

Medication-Induced Tardive Dyskinesia: A Review and Update

Elyse M. Cornett, PhD,¹ Matthew Novitch, BS,² Alan David Kaye, MD, PhD,³ Vijay Kata, MS,³ Adam M. Kaye, PharmD⁴

¹Department of Anesthesiology, Louisiana State University Health, Shreveport, LA ²Medical College of Wisconsin, Wausau, WI ³Department of Anesthesiology, Louisiana State University Health Sciences Center, New Orleans, LA ⁴Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA

Background: Tardive dyskinesia (TD) is a movement disorder that causes involuntary, repetitive body movements and is commonly seen in patients who are on long-term treatment with antipsychotic medications. However, several other classes of medications with different mechanisms are also associated with TD.

Methods: We conducted a PubMed search using keywords and combined word searches that involved medication-induced TD, as well as agents that are associated with causing or are used to treat medication-induced TD. We attempted to include as many recent (publication date of 2015 and later) articles as possible.

Results: The reported incidence of TD seems to be reduced with the use of atypical antipsychotic drugs, yet the risk of developing TD remains with these medications. Furthermore, several other medication classes have a high prevalence of TD and yet are not commonly considered to be TD-inducing. This review highlights the need for a prevention-based focus of TD treatment that starts with a clinical consideration of pharmacologic choices related to each individual patient's history.

Conclusion: This review offers the information current as of 2016 on the pathophysiology, etiology, and epidemiology of TD, as well as the medications associated with TD, mechanisms of medication-induced TD, and treatments for medication-induced TD.

Keywords: *Anti-dyskinesia agents, dyskinesia–drug-induced, dyskinesias, movement disorders, tardive dyskinesia*

Address correspondence to Elyse M. Cornett, PhD, Department of Anesthesiology, Louisiana State University Health, 1501 Kings Highway, Shreveport, LA 71103. Tel: (318) 675-5801. Email: ecorne@lsuhsc.edu

INTRODUCTION

The term dyskinesia refers to involuntary muscle movements that can range from slight tremor to uncontrollable movement of the entire body. The tardive dyskinesia (TD) form of dyskinesia gets its name from the slow—or tardive—onset of involuntary movements of the face, lips, tongue, trunk, and extremities. TD most generally occurs in individuals who are on long-term treatment with dopamine receptor antagonist medications (antipsychotic drugs [APDs]). In fact, TD occurs in 20%-50% of patients taking APDs.¹ However, TD is also associated with a wide variety of other medications.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) classifies TD as a medication-induced movement disorder that can develop after short-term and long-term use of medications, as well as after discontinuation of, change in, or reduction in medications.² In all cases, TD must persist for at least 1 month after a medication is discontinued for a TD diagnosis. While the DSM-V definition of TD is helpful in diagnosing dopamine antagonist–related TD, this definition falls short of the wide range of medications that can also cause TD, especially

because only one of the several hypotheses for why TD occurs involves dopamine. And while many of the non-APD medications that cause TD directly or indirectly affect dopamine neurotransmission, emerging evidence suggests that isolating the definition of a TD diagnosis to dopamine agonists only is incorrect.

In many patients, TD is irreversible and can persist long after the medications that may be causing the symptoms are stopped. Of course, patients need to take the medications that are causing the unwanted side effect of TD; therefore, stopping the medication can be dangerous and may even induce further complications.

METHODS

We conducted a PubMed search using keywords and combined word searches that involved medication-induced TD as well as agents that are associated with causing or are used to treat medication-induced TD. We attempted to include as many recent (publication date of 2015 and later) articles as possible. The search terms we used to gather this information included tardive dyskinesia, medication-induced tardive dyskinesia, neuroleptics, antipsychotics,

typical antipsychotics, atypical antipsychotics, antiemetics, anticholinergics, antidepressants, anticonvulsants, antihistamines, antiparkinson agents, stimulants, anxiolytics, biogenic amines, mood stabilizers, oral contraceptives, incidence, prevalence, dopamine, oxidative stress, pharmacokinetic, genetic polymorphisms, gastroparesis, history, case study, epidemiology, pathophysiology, etiology, prevention, and treatment. In this review based on our literature search, we discuss the pathophysiology and epidemiology of TD, medications that can induce TD, possible solutions for preventing TD, and treatments for managing TD and for managing TD symptoms while a patient is concurrently taking an APD.

