Drug-induced tremors

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Tremor is a common complaint for many patients. Caffeine and β-adrenergic agonists are well-recognised drugs that cause or exacerbate tremors. Other tremorogenic drugs, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, are less well recognised. Recognition of the drugs that can cause or exacerbate tremors can help prompt diagnosis, avoids unnecessary tests, and allows clinicians to quickly take corrective action (usually by discontinuing the tremor-inducing drugs). The aim of this review is to provide clinicians with current information on drugs that are associated with tremor and the correct treatment of these drug-induced tremors.

Types of tremor

Tremor is usually classified according to the behaviour in which it occurs.[1] Action tremor (including postural and kinetic tremor) varies widely in amplitude and frequency (4–12 Hz) and occurs with maintained posture or movement. Intention tremor is terminal kinetic tremor (typically <5 Hz) with larger amplitude during the terminal portion of a target-directed movement. Resting tremor is usually 4–6 Hz, occurs with the limb supported against gravity, and decreases with movement. The table shows the main drugs associated with each tremor type.

Diagnosis of drug-induced tremor

Many clinicians find it difficult to determine whether a drug causes tremor or has simply enhanced a patient's underlying tremor, given that tremor is a highly prevalent disorder and it occurs in all human beings to some degree (physiological tremor). In addition, many patients are receiving multiple medications that can cause or exacerbate tremor, and the identification of a single drug as causative is difficult, if not impossible.

Differentiation of drug-induced tremor from other forms of tremor is important and requires a thorough history and physical examination of the patient. Several factors aid clinicians in the diagnosis of drug-induced tremor: (1) exclusion of other medical causes of tremor (eg, hyperthyroidism, hypoglycaemia); (2) a temporal relation to the start of therapy with the drug; (3) a dose-response relation (ie, increasing the drug dose worsens the tremor, or decreasing the dose ameliorates the tremor); and (4) lack of tremor progression, unlike tremors in Parkinson's disease and essential tremor. Drug-induced tremor is symmetric for most drugs, but in the setting of drug-induced parkinsonism (DIP), patients commonly develop unilateral resting tremor.[3,4] The principles of the diagnosis of drug-induced tremors are shown in panel 1.

Patients at risk

There are multiple risk factors for drug-induced tremor, older age being the most important. Tremor is well known to be more common in elderly people, but perhaps this is because many elderly patients have multiple medical problems that are treated with numerous drugs.

The interaction of patients' underlying illnesses with tremorogenic drugs is important in clinical practice: for instance, metoclopramide-induced parkinsonism is more severe in the setting of renal failure.[5] Liver failure, metabolic derangements, and CNS structural lesions (eg, stroke, multiple sclerosis) predispose patients to drug-induced or drug-exacerbated tremors. Mood and anxiety also substantially affect the manifestation of drug-induced tremor.

Polypharmacy plays a part in many cases of drug-induced tremor. Interaction of antiepileptics can result in raised serum drug concentrations (eg, valproic acid) and

	Action or postural tremor	Intention tremor	Resting tremor
Antiarrhythmics	Amiodarone, mexiletine, procainamide	..	..
Antibiotics, antivirals, and antimycotics	..	Vidarabine	Co-trimoxazole, amphotericin B
Antidepressants and mood stabilisers	Amitriptyline, lithium, SSRIs	Lithium	SSRIs, lithium
Antiepileptics	Valproic acid	..	Valproic acid
Bronchodilators	Salbutamol, salmeterol	Salbutamol, salmeterol	..
Chemotherapeutics	Tamoxifen, cytarabine, ifosfamide	Cytarabine, ifosfamide	Thalidomide
Drugs of misuse	Cocaine, ethanol, MDMA, nicotine	Ethanol	Cocaine, ethanol, MDMA, MPTP
Gastrointestinal drugs	Metoclopramide, cimetidine	..	Metoclopramide
Hormones	Thyroxine, calcitonin, medroxyprogesterone	Epinephrine	Medroxyprogesterone
Immunosuppressants	Tacrolimus, ciclosporin, interferon-alfa	Tacrolimus, ciclosporin	..
Methylxanthines	Theophylline, caffeine	..	..
Neuroleptics and dopamine depleters	Haloperidol, thioridazine, cinnarizine, reserpine, tetrabenazine	..	Haloperidol, thioridazine, cinnarizine, reserpine, tetrabenazine

Additional data from Deuschl et al.[2] MDMA=3,4-methylenedioxymethamphetamine (ecstasy); MPTP=1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; SSRIs=selective serotonin reuptake inhibitors.

Table: **Main drugs known to cause postural, intention, and resting tremors**

tremor. Multiple tremorogenic drugs can have additive effects (eg, β-adrenergic agonists and theophylline in patients with chronic obstructive pulmonary disease).

