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Tremor and Other Hyperkinetic Movements

Reviews

Insights into Pathophysiology from Medication-induced Tremor

John C. Morgan[1*], Julie A. Kurek[1], Jennie L. Davis[1] & Kapil D. Sethi[1]

[1] Movement Disorders Program Parkinson's Foundation Center of Excellence, Department of Neurology, Medical College of Georgia, Augusta, GA, USA

Abstract

Background: Medication-induced tremor (MIT) is common in clinical practice and there are many medications/drugs that can cause or exacerbate tremors. MIT typically occurs by enhancement of physiological tremor (EPT), but not all drugs cause tremor in this way. In this manuscript, we review how some common examples of MIT have informed us about the pathophysiology of tremor.

Methods: We performed a PubMed literature search for published articles dealing with MIT and attempted to identify articles that especially dealt with the medication's mechanism of inducing tremor.

Results: There is a paucity of literature that deals with the mechanisms of MIT, with most manuscripts only describing the frequency and clinical settings where MIT is observed. That being said, MIT emanates from multiple mechanisms depending on the drug and it often takes an individualized approach to manage MIT in a given patient.

Discussion: MIT has provided some insight into the mechanisms of tremors we see in clinical practice. The exact mechanism of MIT is unknown for most medications that cause tremor, but it is assumed that in most cases physiological tremor is influenced by these medications. Some medications (epinephrine) that cause EPT likely lead to tremor by peripheral mechanisms in the muscle (β-adrenergic agonists), but others may influence the central component (amitriptyline). Other drugs can cause tremor, presumably by blockade of dopamine receptors in the basal ganglia (dopamine-blocking agents), by secondary effects such as causing hyperthyroidism (amiodarone), or by other mechanisms. We will attempt to discuss what is known and unknown about the pathophysiology of the most common MITs.

Keywords: Medication-induced tremor, drug-induced tremor, pathophysiology

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*To whom correspondence should be addressed. E-mail: jmorgan@augusta.edu

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Introduction

It is often difficult to determine if a medication has caused a tremor or has simply enhanced a patient's underlying tremor, given that tremor is prevalent and occurs in all to some degree (physiological tremor). In addition, patients often take multiple medications that can cause or exacerbate tremor, and the identification of a single medication as causative is difficult, if not impossible. Differentiation of medication-induced tremor (MIT) from other forms of tremor is important and requires a thorough history and physical examination of the patient. There are several important considerations in the differential diagnosis of MIT: 1) exclusion of other medical causes of tremor (e.g., hypoglycemia, hyperthyroidism); 2) a temporal relation to the initiation of the drug is helpful; 3) a dose–response relationship (i.e., increasing the medication dose worsens the tremor, or decreasing the dose improves the tremor); and 4) lack of tremor progression, unlike tremors in essential tremor (ET) or Parkinson's disease (PD).[1] MIT is also typically symmetrical, but in the setting of drug-induced parkinsonism (DIP), a presentation with unilateral resting tremor is not uncommon.[2,3]

Tremor can occur as a side effect of multiple medications in the treatment of numerous diseases, making it very common in clinical practice. MIT can range in severity from a minor nuisance in some to

disabling in others. In some patients the tremor may not appear unless an individual is predisposed to the tremor in question. There are multiple risk factors for MIT, with older age being the most important in many studies.[1] Tremor is well known to be more common in elderly people, perhaps due to multiple medical problems that are treated with numerous drugs. The interaction of patients' underlying illnesses with tremorogenic drugs is also important: for instance, metoclopramide-induced parkinsonism is more severe in the setting of renal failure.[4] Liver failure, metabolic derangements, and central nervous system (CNS) pathology (e.g., traumatic brain injuries and infarcts) predispose patients to MIT. Anxiety and mood states can also substantially affect the manifestation of MIT. In some cases, treatment with medications, such as dopamine-blocking agents (DBAs) or valproic acid, can reveal underlying presynaptic dopamine deficiency and subclinical PD due to loss of substantia nigra dopaminergic neurons.[5,6]

Polypharmacy plays a part in many instances of MIT. Interaction of antiepileptics can result in raised serum drug concentrations (e.g., valproate) and tremor. Tremor due to medications is frequently temporally associated with starting medication and can occur in the setting of "therapeutic" blood levels as well as toxic states (e.g., lithium).[7–9] Some common medications that can cause or enhance tremors include amiodarone, antidepressants, β-adrenergic agonists, cyclosporine, DBAs, lithium, tacrolimus, theophylline, and valproic acid.[1] Multiple tremorogenic drugs can have additive effects (e.g., albuterol and theophylline in patients with asthma).

