

Pharmacologic management of essential tremor

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Case description

You are seeing Mr W., an 87-year-old man with long-standing hypertension, chronic obstructive pulmonary disease (COPD), generalized anxiety, panic disorder, and essential tremor. His tremor was first diagnosed more than 25 years ago, after he had developed a slowly progressive, bilateral postural and kinetic hand tremor. His symptoms have been reviewed periodically over the years. A serious discussion of treatment options has not been required because his symptoms have not had much effect on his day-to-day life. During today's review of his COPD, Mr W. reports that he has been slowly experiencing increased disability over the past 6 months or so and would like help controlling his symptoms. He is now having difficulties with feeding, carrying his morning cup of coffee, completing crosswords, writing cheques, and other household tasks requiring precise hand movements. The tremor has also become socially embarrassing. Alcohol reduces his tremor, and as a result he has started having 2 glasses of wine with his supper. Pain seems to worsen his tremor.

Mr W. has been taking 10 mg of tranylcypromine (a monoamine oxidase inhibitor [MAOI]) daily for more than 40 years for his anxiety, with good effect. Other medications include 10 mg of amlodipine daily and 25 mg of metoprolol twice daily for hypertension, salbutamol metered-dose inhaler 3 to 4 times daily as needed for shortness of breath, and budesonide-formoterol combination inhaler (200 µg/6 µg) twice daily for COPD. He has had 3 acute exacerbations of his COPD in the past year, requiring treatment with both antibiotics and a systemic corticosteroid. The combination inhaler was started 8 months ago during his second exacerbation of the year. Recent laboratory tests included a normal thyroid-stimulating hormone level. Unfortunately Mr W. continues to smoke, being in the contemplative stage of change.

Bringing evidence to practice

When treating essential tremor, it is important to review medications that might worsen symptoms, explore non-pharmacologic therapies, and consider medications to reduce symptoms.

Review medications that might worsen symptoms. Both the β -agonist (salbutamol) and the corticosteroid (prednisone for COPD exacerbations) are medications that might exacerbate a coexisting

physiologic tremor, making Mr W.'s symptoms more bothersome.¹ Similarly, his smoking (nicotine) and coffee (caffeine) consumption could be contributing to his symptoms, and he should be educated appropriately about this. Addition of the combination inhaler 8 months ago seems to correspond chronologically with the worsening of his tremor. It is possible that the formoterol component (a long-acting β_2 -agonist) is responsible. A long-acting inhaled anticholinergic (eg, tiotropium) would be a reasonable alternative to try. Furthermore, reviewing the prescribing information for tranylcypromine, you note that tremor is a rare but potential side effect of this medication. It would be important to review the history of his generalized anxiety and panic disorder and the need for ongoing treatment. Possible options might include a trial of either holding or replacing this medication. Consider a 14-day washout period when switching from an MAOI to another agent.² Although his alcohol use might help with his tremor, 14 drinks per week is at the upper limit of what is considered a safe drinking pattern.³ Furthermore, it is thought that tremor might temporarily worsen after the effects of alcohol have worn off. Mr W. should be counseled about this, as well as about the risks of self-medicating with alcohol. A formal screen for alcohol abuse or dependence would be prudent.

Explore nonpharmacologic therapies. Reviewing the RxFiles chart for essential tremor,* you note that non-pharmacologic therapies such as relaxation techniques, ensuring adequate rest, hypnosis, and biofeedback can all be considered, although evidence for efficacy is more convincing for milder cases of tremor.⁴ Nonetheless, these would be beneficial to review, especially given Mr W.'s difficulties with anxiety, for which these therapies could also be helpful.

Consider medications to reduce symptoms. In discussing the use of medications to help with essential tremor, it is important to address the reality that no drug is yet available to entirely eliminate tremor. At best, medications can be expected to reduce tremor amplitude (not frequency) by about half in only 50% of people in whom they are tried.⁵ As these drugs can all have adverse effects (especially in the elderly), chronic pharmacotherapy should only be considered if there is functional



*The full version of the RxFiles essential tremor and restless legs syndrome treatment chart is available at www.cfp.ca. Go to the full text of the article online, then click on CFPlus in the menu at the top right of the page.

disability resulting from the tremor. This is clearly the case with Mr W.

Both propranolol (a nonselective β -blocker) and primidone (a barbiturate anticonvulsant) are first-line treatment options (Table 1⁴⁻¹⁷).¹⁸ Mr W.'s metoprolol (β_1 selective β -blocker), which he is already taking for his hypertension, might be providing some relief. However, as a usual treatment dose is 50 to 100 mg

twice daily, he is currently underdosed for treatment of essential tremor. Depending on his heart rate and blood pressure, increasing his metoprolol dose might be an option, though the evidence is stronger for a nonselective β -blocker such as propranolol, especially for long-term therapy. With a history of poorly controlled COPD, the risks of switching Mr W. to a nonselective β -blocker probably outweigh the benefits,