Principles in the treatment of drug-induced tremor

Once the diagnosis of drug-induced tremor is made, there are several therapeutic choices available to the clinician (panel 1). If the tremor does not affect social functioning or occupation, then it is acceptable just to monitor the patient. If the causative drug provides significant benefit for the patient, then the morbidity of the tremor has to be weighed against the benefit of the drug. If the tremor becomes bothersome to the patient in social or occupational functioning, then it is prudent to try and reduce the dose or stop the drug. Switching to an effective, less tremorogenic drug is a good therapeutic choice for many patients—for example, switching lithium to lamotrigine in a patient with bipolar disorder. Patients with drug-induced resting tremor as a part of DIP should be taken off dopamine-blocking agents if possible, or switched to a more atypical agent. If the tremor-inducing drug cannot be discontinued, the tremor may be treated with a symptomatic medication, such as propranolol, which is effective in some cases of drug-induced action tremor. Anticholinergics or amantadine can also improve drug-induced resting tremor as a part of DIP. Treatment strategies for the most widely prescribed tremorogenic drugs currently in use are shown in panel 2.

***Panel 1:* Diagnostic and therapeutic principles in drug-induced tremor**

Diagnostic history

Was the tremor pre-existing?
Enhanced physiological tremor is the most common drug-induced tremor and many patients have previously unnoticed, undiagnosed tremors
Have other medical causes of tremor been ruled out?
For example, hyperthyroidism, hypoglycaemia, essential tremor, Parkinson's disease
Is there a temporal relation to the start of drug therapy or misuse?
Drug-induced tremors are temporally linked to the start or escalation of therapy
Has the tremor worsened with dose escalation?
Drug-induced tremors typically worsen with dose escalation
In periods of drug abstinence or non-compliance has the tremor abated?
Helps determine whether there is a relation to drug ingestion
Is the tremor worsening over time?
Parkinsonian tremor and essential tremor are usually progressive in nature, and drug-induced tremor is typically not progressive

Treatment questions

Is the tremor bothersome to the patient in social or occupational functioning?
Most drug-induced tremors are mild and monitoring of the patient is prudent
Is the tremor part of drug-induced parkinsonism (resting tremor)?
Discontinue the drug if possible, switch to more atypical neuroleptics, add an anticholinergic agent
Is the drug essential for the patient or are there alternatives?
For example, discontinue metoclopramide and try erythromycin for gastroparesis
Can the dose of the drug be lowered or the drug be discontinued?
For example, reduce lithium dose with maintained bipolar disorder control, or switch patient to a less tremorogenic drug (eg, lamotrigine)
Can a drug be added to mask the tremor due to the first drug?
For example, propranolol for valproic acid-induced tremor in an epileptic patient
Can occupational therapy and lifestyle adaptation improve the patient's life?
Weighted utensils or other adaptive equipment may improve functioning

Tremor-inducing drugs

Antiarrhythmics

Amiodarone is a class III antiarrhythmic, and tremor has been reported by about a third of patients who take this drug.[6–9] Amiodarone-induced tremor is postural and intentional, and resembles essential tremor, typically in the 6–10 Hz range.[8] The tremor can emerge at any time during therapy, is dose-dependent, and typically improves within 2 weeks after dose reduction or discontinuation.[8] Maintenance of the dose at 200 mg daily seems to provide good arrhythmia control while minimising side-effects.[10] However, the mechanism of amiodarone-induced tremor is unknown. Given that amiodarone can cause hypothyroidism and hyperthyroidism, it is important to rule out hyperthyroidism as a cause of tremor in amiodarone-treated patients. Charness and colleagues[8] showed that propranolol reduced tremor in two patients on chronic amiodarone therapy who continued to have tremor despite lowering of amiodarone dose.

Procainamide and mexiletine have also been associated with tremor. Procainamide is a class IA antiarrhythmic that caused severe postural and intention tremor in the arms and head of an elderly man, which recurred on rechallenge in a dose-dependent fashion.[11] Mexiletine is a class IB antiarrhythmic and is associated with tremor, dizziness, and memory loss in up to 10% of patients.[12] Tremor has also been associated with increasing plasma concentrations of mexiletine.[13,14] The mechanism of tremor induction by these antiarrhythmics is unknown.

Antibiotics, antivirals, and antifungals

Antibiotics, antivirals, and antifungals are widely prescribed. However, there are very few reports of tremors due to these drugs. Co-trimoxazole (trimethoprim-sulfamethoxazole), which is used to treat *Pneumocystis carinii* pneumonia in patients with AIDS, can cause tremor.[15–17] It causes both resting and postural tremor and typically resolves within several days after discontinuation of the drug.[15,16] There is also one report of action and postural tremor interfering with the handwriting of an immunocompetent man on co-trimoxazole.[18] The mechanism of co-trimoxazole-induced tremor is unknown.

