living and objective tremor rating scores. Surgical complications for the total cohort (n = 53) included lead dislodgement during surgery in one patient (requiring reimplantation the next day), ischaemic changes on ECG in one patient and generalised seizures (not requiring long-term therapy) in another patient. Adverse events for the total cohort that were related to stimulation at 3 months post-surgery were mild and could be reduced by adjusting stimulation parameter settings. These events included paraesthesia (79.2%), headache (11.3%), disequilibrium (9.4%), paresis (7.6%), gait disorder (5.7%), dystonia (5.7%), dysarthria (3.8%), and localised pain (2.9%). The events that persisted at 12 months post-surgery included paraesthesia (20.8%), headache (3.8%), disequilibrium (3.8%), paresis (3.8%), dystonia (3.8%), dysarthria (3.8%) and localised pain (1.9%). Adverse events for the total cohort that were associated

**1** Use of tradenames is for product identification only and does not imply endorsement.

with the deep brain stimulation device during the first year post-surgery, included skin infections in two patients (both of whom were treated with antibiotics), and skin erosion in one patient (requiring replacement of the extension wire). Implantable pulse generator malfunction occurred in one patient that required replacement of the implantable pulse generator. Ondo et al.[124] demonstrated an 83% reduction in contralateral arm tremor in 14 essential tremor patients, 3 months after unilateral thalamic stimulation.

There are very few data regarding the long-term efficacy of thalamic stimulation. In one study in 25 essential tremor patients with an average follow-up of 40 months, a mean improvement in tremor of >50% compared with baseline was reported with unilateral thalamic stimulation.[125] One patient experienced self-limiting seizures postoperatively. Stimulation-related complications were mild and resolved when stimulation parameters were adjusted. These stimulation-related events included paraesthesia (84%), headache (60%), paresis (24%), dysarthria (16%), nausea (16%), disequilibrium (12%), facial weakness (12%), gait disorder (8%), dystonia (8%), mild cognitive deficit (8%), dizziness (8%), hypophonia (4%), anxiety (4%), depression (4%), syncope (4%), drooling (4%) and vomiting during programming (4%). Device-related problems were common and led to additional surgery in 18 patients, including lead replacements due to loss of effect or fracture, lead reposition due to migration, and implantable pulse generator replacement due to malfunction and battery depletion.

Pahwa et al.[126] reported significant improvements in tremor in nine essential tremor patients undergoing staged bilateral deep brain stimulation of the thalamus. After the first surgery, there was a 35% improvement in tremor ratings, including objective measures of tremor, activities of daily living and functional ability, compared with baseline. There was an additional 34% improvement 1 year after the second surgery. When upper limb tremor was evaluated there was a 68% improvement after the first surgery and a 75% improvement after the second surgery. Surgical complications were noted in five patients: asymptomatic intracranial haematoma (n = 1), postoperative seizures (1), haematoma over the implantable pulse generator (1), lead repositioning (1), and implantable pulse generator malfunction (1). Adverse events related to stimulation were mild and resolved with adjustment of the stimulation parameters. The events included paraesthesia (100%), dysarthria (44%), disequilibrium (33%), headache (22%), dyspraxia (22%), choking (11%) and word-finding difficulty (11%). Three of the six patients with dysarthria demonstrated worsening of dysarthria when both stimulators were on.

Voice tremor has also been reported to improve in patients who have undergone deep brain stimulation for hand tremor.[127] This improvement was shown to be most pronounced in patients with severe voice tremor. Similarly, head tremor has been shown to improve in patients undergoing unilateral deep brain stimulation of the thalamus. A 50% improvement in head tremor was observed 12 months after unilateral deep brain stimulation of the thalamus for hand tremor.[128] Obwegeser and colleagues[129] also reported significant improvements in head, voice, tongue and face tremor in 27 patients who underwent thalamic stimulation for essential tremor. The adverse events included dysarthria (15%), disequilibrium (12%), and paraesthesias (10%). After bilateral surgery (n = 13) the percentage of required stimulation adjustments due to dysarthria (29%) was significantly increased compared with unilateral surgery (9%).

### 4.3 Thalamotomy versus Thalamic Stimulation

The clinician must determine whether to recommend thalamotomy or thalamic stimulation for

patients with disabling tremor who are not responding to pharmacological intervention. The advantages of deep brain stimulation include the absence of a destructive lesion in the brain, the ability to change stimulation settings to improve symptoms or reduce the occurrence or severity of adverse events and the option to have bilateral surgery with a reduced risk of speech disturbance and other persistent adverse events. The disadvantages of deep brain stimulation are the increased risk of infection or inflammatory reaction from the implantation of the device, the time and effort necessary to program the device to continually control tremor, additional surgery for the replacement of batteries and the potential for additional surgery due to device failures or malfunction.