PATHOPHYSIOLOGY

The pathophysiology of TD lacks a universally accepted theory and mechanism. Several hypotheses have been proposed that include prolonged blockade of postsynaptic dopamine receptors leading to dopamine receptor supersensitivity, gamma-aminobutyric acid (GABA) depletion, cholinergic deficiency, oxidative stress, altered synaptic plasticity, neurotoxicity, and defective neuroadaptive signaling.³

With regard to the dopamine hypothesis, chronic dopamine blockade can result in upregulation of dopamine receptor responsiveness that can result in an exaggerated response of the postsynaptic dopamine receptors to dopamine. With regard to the oxidative stress hypothesis, antidepressants block dopamine receptors, increasing dopamine synthesis and metabolism. The result of increased dopamine metabolism is an increase in the production of free radicals. Monoamine oxidase, the enzyme that metabolizes dopamine, and dopamine itself can cause lipid peroxidation and the alteration of antioxidant enzymes which can lead to cell death. The basal ganglia, subcortical nuclei comprised of several brain regions including the striatum and substantia nigra, are highly innervated by dopamine neurons and are therefore especially at risk for oxidative stress and the occurrence of TD.⁴ Evidence also suggests that APDs and their metabolites may be directly toxic to neurons through oxidative stress.⁵ However, a 2011 review of clinical studies suggests that the relationship between toxic metabolites of APDs and TD is still unclear.⁶

Genetic Pathophysiology

Evidence suggests a genetic predisposition to TD;^{7,8} however, many of these findings have not been replicated or are inconsistent.⁹ Müller et al have reported familial TD.¹⁰ However, factors such as environmental influence, age as a risk factor, and oxidative stress suggest that TD has many features that cannot be limited to genetics alone. Evidence also suggests that a genetic protection against TD exists.¹¹ In particular, Fedorenko et al report that the *PIP5K2A* gene, commonly associated with schizophrenia, can be mutated in cases of TD.¹¹ *PIP5K2A* may be protective against the neurotoxicity caused by and leading up to TD. Additionally, TD has been associated with polymorphisms of the dopamine D3 receptor Ser9Gly and of the serotonin 2A and 2C receptor genes.^{12,13} This finding supports the theory that dopamine receptor hypersensitivity is related to medication-induced TD.¹⁴ Finally, brain-derived neurotroph-

ic factor Val66Met polymorphisms may be associated with the development of TD and the severity of TD in Caucasians.¹⁵ This finding may support the hypothesis behind oxidative stress and the resulting neurotoxicity of APD-derived free radicals.

ETIOLOGY AND EPIDEMIOLOGY

The occurrence of TD is estimated to be 2%-5% annually,¹⁶⁻¹⁸ and the condition occurs in 15%-30% of those who receive long-term treatment with APDs. The occurrence of TD can also depend on whether the APD is typical (also known as first generation) or atypical (also known as second generation),¹⁸ with a 32.4% occurrence with typical APDs and a 13.1% occurrence with atypical APDs.¹⁹ Individuals who previously developed acute adverse side effects to dopamine antagonists are more likely to develop TD after taking a similar acting medication.²⁰

Atypical APDs are associated with a decrease in the incidence and prevalence of TD. Specifically, a 2015 study of 293 patients showed a 2.5% incidence of TD in those receiving olanzapine for treatment compared to 5.5% of those taking typical APDs.²¹ Atypical APDs are expected to have fewer extrapyramidal side effects compared to typical APDs owing to the lower affinity of atypical APDs to dopamine D2 receptors in the dorsal striatum and associated antagonism of serotonin 5-HT_{2A/2C} receptors.²²

Age, Sex, and Race

Risk factors for developing TD are the use of both typical and atypical APDs, older age, female sex, previous brain injury or dementia, early extrapyramidal symptoms, and African and African American race.^{1,23}

TD occurs in both young and old patients. A 2001 study that followed 102 children and adolescents receiving typical APDs, atypical APDs, or a combination of both for 3 months reported that only 5.9% of youths treated with typical APDs had probable TD, a prevalence much lower than that of the general adult population treated with typical APDs.²⁴ However, the use of typical APDs was significantly associated with TD compared to the use of atypical APDs.

Age-related changes to the body and brain are also a factor in TD. Elderly patients are much more likely to develop medication-induced TD (3.2-fold higher risk) because of age-related progression of neurodegeneration, such as Parkinson disease and exposure to APDs.¹ Additionally, medications used to treat Parkinson disease can cause TD.