The antiviral agent vidarabine was associated with intention tremors and so-called gross tremors in two patients treated for herpes zoster.[19] Other investigators

Panel 2: **Treatment strategies for the most common tremorogenic drugs**

Salbutamol
Reduce frequency or discontinue use; consider using longer-acting β-adrenergic agonist

Amiodarone
Screen for hyperthyroidism; reduce dose to 200 mg daily, if possible; consider adding β-adrenergic antagonist

Amitriptyline or tricyclic antidepressants
Allow time to see whether tremor will improve, or discontinue use and consider using an SSRI or β-adrenergic antagonist (may worsen depression)

Caffeine
Reduce caffeine intake

Ciclosporin
Avoid toxic states and consider reducing dose; try another immunosuppressive drug

Ethanol
Reduce intake or abstain from ethanol; use β-adrenergic antagonists; consider carbamazepine for intention tremors

Lithium
Check drug concentrations and reduce dose; change drug (eg, valproic acid, lamotrigine); use β-adrenergic antagonist (may worsen depression)

Metoclopramide
Discontinue use and monitor patient; consider use of erythromycin or domperidone for gastrointestinal motility disorders; monitor patient for signs of parkinsonism

Neuroleptics
Discontinue use or switch to a more atypical neuroleptic; add an anticholinergic drug

Nicotine
Stop using all forms of tobacco or nicotine gum

Selective serotonin reuptake inhibitors
Wait to see if tremor improves over time; reduce dose if depression allows; use β-adrenergic antagonist (may worsen depression)

Tacrolimus (FK-506)
Reduce dose; try another immunosuppressive drug

Valproic acid
Reduce dose; switch to another antiepileptic; use β-adrenergic antagonist

SSRI=selective serotonin reuptake inhibitor.

have reported a propensity for this drug to cause tremor and encephalopathy.[20–22] Tremor emerged 5–7 days after starting therapy and occurred in more patients treated with 20 mg/kg daily than patients on lower doses. The tremors resolved after discontinuation of the drug.[21,22]

Aciclovir is an antiviral drug in common use for herpetic infections. Five of six patients undergoing bone-marrow transplantation developed tremors related to aciclovir therapy.[23] In another study, 11 of 35 patients developed tremors related to aciclovir, with older age and renal dysfunction identified as major risk factors.[23] Tremor associated with aciclovir is dose related and resolves within a few days of discontinuation.[24]

There are rare associations of antifungal drugs with tremor. Amphotericin B was associated with parkinsonian rest tremor in three children being treated for aspergillosis.[25] This drug also precipitated tremor and leukoencephalopathy in patients undergoing treatment for fungal infections.[26] A 200 mg dose of ketoconazole induced tremor in an elderly man, which recurred on rechallenge.[27] In this case, the tremor was acutely associated with dysarthria and diffuse weakness, and symptoms resolved within a day.[27] Tremor was also reported in one of 31 patients who had had bone-marrow transplants taking fluconazole for candida prophylaxis and treatment, but quickly resolved after discontinuation of the drug.[28]

Antidepressants and mood stabilisers

Tricyclic antidepressants are useful drugs for many disorders, including neuropathic pain, headaches, and depression. In a study nearly 30 years ago, amitriptyline was noted to cause a disabling postural tremor of the hands in some patients.[29] More recently, amitriptyline has been shown to increase the central component of physiological tremor.[30] Five of 15 patients taking amitriptyline had increased postural tremor relative to pretreatment based on clinical examination, whereas all 15 patients had increased tremor on accelerometry.[30] Postural tremor may lead to discontinuation of amitriptyline therapy in a few treated patients, and these tremors can improve over time while patients remain on therapy.[30–33] Tremor can also be caused by other tricyclics, and there is evidence that imipramine-induced tremor responds to β-adrenergic blockade.[34]

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat anxiety and depression, largely replacing tricyclic antidepressants in the treatment of these illnesses. Tremor is probably the most common movement disorder induced by these drugs.[35,36] An estimated 20% of patients started on SSRIs develop tremor without having a previous history of tremor.[37,38] A recent report described 21 patients who developed fluoxetine-induced tremors on a mean dose of 26 mg daily.[39] Tremors were typically postural or action in nature, 6–12 Hz, and emerged 1–2 months after therapy has begun. Tremor remitted within 1 month after discontinuation of fluoxetine in ten patients, although it persisted for at least 15 months in 11 patients.[39]

Serotonin syndrome can occur with SSRIs and other drugs.[40] Tremor is commonly an early manifestation in mild and moderate cases of this syndrome, and is more prominent in the legs.[40] SSRI withdrawal syndrome is also characterised by tremulousness, irritability, anxiety, and paresthesias. This syndrome can occur during withdrawal from any SSRI, but is probably more common with SSRIs with shorter half-lives, such as fluvoxamine or paroxetine.[41]

Tremor is the most common movement disorder caused by lithium, and is probably the most frequently