Tasker,[130] Schuurman and coworkers[131] and Pahwa and colleagues[132] have compared essential tremor patients who had undergone thalamic stimulation to those who underwent thalamotomy. Each study reported similar efficacy for the procedures, however, those undergoing thalamotomy had a higher risk of complications. Adverse events reported by Tasker[130] for deep brain stimulation of the thalamus (n = 19) and thalamotomy (n = 26), respectively, were intracerebral haematoma (0%, 4%), emotional lability and confusion (5%, 4%), permanent dysarthria (5%, 4%), transient dysarthria (5% resolved with stimulation adjustments, 8%), ataxia (0%, 15%), gait disturbance (5%, 12%), permanent paraesthesias (0%, 19%), transient paraesthesias (47% resolved with stimulation adjustments, 4%), nausea and faintness (5%, 0%), and pain/swelling at stimulator site (16%, 0%).

According to Schuurman et al.,[131] the adverse effects with deep brain stimulation of the thalamus resolved when the stimulators were adjusted or turned off. One patient in the stimulation group had a haematoma near the pulse generator and another patient had an infection at the pulse generator site which led to removal and replacement after antibiotics. Three patients in the thalamotomy group had cognitive dysfunction. Similarly, adverse effects reported by Pahwa et al.[132] for deep brain stimulation of the thalamus (n = 17) and thalamotomy (n = 17), respectively, included intracerebral haemorrhage (0%, 6%), cognitive changes (0%, 29%), hemiparesis (0%, 12%), paraesthesia (59%, 6%), headache (53%, 41%), seizures (6%, 6%), dizziness (12%, 0%), disequilibrium (6%, 0%) and dysarthria (6%, 0%).

### 4.4 Gamma Knife Radiosurgical Thalamotomy

In some high-risk surgery patients who may not be candidates for thalamotomy or deep brain stimulation of the thalamus, gamma knife radiosurgical thalamotomy may be considered. Young et al.[133] reported that 92% out of 52 essential tremor patients experienced significant improvement in tremor with gamma knife radiosurgery. Furthermore, significant improvements were maintained in the 17 patients who were followed for at least four years.

Niranjan et al.[134] reported nearly complete resolution of tremor in six out of eight essential tremor patients who underwent gamma knife radiosurgical thalamotomy. No immediate complications were seen after surgery; however, after approximately 8 months, one patient developed arm and leg weakness as well as dysarthria. No other complications were reported.

In a case report, Siderowf and colleagues[135] reported an essential tremor patient who developed a complex movement disorder following gamma knife radiosurgical thalamotomy. Three months post-surgery the patient developed dizziness and at 4 months peri-oral and right arm numbness and mild dysarthria developed. The patient's symptoms had progressed and at 7 months resting and action tremor, right arm and leg dystonia and right arm choreoathetosis developed. These symptoms progressed for another 4–5 months at which time

they stabilised. In order to fully evaluate the safety of gamma knife radiosurgical thalamotomy, further studies of long-term complications need to be done.

## 5. Non-Pharmacological and Non-Surgical Treatments

It is well known that adding weights to a limb with tremor can reduce the amplitude of the tremor but does not eliminate the tremor.[136] The use of weights may be helpful for patients who have failed to respond to pharmacological or surgical therapies. Weights may be particularly helpful while performing directed tasks such as eating or drinking. This technique can be helpful in identifying psychogenic tremor, as weights tend to decrease organic tremor but increase psychogenic tremor.[136] The use of relaxation techniques such as meditation, yoga, hypnosis and biofeedback approaches can transiently reduce tremor in some patients.[137-140] These techniques are particularly useful during times of increased stress.

## 6. Conclusions

Pharmacological treatment for essential tremor is effective in approximately 50% of patients. Treatment for essential tremor is recommended if the tremor causes functional disability. If the tremor is disabling only during periods of stress and anxiety, propranolol and benzodiazepines can be used during those periods when the tremor causes functional disability. There are few risks with the occasional use of these medications in low doses. Patients who have functional disabilities that interfere with daily activities may require medications on a daily basis.

The use of propranolol or primidone is recommended as initial therapy. If these drugs alone do not provide adequate tremor control, a combination of propranolol and primidone can be tried. Propranolol is usually well tolerated and provides some tremor control in the majority of patients. The primary adverse events associated with propranolol include bradycardia, hypotension, nausea, vomiting, paraesthesias, weakness and fatigue. Similarly, primidone typically provides some tremor relief with the most common adverse events being dizziness, nausea, drowsiness and fatigue. The combination of propranolol and primidone may provide greater control in tremor without a concomitant increase in adverse events. Patients who do not have adequate tremor control with these medications may find some benefit from the use of benzodiazepines, gabapentin or topiramate. Although these medications tend to be well tolerated, their efficacy has not been undisputedly documented in controlled clinical trials.

If the patient still has disabling tremor after medication trials, surgical options are usually considered. Surgical options include thalamotomy and deep brain stimulation of the thalamus. These surgical options provide adequate tremor control in approximately 90% of the patients. Surgical morbidity and mortality for these procedures is low. Deep brain stimulation and thalamotomy have been shown to have comparable efficacy but fewer complications have been reported with deep brain stimulation. In patients undergoing bilateral procedures deep brain stimulation of the thalamus is the procedure of choice to avoid adverse effects seen with bilateral ablative procedures. The use of medication and/or surgery can provide adequate tremor control in the majority of the patients.

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