### Summary

**Search methodology / Databases searched**
PubMed (1960’s to 8/2005)
Product information inserts
Book chapters written or edited by the authors

**Inclusion/exclusion criteria**
N/A

**Types of tremor**
Tremor is usually classified according to the behavior in which it occurs

- **Action tremor**
  - postural
  - kinetic
  - varies widely in amplitude and frequency (4-12 Hz)
  - occurs with maintained posture or movement

- **Intention tremor**
  - terminal kinetic tremor (<5Hz)
  - larger amplitude during the terminal portion of a target-directed movement

- **Resting tremor**
  - usually 4-6 Hz
  - occurs with the limb supported against gravity
  - decreases with movement

**Drugs associated with tremor types**

<table>
<thead>
<tr>
<th>Type of Tremor</th>
<th>Drugs Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action tremor</td>
<td>amitriptyline, lithium, -SSRIs, valproic acid, salmeterol, haloperidol, amphotericin beta, -tetrabenazine, -cimetidine, -cytarabine, -thyroxine</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>vidarabine, -lithium, -salbutamol, salmeterol, -cytarabine</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>co-trimoxazole, -medroxyprogesterone, -amphotericin beta, -haloperidol, -SSRIs, -thiroidazine, -lithium, -cinnarizine, -haloperidol, -reserpine, -tetrabenazine</td>
</tr>
</tbody>
</table>

**Diagnosis of drug-induced tremor**
Difficult to differentiate between drug that has enhanced underlying tremor or has initiated the tremor
If the patient is receiving multiple medications that are associated with tremor, it is difficult to identify the single drug associated with the tremor
Requires thorough history and physical exam
- exclude other medical causes of tremor (hyperthyroidism, hypoglycemia)
- identify a temporal relation to the start of therapy with a given drug
- determine a dose response relationship
- identify whether there is a lack of tremor progression (that would be associated with Parkinson’s or essential tremor)

**Patients at risk**
Older age is the most important risk factor
Metoclopramide-induced parkinsonism is more severe in the setting of renal failure
Liver failure, metabolic derangements and CNS structural lesions predispose patients to drug induced or drug exacerbated tremors
Mood and anxiety substantially affect manifestation
Polypharmacy plays a part in many cases (additive effects)

**Principles in treatment of drug-induced tremor**
If the tremor does not affect social or occupational functioning, it is acceptable to monitor
If the causative drug provides significant benefit, the morbidity must be weighed against the benefit
Dose reduction or switching to an effective, less tremorogenic drug may be an alternative

**Principles of treatment**
If the tremor inducing drug cannot be switched or discontinued, it may be possible to add a tremor-reducing drug such as propranolol in action tremor
Anticholinergics or amantadine can also improve drug induced resting tremor

### Tremor inducing drugs

**Antiarrhythmics**
Amiodarone-induced tremor is reported in about one third of patients
- it is postural and intentional, resembling essential tremor
- tremor can emerge at any time during therapy, is dose dependent and typically improves within 2 weeks of dose reduction or discontinuation

**Antibiotics, antivirals and antifungals**
Co-trimoxazole causes both resting and postural tremor
- resolves within several days after discontinuation

**Antidepressants and mood stabilizers**
TCAs: amitriptyline and imipramine
- amitriptyline induced postural tremor may improve over time (or may lead to discontinuation)
- imipramine induced tremor responds to beta-adrenergic blockade
Immunosuppressants and immunomodulators
Ciclosporin
-estimated 40% incidence of postural and intention tremor
-usually mild to moderate
-correlated with higher doses
Tacrolimus
-associated with liver transplant
-severe, but ameliorated with dose reduction
-also associated with rheumatoid arthritis (9%)
Interferon alfa
-estimated 22% incidence in melanoma treatment
-n = 1 elderly patient associated with chemotherapy

Theophylline and aminophylline
Meta-analysis of use in COPD showed no tremor increase
-theophylline may improve essential tremor
-can precipitate resting and postural tremors (most commonly as drug induced parkinsonism)
(due to agent, dose, and underlying susceptibility)
-risk factors for drug induced parkinsonism

Tremor inducing drugs (continued) Bronchodilators
Salbutamol
-estimated 7% to 20% incidence
-dose related and may occur more commonly with oral dosing
Salmeterol
-estimated 1.7% incidence (50 μg/bid)
-estimated 5.7% incidence (100 μg/d)
Chemotherapeutics
Thalidomide
-estimated 36% incidence (mild to moderate and reversible)
Cytarabine
-intention tremor can occur and fine motor skills and handwriting can be impaired for up to 2 years in children
-cerebellar toxic effects in older patients
-estimated 8% to 23% incidence (most commonly at higher doses)
-high risk in patients with prior neurological deficit or hepatic abnormalities
Ifosfamide (transient tremor)
Vincristine (n = 1; coarse tremor)
Cisplatin (mild tremor in hypomagnesemic patients)
Tamoxifen (dose limiting toxic effects are neurological, including tremor)

Drugs of misuse
Not summarized

Gastrointestinal drugs
Metoclopramide
-parkinsonian resting tremor
-more common in patients with renal failure
-dose reduction recommended
-essential-like tremor (responds to ethanol)
Cimetidine (n = 3 exacerbated action or postural; improved with propranolol)
Misoprostol (n = 1 seen in high dose)
Bismuth salts (tremor can be both acute and chronic)

Hormones
Levothyroxine (overdose)
-thyrotoxic tremor responds to nadolol
-respons to treatment of thyrotoxicosis by carbimazole
Medroxyprogesterone (associated with treatment of advanced breast cancer; not with injectable form used for birth control)
Epinephrine and norepinephrine
-enhance physiological tremor

Antiepileptic drugs
Valproic acid
-resembles essential tremor and may exacerbate underlying tremor
-estimated 25% incidence (80% may show evidence of tremor on accelerometry recordings)
-typically action or postural type, although rest tremor may occur
-seems to be dose related and abates with dose reduction
-more pronounced with standard preparation than controlled release formulations
-propranolol, amantadine or acetazolamide may ameliorate sx
Few reports of tremor with other antiepileptic drugs
Tiagabine
-association in a dose dependent manner
-21% = 56 mg; 14% = 32 mg
Gabapentin (estimated 6% to 8% incidence)
Oxcarbazepine (estimated 4% incidence)
Lamotrigine (estimated 4% incidence)
- n = 1 disabling when added to valproic acid
Antiepileptic drugs seem to be useful for essential tremor and other forms of tremor
-primidone first line for essential tremor
-carbamazepine may improve cerebellar tremors
-gabapentin effective in essential and orthostatic tremor
-topiramate somewhat effective in essential tremor

Conclusion: Drug induced tremor is an important clinical problem experienced by many patients that may be overlooked by treating clinicians. Although psychotropic drugs are commonly implicated as a cause of drug induced tremor, there are many non-psychotropic drugs that can cause or exacerbate tremors. In many instances, drug induced tremor improves or abates when the drug is stopped. Beta adrenergic antagonists may reduce various forms of tremor in some cases.