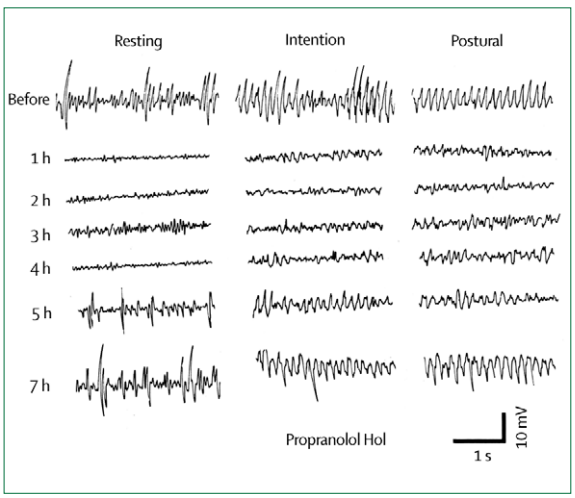

Figure 1: **Accelerometry in a 58-year-old man with valproic-acid-induced tremor for 9 months**
All forms of tremor improve after administration of 20 mg propranolol. Serial recordings show return of tremors over time coincident with propranolol clearance. Adapted with permission of Lippincott, Williams and Wilkins publishers.[57]

encountered drug-induced tremor in clinical practice.[42] One review estimated that about 27% of patients treated with lithium develop tremors, with individual studies showing wide variability from 4% to 65%.[43] Unlike tricyclic-related tremor, one study found that 32% of patients felt that the tremor resulted in non-compliance and some disability.[44] However, for most patients on chronic lithium therapy, the tremor is usually mild and not disabling. Lithium-induced tremor seems to be more common in men than women,[45,46] and occurs most often in elderly patients.[47,48]

The tremor induced by lithium is typically 8–12 Hz, thereby falling into the category of enhanced physiological tremor, and mainly affects the hands.[42] Tremor can occur over a wide range of lithium concentrations, with a correlation to lithium dose possible in some patients.[47] Concomitant therapy with certain drugs, such as antidepressants (tricyclics or SSRIs) or valproic acid, can potentiate the tremorogenic features of lithium.[43,49] Lithium-induced tremor can improve over time, similar to tricyclic-induced tremor.[48]

DIP with rest tremor can occur rarely in patients with bipolar disorder treated with lithium. Elderly, chronically treated patients are at high risk of developing DIP.[50] High serum concentrations of lithium also put patients at risk of DIP, and a reduction in serum concentrations can improve DIP in many patients.[50,51] One patient experienced improvement in lithium-induced DIP with pramipexole treatment.[51] However, this report was anecdotal and more data are needed.

The mechanism of lithium-induced tremor is unknown, so the first step is to reduce the dose or discontinue the drug, if possible. β-adrenergic antagonists ameliorate lithium-induced tremor, and the non-selective β-adrenergic antagonist, propranolol, seems to be the most effective.[52]

Antiepileptic drugs

Valproic acid is the most common antiepileptic drug associated with tremor. Given the wide use of valproic acid for bipolar disorder, epilepsy, and migraine prophylaxis, tremor due to this drug is also very common in clinical practice.[53,54] The clinical and electrophysiological features of valproic-acid-induced tremor resemble essential tremor, and the drug may exacerbate underlying tremor.[55,56] 25% of patients who receive valproic acid may complain of drug-induced tremor. However, 80% of patients may show evidence of tremor on accelerometry recordings.[56] The tremor is typically of action and postural types, although rest tremor may occur, along with head and truncal tremor.[55,56] The tremor seems to be dose related, and with dose reduction the tremor usually abates within several weeks.[55,56] The amplitude of valproic-acid-induced tremor seems more pronounced with standard preparations than with controlled-release formulations.[57] If dose reduction is not possible, then propranolol, amantadine, or acetazolamide may provide benefit for valproate-induced tremor.[58,59] Figure 1 shows the improvement of valproic-acid-induced tremor in a patient treated with propranolol.[58]

There are few reports of tremor with other antiepileptic drugs. The prevalence, type, and severity of tremors with newer drugs is largely unknown as tremor reports are based only on adverse-event reporting in clinical trials and not on accelerometry or other clinical data. Tiagabine was associated with tremor in a dose-dependent manner in 21%, 14%, and 1% of patients taking 56 mg, 32 mg, or placebo, respectively.[60] Tremor occurred in 6·8% of patients taking gabapentin compared with 3·2% of patients on placebo as adjunctive epilepsy therapy.[61] Tremor was an adverse event in 4% of patients on oxcarbazepine monotherapy compared with 0% on placebo, with 1·8% of patients discontinuing the drug due to tremor.[62] Lamotrigine was associated with tremor in 4% of patients (*vs* 1% on placebo) in adjunctive trials.[63] However, there was no difference in tremor incidence in a placebo-controlled monotherapy trial.[63] In postmarketing experience, lamotrigine was associated with a disabling tremor when added to valproic acid in one patient,[64] and with tremors, unsteadiness, and chorea in a child treated for myoclonic jerks.[65]

Antiepileptic drugs seem to be useful for essential tremor and other forms of tremor. Primidone is used extensively as a first-line treatment for essential tremor.[66] Carbamazepine improved cerebellar tremors in a small series.[67] Gabapentin has been reported to be effective in treating essential tremor[68–70] and orthostatic tremor.[71,72] Topiramate seems somewhat effective in the therapy of essential tremor.[73,74] There are conflicting reports regarding the efficacy of levetiracetam in essential

tremor.[75–77] Zonisamide may also have some efficacy for tremor, as reported in a small crossover pilot trial.[78]

Tremor-inducing antiepileptic drugs, such as valproic acid, have multiple mechanisms of action, including reduction of high-frequency neuronal firing and sodium-dependent action potentials, as well as increasing GABAergic neurotransmission. Like valproic acid, two newer antiepileptic drugs (gabapentin and topiramate) that improve essential tremor also increase GABAergic neurotransmission, so this mechanism of action is unlikely to be the cause of valproic-acid-induced tremor.