Table 1. Drug treatment options for ET

CLASS AND ROLE	DRUG	DOSE (ORAL) IN ET	COST/MO, \$	COMMENTS
β-blockers • First-line treatment in moderate to severe limb ET; might be helpful for head tremor ⁶	Propranolol • Inderal, generic	10-40 mg, 3 times daily 120-160 mg LA daily Range: 60-320 mg/d	10 40	<ul style="list-style-type: none"> • CI: asthma, uncompensated heart failure, low HR (<50 BPM), low BP (<90 mm Hg)⁷ • SE: wheezing, headache, dizziness, drowsiness, and insomnia; decreased HR and BP • Lower amplitude not frequency of tremors • Stronger evidence for propranolol, a nonselective β-blocker
	Metoprolol • Lopresor, generic	50-100 mg twice daily 100 mg SR daily	15	
Anticonvulsants • Primidone is a first-line option in moderate to severe limb ET, especially for those who cannot tolerate β -blockers (primidone more effective than phenobarbital) ^{8,9} • Others second-line	Primidone • Mysoline, generic	62.5 mg at bedtime (increase by 62.5 mg every 7 d) 125-250 mg 3 times daily Range: \leq 250-1000 mg/d	10 10-12	<ul style="list-style-type: none"> • SE: vertigo, ataxia, unstable gait, drowsiness, headache, polyuria, and rash; start with low dose • Combination propranolol and primidone occasionally useful • Effective in trials but high dropout rates and poor tolerance^{10,11} • SE: dizziness, unstable gait, drowsiness, decreased weight, paresthesia, confusion, and difficulty with word finding • Limited trials; efficacy inconsistent¹²⁻¹⁴ • SE: sedation, dizziness, fatigue, drowsiness, and decreased libido; abuse potential¹⁵
	Topiramate • Topamax, generic	100-200 mg twice daily (Start: 25 mg twice daily to limit SE)	100-150	
	Gabapentin • Neurontin, generic	400-600 mg 3 times daily (Start: 100-200 mg to limit SE)	66-115	
Benzodiazepines • Intermittent use for stressful situations that make tremor worse	Clonazepam • Rivotril, generic	0.25-0.5 mg 3 times daily (up to 6 mg/d but increases sedation)	16	<ul style="list-style-type: none"> • Limited benefit for tremor, but has hypnotic effect and might help decrease anxiety • SE: tolerance, falls, dependence, daytime sedation, and abuse potential
	Alprazolam • Xanax, generic	0.25-0.5 mg 3 times daily (average 0.75 mg/d)	16	
Other options	Amantadine, atenolol, botulinum toxin A, clonidine, clozapine, flunarizine, levetiracetam, ¹⁶ methazolamide, phenobarbital, pregabalin, ¹⁷ sotalol	Varies	Varies	None

BP—blood pressure, BPM—beats per minute, CI—contraindications, ET—essential tremor, HR—heart rate, LA—long acting, SE—side effects, SR—sustained release.


Data from Jensen and Regier⁴ and Lyons and Pahwa.⁵

especially because primidone is an effective alternative. The combination of primidone and propranolol has also been shown to provide benefits superior to those of either drug alone (with no additional adverse effects).¹⁹ Thus, simply adding primidone to Mr W.'s current regimen without holding the metoprolol would be a reasonable option.

One of the recognized difficulties with primidone is a high rate of intolerable side effects, especially in the elderly. The most common side effects (which sometimes resolve with continued use) are nausea, malaise, and fatigue. Other common side effects include ataxia and vertigo. Low-dose initiation and slow titration to the lowest effective dose are recommended to help limit these troublesome side effects (Table 1⁴⁻¹⁷). If used, Mr W. should be informed that primidone is a central nervous system depressant and should not be used in combination with alcohol. When initiating primidone, it is important to recognize that it induces cytochrome P450 isoenzymes and is therefore capable of increasing the hepatic clearance of many drugs. Consulting a clinical pharmacist or drug interaction resource would help to identify possible drug interactions. In Mr W.'s case, the increased clearance of doxycycline might make it less useful in treating any future COPD exacerbations. Additionally, it would also be important to recognize that MAOIs, like his tranylcypromine, might inhibit primidone metabolism, potentially resulting in increased central nervous system depression. This would not preclude the use of primidone, but a reduced dose might be required.

Mr W.'s observation that pain seems to worsen his symptoms is consistent with reports in the literature that symptoms might be exacerbated by physical and emotional stress, as well as by sleep deprivation.²⁰

Bringing evidence to practice

- Low primidone doses of 250 mg daily might be better tolerated and equally as effective as or more effective than high doses (ie, 750 mg daily).²¹
- Primidone appears to be superior to its metabolite phenobarbital in direct comparisons.^{22,23}
- Both primidone and propranolol are effective in essential limb (ie, hand) tremor.^{8,9} Propranolol might also be more effective for head tremor.⁶
- Other drugs, such as anticonvulsants (eg, gabapentin, topiramate, pregabalin) and benzodiazepines, might be useful in select patients, although side effects are often an issue (Table 1⁴⁻¹⁷). 

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