In some settings it is prudent to watch and wait after starting a new medication because many MITs can become less bothersome to a patient or even improve over time.[10–14] This would certainly apply if a patient really needed to take a particular drug for their medical condition (e.g., cyclosporine or tacrolimus in the setting of kidney transplantation). Alternatively, a controlled-release preparation may cause less tremor in a patient due to less peak-to-trough variability as has been shown for controlled-release versions of valproic acid and, more recently, tacrolimus.[15,16] Luckily, the vast majority of MITs respond to dose reduction or stopping the offending drug. Exposure to toxic levels of certain drugs (e.g., ethanol, lithium, etc.) for longer periods of time can lead to permanent tremors, especially if they affect the cerebellum.

In this manuscript we will discuss insights into the pathophysiology of tremor by highlighting proposed mechanisms of MIT for the following better-known tremorogenic medications: amiodarone, amitriptyline, β-adrenergic agonists, cyclosporine, DBAs, fluoxetine, lithium, tacrolimus, theophylline, and valproic acid. Table 1 illustrates the major tremorogenic drugs discussed in this paper and the phenomenology of the tremor seen with these different medications/drugs. We will also briefly discuss tremors that can occur in withdrawal states with certain drugs such as ethanol and propranolol. While the frequency and epidemiology of MIT due to these drugs is fairly well characterized, there are very few data on the mechanisms of how these drugs induce tremors. MITs can originate from both central and peripheral mechanisms, but it appears most MITs are a result of enhancement in physiological tremor.

Methods

For this review, we first identified the major classes of drugs associated with tremor and the most common offending drugs by class.[1] We then searched PubMed on November 2016 for manuscripts using the search terms "tremor" and the drug (or class of drug) of interest

Table 1. **Common Medication-induced Tremors and Typical Tremor Phenomenology**

Medication Class	Action or Postural Tremor	Intention Tremor	Resting Tremor
Antiarrhythmics	Amiodarone	–	Amiodarone
Antidepressants/mood stabilizers	Amitriptyline, lithium, SSRIs	Lithium	Lithium, SSRIs
Antiepileptics	Valproic acid	–	Valproic acid
β-Adrenergic agonists	Albuterol, salmeterol	Albuterol, salmeterol	–
Chemotherapeutics	Cytarabine	Cytarabine	–
Drugs of abuse	Cocaine, ethanol	Ethanol	Cocaine, ethanol
Gastrointestinal drugs	Metoclopramide	–	Metoclopramide, promethazine
Hormones	Thyroxine, epinephrine	Thyroxine, epinephrine	–
Immunosuppressants	Tacrolimus, cyclosporine	Tacrolimus, cyclosporine	–
Methylxanthines	Theophylline	–	–
DBAs/dopamine depleters	Haloperidol, tetrabenazine	–	Haloperidol, tetrabenazine

Abbreviations: DBA, Dopamine-blocking Agent; SSRI, Selective Serotonin Reuptake Inhibitor.

with the following results: 1) valproic acid yielding 137 citations, 2) theophylline yielding 105 citations, 3) tacrolimus yielding 81 citations, 4) cyclosporine yielding 107 citations, 5) lithium yielding 255 citations, 6) amitriptyline yielding 49 citations, 7) tricyclic antidepressants yielding 192 citations, 8) amiodarone yielding 33 citations, 9) beta-adrenergic agonists yielding 607 citations, 10) dopamine-blocking agents (DBAs)/antipsychotics yielding 731 citations, and 11) selective serotonin reuptake inhibitor yielding 267 citations.

We reviewed the titles of each of these papers for appropriateness and eliminated all non-English language papers. We especially looked for keywords in the title or abstract of these manuscripts that dealt specifically with tremor and the mechanism of the tremor. Full papers dealing with tremor due to medications of interest were obtained and reviewed for this review. In some instances, additional manuscripts were identified from these articles (if relevant) and pulled for review as well. From our search and review, we focused on medications with the most data: amiodarone, amitriptyline, β-adrenergic agonists, cyclosporine, DBAs, fluoxetine, lithium, tacrolimus, theophylline, and valproic acid. We also reviewed a small amount of literature looking at drug withdrawal states as a tremor-inducing situation and present our findings in this setting.