Bronchodilators

Salbutamol is a β_2-adrenergic agonist that is used daily by millions of patients with chronic obstructive pulmonary disease and asthma, making this drug one of the most prevalent causes of drug-induced tremor. In large clinical trials, 7–20% of patients complained of tremor due to inhaled salbutamol with similar numbers of patients complaining of tremor due to isoprenaline (14%).[79,80] Tremor associated with β_2-adrenergic agonists is dose-related[81,82] and may occur more commonly with oral dosing.

Salmeterol, a β_2-adrenergic agonist with a long half-life, is associated with tremor in 1·7% of patients chronically treated with 50 µg twice daily, although 5·7% of patients receiving a single dose of 100 µg salmeterol reported tremor.[83] In a study of 15 407 patients taking salmeterol in the UK, tremor was reported in one of 128 patients, and one of 256 patients discontinued the drug secondary to tremor.[84]

Although the exact mechanism for tremor induction by β-adrenergic agonists is unknown, there is some evidence that β-adrenergic agonists act directly on muscle.[85] When patients were ischaemically prevented from receiving an infusion of epinephrine in their arm, tremor did not occur in the ischaemic arm.[85] β_2-Adrenergic receptors are located on the plasma membranes of extrafusal fibres and muscle spindles.[86] Stimulation of these receptors by β-adrenergic agonists is thought to enhance physiological tremor by increasing the gain of the γ-loop and by disorganising integrated contraction of muscle fibres.[86] Tolerance to these drugs can develop over time.

Chemotherapeutics

Few chemotherapeutic drugs are tremorogenic. Thalidomide has emerged as a treatment for multiple myeloma, with tremor occurring in 36% (ten of 28) of patients on monotherapy in one trial.[87] Unlike thalidomide-associated neuropathy (commonly irreversible), tremors associated with thalidomide therapy are mild or moderate and reversible in most cases,[87,88] although tremor can be severe in some.[89]

Cytarabine is used to treat various cancers and causes nystagmus, dysarthria, and ataxia because of cerebellar toxicity.[90] Intention tremor can occur,[91] and fine motor skills and handwriting are impaired for up to 2 years after treatment in children treated for leukaemia with cytarabine.[92] Cytarabine seems to damage cerebellar Purkinje cells in the lateral hemispheres.[93] Cerebellar toxic effects can occur in 8–23% of treated patients, and occur most commonly at higher doses in older patients and in patients with prior neurological deficits or hepatic abnormalities.[90,94,95]

Ifosfamide chemotherapy has been associated with transient tremor.[96] Vincristine caused coarse tremor in an elderly woman who was inadvertently given the drug intraventricularly for leukaemia involving the meninges.[97] Cisplatin has been indirectly associated with mild tremor in hypomagnesaemic patients undergoing treatment of testicular cancer.[98] Tamoxifen is an antioestrogenic drug used in the treatment of breast cancer, and in early studies, the dose-limiting toxic effects of tamoxifen were neurological and included tremor.[99]

Drugs of misuse

Whereas ethanol ameliorates some movement disorders (myoclonus-dystonia and essential tremor), it is also associated with multiple forms of tremor. Ethanol can cause postural tremor, a so-called metabolic tremor associated with alcoholic liver disease, and a 3 Hz leg and trunk tremor associated with alcoholic cerebellar degeneration.[100] In one study, 47 of 100 abstinent alcohol users and only three of 100 controls had postural tremor.[101] However, functional disability due to tremor occurred in only 17% of chronic alcohol users. Alcoholic tremor had a frequency of 8·6 Hz and responded well to propranolol.[101]

Cigarette smoking increases tremor amplitude at least two times over all frequencies,[102] and seems to increase tremor independently of age, sex, and anxiety.[103] Smoking-related tremor is probably due to nicotine, as chewing gum containing 4 mg nicotine increased tremor to the same degree as smoking two cigarettes.[103]

In the late 1970s and early 1980s, many designer drugs emerged. A meperidine analogue, 4-propyloxy-4-phenyl-N-methylpiperidine (MPPP), was sold as synthetic heroin on the streets in California. Unfortunately, some chemists attempting to synthesise MPPP made mistakes in their synthetic procedure and this resulted in batches of MPPP contaminated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), an inhibitor of complex I of the mitochondrial electron transport chain that is selectively toxic for dopaminergic neurons of the substantia nigra. MPTP caused an acute-onset chronic DIP in many drug users in the late 1970s and early 1980s.[104] These patients displayed typical akinetic-rigid features in addition to rest tremor, and responded to levodopa.[104] The discovery of MPTP has since led to many advances in basic research and helped the development of animal models of Parkinson's disease.