Tremor phenomenology

In order to understand the phenomenology of MIT, discussed below, we will briefly review the basics of tremors.[17,18] Tremors are typically characterized by rhythmic oscillations of a body part about a joint and are best classified by the situation in which it occurs. Two major categories of tremor are resting tremor and action tremor. Resting tremor (as typically occurs in DIP or PD) is commonly 4–6 Hz in frequency and occurs when the affected body part is fully supported without ongoing voluntary muscle contraction. Action tremor, in contrast, occurs with voluntary movement and can be divided into postural tremor and kinetic tremor. Postural tremor occurs classically when maintaining the arms in an outstretched position against gravity. Kinetic tremor includes tremor that is task specific or with goal-directed movements. Intention tremor is a subheading of kinetic tremor that is a terminal kinetic tremor (as can be seen when nearing the target on finger-to-nose testing). Finally, isometric tremor is a kinetic tremor that occurs with active muscle contraction against a fixed object.

The majority of MIT are posture holding or kinetic, but some medications (especially lithium, DBAs, valproic acid) can cause resting tremors. PD is a classic cause of resting tremor that typically occurs unilaterally and improves with motion but can recur as re-emergent tremor when a sustained posture is maintained. Resting tremor typically worsens with distraction and goes away during sleep. Physiological tremor is an action tremor that is mediated by both central and peripheral mechanisms.[17,18] It consists of low-amplitude, high-frequency (8–12 Hz) oscillations depending on the stiffness, mass, and other properties of the tremoring body part. The origins of physiological tremor are from several sources including a mechanical component (cardioballistics, subtetanic motor unit firing, and the eigenfrequency), an 8–12 Hz central component, and in some cases an enhancement of the mechanical component by short- and long-loop reflexes.[17,18] In situations where the motor units of a body part become entrained and discharge in groups, physiological tremor becomes enhanced physiological tremor (EPT).[18] The segmental stretch reflex plays an important role in EPT given it helps synchronize motor outflow to produce rhythmical contractions that reinforce the mechanical properties of muscle spindle endings. EPT occurs with withdrawal from ethanol, fever, anxiety, hyperthyroidism, hypoglycemia, shivering due to cold, and other situations.[18] Many MITs are proposed or proven (amitriptyline) to occur by the mechanism of EPT.[10] EPT has the same central and peripheral components of physiological tremor, but the 8–12 Hz central component and muscle stretch reflex play a greater role in generation of the tremor. EPT can be very similar in appearance and characteristics to ET when EPT becomes clinically symptomatic.

Medication-induced tremors: background and pathophysiology

MIT is very common in clinical practice and we attempted to identify the major drugs (as above in Methods) associated with tremor and the identified or proposed mechanism of tremorogenesis. We discuss these drugs in alphabetical order by their major drug class.

Antiarrhythmics

Amiodarone. Amiodarone can cause ataxia, peripheral neuropathy, and tremor in cardiac patients treated for arrhythmias.[19–22] The tremor due to amiodarone may have multiple etiologies. Amiodarone is a class III antiarrhythmic, and tremor has been reported by about a third of patients who take this drug.[19] Amiodarone-induced tremor is postural and intentional, and typically is in the 6–10 Hz range.[19] There are also rare reports of a Parkinsonian resting tremor with amiodarone therapy.[23] Amiodarone-induced tremor is dose dependent, may emerge at any time during therapy, and typically improves within several weeks after dose reduction or discontinuation.[19] Maintenance of the dose at 200 mg daily seems to minimize side-effects while providing good arrhythmia control.[22]

The mechanism of amiodarone-induced tremor is unknown. Amiodarone is known to cross the blood–brain barrier, but amiodarone and its active metabolite, desethylamiodarone, were only detected in the brain at very low levels relative to the lung, pancreas, and adipose tissue.[24] Given that amiodarone can cause hypothyroidism and hyperthyroidism, it is important to rule out hyperthyroidism as a cause of tremor in amiodarone-treated patients. This potential mechanism of causing tremor by inducing hyperthyroidism is unique to amiodarone (outside thyroxine or other thyroid hormone therapy, of course). Propranolol reduced tremor in two patients on chronic amiodarone therapy who had bothersome tremors despite lowering of the amiodarone dose.[19]

Recent research indicates that the incidence of amiodarone-induced neurological side effects may be considerably lower than the third or more of patients reported by some authors. Orr and Ahlskog[25] found that only 2.8% of patients treated with amiodarone in the recent Mayo

Clinic experience developed a neurotoxic side effect and they related this lower incidence of tremor and other side effects to lower doses (now 200 mg per day) of amiodarone in practice over time compared to the past.

Antidepressants/mood stabilizers

Amitriptyline. Tricyclic antidepressants are useful drugs for many disorders, including neuropathic pain, headaches, and depression. In a study nearly 40 years ago, amitriptyline was noted to cause a disabling postural and action tremor of the hands in some patients.[26] Postural tremor may lead to discontinuation of amitriptyline therapy in a few treated patients, but in many cases amitriptyline-induced tremors can improve over time while patients remain on therapy.[10–13]

While most MITs are due to an uncharacterized mechanism, it appears amitriptyline accentuates the central component of physiological tremor.[10] In this study, patients were evaluated for tremor before and after starting amitriptyline for depression or chronic pain syndromes. Fifteen subjects were enrolled and studied with accelerometry and forearm flexor/extensor electromyography (EMG). While there was only an obvious clinical change in approximately one-third of patients treated with amitriptyline, there was an increase in the spectral power of tremor in all 15 subjects by electrophysiological measures.[10] EMG frequencies were in the 8–18 Hz range while accelerometer frequencies were in the 6–11 Hz range and did not change. The frequency bands of significant coherence corresponded with the EMG frequencies and were independent of changes to the hand's resonant frequency by added inertia, indicating the enhanced tremor came from a central process, not a peripheral one.[10] The authors concluded that the increase in the EMG–EMG coherence was indicative of increased drive to the motor units by central mechanisms and by their report this was the first demonstration of enhancement by any drug of the central component of physiological tremor.[10]

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are very commonly prescribed to treat depression and anxiety, largely replacing tricyclic antidepressants in the treatment of these illnesses. While numerous movement disorders have been reported with SSRIs, tremor is probably the most common movement disorder induced by these drugs.[27,28] Approximately 20% of patients started on SSRIs develop tremor without having a previous history of tremor. Serrano-Dueñas[29] described 21 patients who developed fluoxetine-induced tremors on a mean dose of 26 mg daily. Tremors were typically postural or action in nature, 6–12 Hz, and emerged 1–2 months after therapy began. Tremor remitted within 1 month after discontinuation of fluoxetine in 10 patients, although it persisted for at least 15 months in the other 11 patients.[29]

The mechanism for SSRI-induced tremor is unknown, but Serrano-Dueñas has hypothesized that the tremor is due to stimulation of serotonergic receptors found in the inferior olive.[29] He also proposed that overexcitation of the red nucleus and the inferior olivary nuclei could lead to overstimulation of thalamic and cortical neurons and resultant tremor. There is evidence that antagonism at 5HT1c, 5HT2, and 5HT3 receptors by clozapine results in reduction of ET, indicating a possible role of serotonin in the generation or exacerbation of tremor.[30]

In the harmaline-induced tremor model in rats, citalopram was also shown to exacerbate tremors.[31] Pretreatment with citalopram, in a dose-dependent fashion, exacerbated the intensity, duration, and amplitude of harmaline-induced tremor on EMG.[31] There was also a significant decrease in serotonin turnover (5HIAA/5HT ratio) in the brain stem suggesting a possible role of serotonergic impairment in citalopram's augmentation of harmaline-induced tremor. The authors suggested that reduction in serotonergic neurotransmission in the brainstem (inferior olive) is potentially the mechanism for tremor exacerbation in this model.[31]

Serotonin syndrome can occur with SSRIs and other drugs.[32] Tremor is commonly an early manifestation in mild and moderate cases of this syndrome, and is more prominent in the legs.[32] SSRI withdrawal syndrome is also characterized by tremulousness, irritability, anxiety, and paresthesias.[33] This syndrome can occur during withdrawal from any SSRI, but is probably more common with SSRIs with shorter half-lives, such as paroxetine.[33]