There are very few reports of tremors related to other drugs of abuse. 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) can cause a serotonin syndrome in some patients. One patient had sustained postural tremors of both arms for at least 10 days after one dose.[105] Another chronic MDMA user developed parkinsonism associated with unilateral rest tremor and bilateral postural arm tremor that was levodopa responsive.[106] Cocaine can also cause chronic movement disorders, including resting tremor and parkinsonism,[107] with resting tremor evident even after 3 months of abstinence in one study of cocaine-dependent patients.[108] Stimulants such as methylphenidate can also cause tremors, particularly in combination with desipramine.[109]

Gastrointestinal drugs

Metoclopramide is a dopamine-receptor blocking drug in widespread use for gastro-oesophageal reflux disease and gastroparesis, despite well-documented side-effects. This drug can induce a parkinsonian resting tremor[110] or an essential-like tremor that responds to ethanol.[111] Metoclopramide-induced parkinsonism and tremor are more common in patients with renal failure than in those without renal failure, and dose reduction is prudent in this setting.[4] Metoclopramide may cause tremor by acting as a cholinomimetic tremorogen[112] or due to its dopamine-receptor-blocking properties.

Cimetidine (a histamine H_2 receptor antagonist) was shown to exacerbate action or postural tremors in three patients in one report, and propranolol treatment significantly improved tremor in all three patients.[113] The investigators proposed that histaminergic pathways may normally be involved in suppression of physiological and essential tremors.[113]

Misoprostol (a prostaglandin E1 analogue used to treat gastric ulcers and other disorders) has been associated with tremor and many other symptoms in the setting of acute toxic effects.[114] This occurred after an elderly woman accidentally ingested 3 mg misoprostol (15 times the maximum recommended dose).[114]

Bismuth salts were first reported to cause an encephalopathy with myoclonus and ataxia in 1974.[115] Although most features of bismuth encephalopathy are reversible, the associated tremor can be both acute and chronic in many patients.[115,116] The mechanism of bismuth-induced encephalopathy and tremor is unknown, but necropsies have shown higher concentrations of bismuth in grey matter relative to white matter, perivenular lymphocytic infiltration, and abundant intracytoplasmic lipofuscin.[117]

Hormones

Tremor is common after levothyroxine overdose.[118] The dietary supplement tiratricol is sold as a weight loss aid and has resulted in symptomatic hyperthyroidism with tremor in one elderly patient.[119] Peak tremor frequency in thyrotoxicosis seems to be equal to that of physiological tremor in healthy individuals, although the power of thyrotoxic tremor is increased.[86] Thyrotoxic tremor responds to β-adrenergic antagonists such as nadolol and to treatment of the thyrotoxicosis by carbimazole.[86]

Medroxyprogesterone acetate was commonly associated with tremor in the treatment of advanced breast cancer.[120] However, tremor is not listed as an adverse event in the product information of the injectable form of this drug that is used for birth control (depo-provera).[121]

Epinephrine and norepinephrine have been extensively studied in human beings and seem to act by enhancing physiological tremor at the level of the muscle.[85,86] In a recent study, tremor was noted as a side-effect in all children injected with an epinephrine preparation used for patients at risk for anaphylaxis.[122]

Subcutaneous injection of 100 IU sodium calcitonin caused a widespread fine tremor affecting the head, arms, and legs of a 35-year-old woman undergoing treatment of reflex sympathetic dystrophy.[123] The tremor lasted 1 h and was not due to changes in blood calcium concentrations, recurred with rechallenge, and did not occur after injection of placebo.[123]

Immunosuppressants and immunomodulators

Ciclosporin and tacrolimus are calcineurin inhibitors and are widely used in immunosuppressive regimens to help prevent rejection of transplanted organs, and in the treatment of autoimmune disorders such as myasthenia gravis (ciclosporin). A recent review of ciclosporin neurotoxicity reported that postural and intention tremor are reported in up to 40% of patients.[124] Ciclosporin-induced tremor is usually mild to moderate, generalised in nature, and correlated with higher blood concentrations. Some patients experience tremor even at lower doses, although dose reduction is not always required.[124]

Tacrolimus was associated with tremor in the first reports of neurological toxicity related to the drug after liver transplantation.[125,126] Tremor was seen in eight of 22 paediatric liver transplant patients on the drug,[126] and occurred in ten of 44 patients undergoing orthotopic liver transplantation.[125] The tacrolimus-associated tremor described in the latter ten patients affected the hands, was severe, interfered with handwriting, and worsened with action.[125] Dose reduction ameliorated the tremor, although several patients continued to have "fine, nonsignificant" tremors.[125] Patients treated with tacrolimus for rheumatoid arthritis also had tremor as a common side-effect, occurring in 9% (81/896) of patients.[127]