Lithium. Lithium-induced tremor is perhaps one of the most commonly encountered MITs in clinical practice.[7–9] Approximately 27% of patients treated with lithium developed tremors in one review, with individual studies showing a wide range of variability from 4% to 65%.[8] Unlike tricyclic antidepressant-related tremor, one study found that 32% of patients felt that lithium-related tremor caused some disability or resulted in non-compliance with therapy.[9] For most patients on chronic lithium therapy the tremor is usually mild and not disabling, however. Lithium-induced tremor occurs most often in elderly patients and appears to be more common in men than women.[14,34–37]

Lithium-induced tremor is typically in the 8–12 Hz range, thereby falling into the category of, EPT and it mainly affects the hands.[7] Tremor can occur over a wide range of lithium concentrations with a correlation to lithium dose possible in some patients.[37] Certain concomitant drug therapies such as tricyclic antidepressants, SSRIs, or valproic acid can potentiate lithium-related tremor.[7,38] As with amitriptyline-induced tremor, lithium-induced tremor can improve over time with continued therapy.[14]

Rarely, lithium can cause DIP and resting tremor in some treated patients; however, this can frequently improve with a reduction in dose of lithium.[7,39] Lithium can sometimes cause long-standing cerebellar tremor in the setting of toxicity as another potential mechanism of tremorogenesis.[7]

The exact mechanism of lithium-induced tremor is unknown but reduction of the dose or discontinuance of the drug usually leads to improvement.[7–9] Lithium-induced tremor has actually never been properly studied for potential mechanisms of causation. It does appear however that brain levels of lithium are related to the presence of tremor and by most accounts lithium-induced tremor is thought to arise from the central nervous system. Like with SSRIs, it is hypothesized that there may be effects on brainstem serotonergic neurons or other

effects on potential central oscillators.[7–9] There is some evidence from animal studies with other serotonergic agents such as SSRIs supporting this hypothesis. Some authors, however, have found that lithium-induced tremor was not influenced by the serotonergic affinity of the antidepressants that were added to the therapeutic regimen. In addition, β-adrenergic antagonists can help lithium-induced tremor and the non-selective β-adrenergic antagonist, propranolol, appears to be most effective.[7–9]

Recent work in the laboratory has shown that lithium treatment in mice lowers brain tau levels and increases substantia nigra and cortical iron, which is closely associated with neurodegeneration, cognitive loss, and Parkinsonian features.[40] These changes may explain why some tremors and parkinsonism may develop in lithium-treated patients over time.

Antiepileptics

Valproic acid. Valproic acid is an older antiepileptic that is very commonly used for migraine prophylaxis, seizures, and mood stabilization. This medication, like lithium, is one of the most commonly seen MIT in practice, even today.[41,42] Similar to SSRIs, up to 80% of patients treated with valproic acid may show evidence of tremor on accelerometry recordings with perhaps only 25% of patients complaining of tremor.[41–44] The tremor is typically with action, but can occasionally occur at rest as well. The tremor appears to be dose related and can improve with dose reduction, usually abating within several weeks. Tremor amplitude appears to be more pronounced with immediate release preparations relative to controlled-release preparations, perhaps due to greater peak-to-trough variation in drug levels.[15]

The clinical and electrophysiological features of valproic acid-induced tremor appear typical of EPT given treated patients had a reduction in their tremor frequency by 3 Hz or more by weight loading.[15,45] This is typical of an alteration in the frequency of the mechanical component of physiological tremor.

Valproic acid has multiple mechanisms of action including reduction of high-frequency neuronal firing of sodium-dependent action potentials, as well as increasing GABAergic neurotransmission.[15,41–47] Two other antiepileptics that improve ET (gabapentin and topiramate) also increase GABAergic neurotransmission, so these mechanisms of action are unlikely to be the cause of valproic acid-induced tremor.

If dose reduction or switching to a controlled-release preparation is not possible, then acetazolamide, amantadine, or propranolol may provide some benefit for the tremor.[46,47] Valproic acid can also cause parkinsonism in the setting of antiepileptic therapy or mood stabilization and clinicians should be aware of this as well.[6,48] In mice, there is some evidence that valproic acid might be toxic to dopaminergic neurons.[49]

β-Adrenergic agonists

Perhaps one of the best-known MIT is that associated with β-adrenergic agonists. Epinephrine and norepinephrine are endogenous non-selective adrenergic agonists that are associated with sympathetic activation and the "fight or flight response." Sympathomimetics are commonly used in practice with inhaled β-adrenergic agonists in wide use for respiratory illnesses.[50] Albuterol, salmeterol, and formoterol are perhaps most commonly used in the United States, with albuterol considered shorter acting (lasting 6 hours or less) and salmeterol and formoterol longer acting (up to 12 hours).[50] Fortunately for patients, tolerance to sympathomimetic drugs can develop over time.