22% of treated patients developed significantly increased action tremor in a trial of interferon alfa for melanoma.[128] Long-term interferon alfa-2a use has been associated with a slow facial tremor in a middle-aged woman with leukaemia.[129] Interferon-alfa chemotherapy was also associated with parkinsonism in an elderly

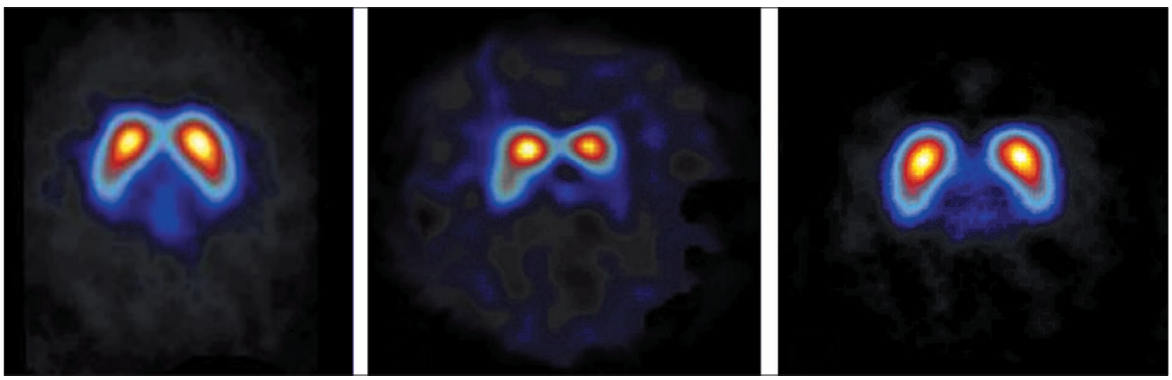

Figure 2: **Striatal dopamine transporter imaging with [^{123}I]β-carboxymethyoxy-3-β-(4-iodophenyl) tropane**
Left: a healthy control patient. Middle: a patient with Parkinson's disease. Right: a patient with drug-induced parkinsonism. Courtesy of Dr D L Jennings (Institute for Neurodegenerative Disorders, New Haven, CT, USA).

man,[130] perhaps because of its known action of inhibiting dopaminergic systems.

Methylxanthines

Theophylline and aminophylline are used in the treatment of pulmonary disease, and aminophylline augments the strength of essential tremor after intravenous infusion.[131] However, tremor was not significantly increased due to these drugs in a recent meta-analysis of chronic obstructive pulmonary disease clinical trials.[132]

There is some evidence that theophylline (an adenosine A_{2A} antagonist) may improve essential tremor, and 150 mg theophylline daily can quantitatively reduce tremor to the same extent as 80 mg propranolol daily. Tremor reduction required 2 weeks of theophylline treatment and only 1 week of propranolol therapy.[133]

In a study by Koller and co-workers,[134] caffeine subjectively worsened tremor in 2% of controls, 8% of patients with essential tremor, and 6% of patients with Parkinson's disease. However, clinical studies have failed to show an aggravation of physiological, essential, or parkinsonian tremor by 325 mg oral caffeine.[134] In accelerometry studies, 450 mg caffeine daily seems to increase finger tremor in fasting patients but not in the same patients on their usual diet.[135] In another accelerometry study, a dose of caffeine equal to two or three cups of coffee increased whole-arm tremor in healthy individuals.[136]

Neuroleptics and dopamine-depleting agents

Neuroleptics are dopamine-receptor-blocking drugs used in the treatment of psychosis, tics, and many other disorders. These drugs can precipitate resting and postural tremors, most commonly as part of DIP.[137,138] DIP may affect 15–60% of patients treated with typical neuroleptics, depending on the neuroleptic used, the dose given, and patients' underlying susceptibility.[138] Risk factors for DIP include older age, female sex, familial predisposition, and AIDS.[138]

Most patients who develop DIP are on sufficient doses of dopamine antagonists to block 80% of central dopamine receptors.[139] Tremor heralded DIP onset in 35% of patients in a large study of 3775 patients, with 60% of patients manifesting tremor at some point during their illness.[3] Tremor onset was typically in the arm and was asymmetric. Thioridazine and fluphenazine were more likely to induce tremor than chlorpromazine.[3] Depot preparations of typical neuropleptics are more likely to cause DIP over time in patients with schizophrenia.

Newer, more atypical neuroleptics (ie, risperidone, olanzapine, quetiapine, and ziprasidone) are less likely to cause DIP, although at higher doses even these drugs can cause DIP. DIP is typically completely reversible unless the patient has underlying Parkinson's disease that was unmasked by neuroleptic exposure. Patients with DIP have normal β-carboxymethyoxy-3-β-(4-iodophenyl) tropane single-photon emission CT images indicating a postsynaptic dopaminergic deficit,[140] unlike in Parkinson's disease in which there is a presynaptic loss of the dopamine transporter as substantia nigra neurons die (figure 2). The rate of reversibility of DIP depends on many factors and can take anywhere from several months up to 15 months. Discontinuation of neuroleptics or switching to a more atypical agent is best in patients who can tolerate coming off these drugs. Patients who must remain on more typical neuroleptics can be treated with anticholinergics or amantadine with improvement in tremor and other parkinsonian symptoms. Prophylactic concomitant use of antiparkinsonian drugs is controversial and unfounded on the basis of current data (except perhaps in high risk groups, such as patients with AIDS).

Tardive tremor can also occur after long periods on neuroleptic therapy.[141] Tardive tremor is distinct from rest tremor in DIP in that tardive tremor improves with neuroleptic drugs or dopamine-depleting therapy.[141] Tardive tremor is larger in amplitude than parkinsonian tremor and can interfere with activities of daily living.

Cinnarizine and flunarizine are calcium channel antagonists with additional dopamine-blocking properties. These drugs are used in the treatment of vertigo and are often associated with DIP and rest or postural tremor. 51% of patients with cinnarizine-induced parkinsonism develop postural tremor with 37% having bilateral rest tremor.[142] The tremorogenic action of these drugs is probably due to their ability to deplete dopamine presynaptically and to block postsynaptic dopamine receptors.[142]

Dopamine-depleting drugs can also cause tremor and parkinsonism. Tetrabenazine is used worldwide for hyperkinetic movement disorders and can cause resting tremor, parkinsonism, and depression.[143] Methyldopa and reserpine are antihypertensive dopamine-depleting agents that can cause resting tremor, parkinsonism, and depression.[144,145]

Other drugs

Whereas most β-adrenergic antagonists reduce various forms of tremor, pindolol may induce or exacerbate tremors. In one report, five patients treated with pindolol developed fine tremor of the arms and hands.[146] Another man developed tremor of both hands while taking 30 mg pindolol twice daily.[147] Pindolol-induced tremor is postural and action in nature, and in one patient the frequency was 6·5 Hz.[147] Tremor onset typically occurred within hours or days and resolved 24–72 h after stopping the drug in most patients.[146] Tremor developed in patients taking as little as 2·5 mg daily or as much as 60 mg daily.[146,147] In a controlled trial of pindolol versus propranolol in essential tremor, pindolol actually increased tremor amplitude.[148] Pindolol-induced tremor is more likely to be secondary to its partial β-adrenergic agonist activity.[146,147]

Ephedrine, pseudoephedrine, and phenylpropanolamine are sympathomimetic drugs that can induce tremor in some patients.[149,150] These drugs were typically found in prescribed and over-the-counter cold and appetite suppressant preparations, although their availability has now been restricted in many countries. Acute amphetamine-like CNS effects (including tremors) were noted in patients taking phenylpropanolamine.[149] Phenylpropanolamine (November, 2000) and ephedrine (February, 2004) were removed from the market in the USA due to increases in cardiovascular and cerebrovascular risk. Pseudoephedrine remains in use for colds and appetite suppression. 39% of patients complained of tremor in a study of pseudoephedrine and loratadine combination therapy for allergic rhinitis.[150]

Conclusions

Drug-induced tremor is an important clinical problem experienced by many patients. Treating clinicians can overlook pre-existing tremor before patients begin taking a tremorogenic drug. It is therefore important to look for an underlying cause for tremor (eg, physiological tremor, essential tremor, Parkinson's disease, cerebellar dysfunction, or psychogenic tremor) in patients with suspected drug-induced tremor. A temporal relation to the start of pharmacotherapy is very useful in making the diagnosis of drug-induced or drug-exacerbated tremor. Increased knowledge of tremorogenic drugs will help avoid needless tests and studies in these patients.

Although psychotropic drugs, such as SSRIs, tricyclic antidepressants, neuroleptics, and lithium, are commonly implicated as a cause of drug-induced tremor, there are many non-psychotropic drugs that can cause or exacerbate tremors. Most tremor-inducing drugs cause postural tremor, although many drugs can also cause resting and intention tremors. Fortunately, in many instances, drug-induced tremor improves or abates when the drug is stopped. The list of tremorogenic drugs is only going to grow as new drugs are introduced and used in a growing population.

Search strategy and selection criteria

References for this review were identified by searches of PubMed using the terms "tremor", "tremorogenic", "drug", "medication", "drug-induced", "medication-induced", generic names for the major drug classes (eg, "antiarrhythmics", "antiepileptics"), and tremorogenic drugs (eg, "amiodarone", "valproate"). Additional references and book chapters that were cited in relevant articles were also used. Most papers used in this review were published in English, although non-English articles with English abstracts were included if relevant. The search covered articles in the PubMed database from the 1960s to August, 2005. Product information inserts were also used to identify tremor as an adverse event for many medications. Book chapters that were written or edited by the authors were also used to prepare this review.

Authors' contributions

JCM and KDS designed and developed the framework of the review and approved the final version. JCM did the literature search, wrote the initial draft of the review, and designed the panels. KDS made additions to the review and edited it for content.

Conflicts of interest

We have no conflicts of interest.

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