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.[51,52] A classic experiment by Foley et al.[51] demonstrated that when subjects were ischemically prevented from receiving an infusion of epinephrine in their arm, tremor did not occur in the limb. In another experiment by Young et al.,[53] normal and ET subjects receiving intra-arterial injection of the β-adrenergic agonist isoproterenol into one arm experienced an increase in tremor amplitude of approximately 2.7-fold relative to baseline. Intravenous or intra-arterial injection of propranolol reduced the enhanced action tremor in both normal and ET subjects, but ET subjects with postural tremor were unaffected by the infusion of propranolol.[53] The authors proposed that ET likely has another mechanism generating the tremor beyond peripheral mechanism and now it is known that this tremor has a central generator that has not been precisely localized in the cerebello-thalamo-cortical circuit.[17,18]

β_2-Adrenergic receptors are located on the plasma membranes of extrafusal fibers and muscle spindles. Stimulation of these receptors by β-adrenergic agonists is thought to enhance physiological tremor by sensitizing muscle spindles and γ-fibers with subsequent synchronization of the afferent volley to the CNS.[17,18,54] More recent data indicate that the β-adrenergic agonist salbutamol and the non-selective β-adrenergic receptor blocking agent propranolol may both affect corticomuscular coherence and tremor partially through a CNS action.[55]

Dopamine-blocking agents

DBAs are commonly used in psychiatric practice for psychosis (neuroleptics) or as adjunctive therapy for mood disorders. They are also commonly used in the setting of gastroparesis (metoclopramide) or nausea (prochlorperazine, promethazine). Dopamine-depleting agents such as tetrabenazine can also cause tremor and parkinsonism by reversibly depleting dopamine through VMAT2 transporter inhibition. Typically, the effectiveness of DBAs is correlated with D2 dopamine receptor blockade. Clozapine and the novel antipsychotic pimavanserin challenge this notion and are unlike most DBA in that their effectiveness in treating psychosis is correlated with antagonism (clozapine) or inverse agonism (pimavanserin) at $5HT_{2A}$ (serotonergic) receptors.[56]

The mechanism of DBA causing tremor appears to be due to blockade of dopamine receptors, disrupting normal nigrostriatal dopaminergic neurotransmission. Parkinsonian resting tremor appears to have origins in the cerebello-thalamo-cortical circuit and in the basal ganglia receiving areas of the thalamus (the ventralus intermedius (VIM)).[17,18,57] Tremor severity in PD doesn't correlate with loss of dopamine in the nigrostriatal pathway, however.[17] Depletion of dopamine leads to increased firing of globus pallidus internus (GPi) neurons releasing GABA thereby leading to a net hyperpolarization of neurons in the thalamus. Dopaminergic medications ameliorate this abnormal hyperpolarization of thalamic

neurons by the GPi by restoring a better balance between the direct and indirect pathways in the basal ganglia. It appears from recent research that both the subthalamic nucleus (STN) and the thalamus may have pacemaking abilities in PD-related tremor.[57]

As mentioned previously, resting tremor in DIP due to DBA can be asymmetric in many patients.[2–5] Treatment of MIT due to DBA is aimed at reducing the dose of the offending drug or attempting to eliminate it completely. In many suspected DIP cases, however, treatment with DBA may unmask presynaptic dopamine deficiency due to an underlying Parkinsonian syndrome.[58] In these patients, symptoms will continue and even progress after the DBA is withdrawn despite perhaps some initial improvement. If this is not possible then anticholinergics or amantadine are often used to combat symptoms. Tardive tremor can also occur after extended periods on neuroleptic therapy.[58] Tardive tremor is distinct from resting tremor in DIP given that tardive tremor *improves* with neuroleptic therapy or dopamine-depleting therapy.[59] Tardive tremor is larger in amplitude than Parkinsonian tremor and can interfere with activities of daily living.[59] A recent report by Rodrigues et al.[60] demonstrated that resting tremor and postural tremor in the setting of DIP caused by aripiprazole were responsive to thalamic deep brain stimulation. This is similar to findings in PD where deep brain stimulation of the VIM nucleus of the thalamus, subthalamic nucleus, or GPi can improve resting tremor.

Immunosuppressants

Cyclosporine and tacrolimus are calcineurin inhibitors that are commonly used in immunosuppressive regimens for liver and kidney transplantation. Both drugs commonly cause tremors that appear to be due to enhancement of physiological tremor.[61]

Cyclosporine. Up to 40% of patients taking cyclosporine will have neurological side effects including tremors, headache, paresthesias, seizures, encephalopathy, visual disorders, or other symptoms.[62–64] With this diffuse set of neurological symptoms and signs, there has been significant effort in trying to delineate the mechanism for these neurological problems. Tremor is the most common neurological adverse event and can occur in 20–40% of patients depending upon the clinical setting.[62–64] It appears that patients treated chronically with cyclosporine tend to have a mild postural tremor that typically does not significantly interfere with daily activities.[62–64] Many patients historically will relate a history of mild tremor during the earlier course of treatment, but after some time the tremor has abated or improved, similar to many MITs. Toxic states and higher blood levels are associated with more patient complaints and perhaps larger tremor amplitude.[61–64] Interestingly, in a single case report, a 37-year-old female who was labeled with ET exacerbated by cyclosporine therapy following renal transplantation safely and successfully underwent thalamic deep brain stimulation surgery without infections and with good response.[65]

There are numerous possible mechanisms for cyclosporine-induced tremor, but the tremor appears typical of EPT in its characteristics given a shift in the dominant EMG frequency to a lower frequency with weighting.[61] Cyclosporine has effects on dopaminergic neurotransmission and it may influence receptor physiology, phosphorylation pathways, and transcription as well.[62–65] A recent study in pigs demonstrated gross normal brain pathology after chronic treatment with low-dose cyclosporine; however, on histological examination, there were signs of neuronal, perivascular, and meningeal granulocytic and mononuclear infiltrates in one of the five pigs.[66]

Tacrolimus. Tremor was reported with tacrolimus in the first reports of neurological toxicity related to the drug after liver transplantation.[67,68] Eight of 22 pediatric and 10 of 44 adult patients undergoing orthotopic liver transplantation reported tremor with tacrolimus therapy.[67,68] The tacrolimus-associated tremor described in the 10 adult patients was severe, worsened with action, and affected the hands, interfering with handwriting.[67] Dose reduction reduced the tremor, although several patients continued to have mild, non-bothersome tremor.[67] Tremor due to tacrolimus therapy also occurs in other disease states with 9% (81/896) of rheumatoid arthritis patients reporting tremor in one study.[69]

As with controlled-release valproic acid, recent data indicate that reducing peak-to-trough variability by using a controlled-release preparation of tacrolimus can reduce tremor in kidney transplant recipients experiencing tremor with immediate-release tacrolimus.[16] This modification also improved tremor amplitude with posture holding and improved tremor-related quality of life.[16]

Methylxanthines

Theophylline. Theophylline is an adenosine-2A receptor antagonist and may provide benefit in PD similar to other adenosine-2A antagonists such as istradefylline, caffeine, and tozadenant.[70] In a small crossover trial in PD, however, theophylline appeared to cause more tremor in the treatment of PD patients when levodopa was withdrawn.[71] Intravenous aminophylline also caused more power in the accelerometer measurement of tremor in patients with ET and in those with tremor related to hyperthyroidism.[72,73] Theophylline also increases tremor power in the typical physiological frequency (8–12 Hz) in euthyroid normal individuals.[73]

The exact mechanism of theophylline-induced tremors is largely unknown, but is likely a result of enhancement of physiological tremor. It is known that theophylline has the ability to mobilize intracellular calcium, antagonize adenosine receptors, and also may produce a slight rise in catecholamine levels in the central nervous system.[72,73] Any of these mechanisms may be at play, but the slight rise in catecholamine levels in the CNS is thought to be too minimal to affect a tremulous response.

Withdrawal states and toxin-induced tremors

Tremors can occur in the setting of withdrawal states, especially with benzodiazepines, ethanol, and opiates. One well-performed study found that patients undergoing ethanol withdrawal had tremors in the range of 8–12 Hz.[74] When patients abruptly stop β-adrenergic antagonists such as propranolol, an increase in action and postural tremor

can be observed as well. Even 1 month after discontinuing propranolol, increased tremor power was observed in subjects without underlying tremor disorders who were being treated for cardiac conditions.[75] Most withdrawal-related tremors appear typical of EPT as with most MIT.

When toxic levels of certain medications (such as lithium, phenytoin, or the chemotherapeutic cytarabine) and some drugs of abuse (ethanol) are experienced by patients, cerebellar damage can ensue and this can lead to a prominent and sometimes permanent cerebellar/intention tremor.[7–9,76] Cytarabine appears toxic to Purkinje cells especially in the lateral cerebellar hemispheres.[76] Chronic ethanol abuse can also cause anterior vermis and lateral hemisphere damage to many cell types including Purkinje cells and cause a similar tremor.[77]

Summary and future directions

MITs are common in clinical practice, occur with many medications, and are often very treatable by reducing the dose of the drug, switching to a controlled-release preparation, or switching to another agent. In some cases, it is not possible to reduce the dose of the offending agent and additional medication (e.g., propranolol) may be necessary to try and treat the tremor. In rare instances where clinically appropriate, deep brain stimulation surgery may be necessary to ameliorate the tremor.

The vast majority of tremors that are diagnosed as MIT are mechanistically due to EPT, but clinicians should beware that a patient may have underlying ET or PD that is unmasked when treated with an exacerbating agent.[17,18] They should also beware of the very unusual case with amiodarone, which can cause tremor by inducing hyperthyroidism in addition to its own mechanism of inducing tremor. In the case of DIP, an [^{123}I]-ioflupane scan (DATSCAN) can be very revealing, in some cases demonstrating loss of striatal dopamine transporter binding in subjects that would have been diagnosed with DIP when they actually have underlying PD.[5]

EPT is by far the most common mechanism of tremor generation by medications[17,18] (Table 2). Physiological tremor has many components that can be influenced by medications with some influencing the central component (amitriptyline) and others altering the peripheral component (β-adrenergic agonists, cyclosporine, etc.). Other mechanisms include blockade of dopaminergic neurotransmission in the nigrostriatal pathway by DBA or dopamine-depleting agents. Cerebellar damage due to longstanding abuse (ethanol) or toxic states can also cause intention tremors that can be quite bothersome.

It is interesting to note that Raethjen et al.[10] published the first work that demonstrated a definitive effect on the central component of physiological tremor by *any* drug (amitriptyline) in 2001. In addition, recent work on valproic acid and theophylline demonstrating these drugs cause tremor by likely enhancing physiological tremor is relatively new as well.[15,45,61] There is significant need for further mechanistic delineation of how many tremorogenic drugs enhance physiological tremor or cause tremor by other mechanisms.

Finally, it will be important to further define the most vital anatomical structures for the generation of tremor in the CNS and further understand the physiology of these interconnected players. It will also be important to develop further knowledge of neurotransmitters and their

Table 2. **Mechanisms of Medication-induced Tremor for More Common Offending Agents**

Medication/Drug	Mechanism(s)	Reference(s)
Amiodarone	Likely EPT, possible hyperthyroidism in some	19,23,25
Amitriptyline	EPT (enhances central component)	10
β-Adrenergic agonists	EPT (enhance the mechanical reflex component)	51–55
Cyclosporine	EPT (enhances peripheral component)	60
Cytarabine	Cerebellar toxicity to Purkinje cells	75
DBA	Blockade of striatal dopamine receptors	17,18,57,58
Ethanol	EPT in withdrawal states Cerebellar toxicity in alcoholism	73,76
Lithium	Likely EPT	7–9,38
SSRIs	Likely EPT	29
Tacrolimus	EPT (enhances peripheral component)	60
Theophylline	Likely EPT	71,72
Valproic acid	EPT? dopaminergic dysfunction as well	15,48

Abbreviations: DBA, Dopamine-blocking Agent; EPT, enhanced physiological tremor; SSRIs, Selective Serotonin Reuptake Inhibitor

receptors that may influence tremor or actually suppress it. Hopefully this further knowledge will lead to better therapeutics for pathological tremors and allow us to develop less tremorogenic drugs.

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