Race also plays a factor in determining the prevalence and incidence of medication-induced TD. A 2004 evaluation of 1,149 patients with TD who were on long-term APD treatment reported that African Americans were more likely to develop TD than Americans of European descent.²⁵ In a 2009 study, Go et al investigated individuals of Filipino descent who took a daily dose of 700 mg chlorpromazine and had an APD exposure history of at least 5 years.²⁶ They compared the results to other studies involving Asian and Caucasian individuals and reported a prevalence of TD of 20.3%, noting that TD occurred more in females and in older age groups. Surprisingly, patients of Filipino and Asian descent had a lower prevalence of TD compared to patients of Caucasian descent, even though the Filipino and Asian patients consistently used typical APDs. A higher preva-

lence of TD was also seen in patients who had been taking APDs for longer periods of time. Other factors that Go et al investigated included history of substance abuse, type 2 diabetes, and electroconvulsive therapy, and they found no association between these variables and a TD diagnosis.²⁶ Interestingly, Yassa et al determined that the prevalence of TD is higher in individuals who smoke cigarettes;²⁷ however, this finding may not be a cause-effect relationship as individuals who take APDs report that nicotine helps relieve unwanted side effects of TD and APDs,²⁸ and a study by Bordia et al indicated that nicotine decreased TD symptoms in rats.²⁹

With regard to sex differences, the incidence of drug-induced TD is higher in women who have incidence rates as high as 30% after 1 year of cumulative exposure to APDs.¹ Some studies suggest that both sexes are equally susceptible to TD; however, postmenopausal women might have a higher risk of developing TD.² Evidence suggests that estrogen modulates dopamine-mediated behaviors and can exhibit an antioxidant effect, which could protect against TD.^{30,31} TD is the exception to the age-related increase in incidence of tardive syndrome, which tends to occur more often in young male patients.¹

MECHANISM OF ADVERSE MEDICATION REACTIONS

The exact mechanisms of adverse medication reactions that cause TD are not well defined. However, the blockade of dopamine receptors by dopamine antagonists is the most widely accepted theory.¹ Chronic dopamine blockade caused by dopamine D2 receptor antagonists or APDs could result in an upregulation of dopamine receptor responsiveness, resulting in a compensatory supersensitivity of the receptors, especially in the basal ganglia. However, some studies suggest that D3, D4, and D5 receptors are also involved in the pathogenesis of TD.^{32,33} D3 and D5 receptors have a consistent positive correlation with TD, but evaluations of D4 yield inconsistent results.^{32,33}

Anticholinergic agents are also linked to TD, and taken together with the dopamine receptor supersensitivity hypothesis, an imbalance of dopamine and acetylcholine is likely involved in TD pathogenesis.³⁴ Evidence also suggests an imbalance of serotonin. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine inhibit dopamine neurons in the nigrostriatal pathway by increasing serotonin in the raphe nucleus. SSRIs act by potentiating the inhibitory effects of serotonin on dopamine production in the basal ganglia.³⁵ This decrease in dopamine production by serotonin could contribute to the pathogenesis of TD.

Evidence also indicates the involvement of GABA in TD. Damage to GABAergic neurons by medications that affect GABA functioning in the striatum, a brain region involved with oral musculature movements, could explain some of the hallmark symptoms of TD.³⁴ Muscimol, a GABA-mimetic agent, decreases abnormal movements in TD subjects.³⁶ Furthermore, evidence suggests a direct link between GABA and dopamine in that GABA neurons can directly inhibit dopamine neurons in discrete brain regions.³⁷ These data suggest a delicate balance between dopamine and GABA that, if interrupted, could result in TD.

MEDICATIONS THAT CAN INDUCE TARDIVE DYSKINESIA

Antipsychotic Drugs

APDs are typically prescribed for patients with schizophrenia and similar mental disorders. As mentioned previously, APDs belong to 1 of 2 exclusive groups: typical or atypical. The exception is aripiprazole which is a partial dopamine agonist and is therefore classified as a third-generation APD. Typical APDs are the most likely to cause TD. Typical APDs bind strongly to dopamine D2 receptors, causing a wide range of side effects and likely contributes to the occurrence of TD.^{1,38} Certain butyrophenones such as haloperidol have been shown to induce dyskinesia by the influx of proinflammatory cytokines and neurotransmitters,³⁹ while the risk of atypical APDs such as clozapine and quetiapine to influence the development of TD is reduced,⁴⁰ likely because they do not exclusively affect dopamine function.

Atypical APDs bind weakly to dopamine D2 receptors and seem to be associated with a decreased prevalence of TD. However, the assumption that atypical APDs are beneficial in reversing the symptoms of TD is incorrect, even though atypical APDs are administered when prescribing typical APDs is no longer an option for the patient. Overall, little available evidence suggests that atypical APDs directly reduce the incidence of TD.^{1,16,41} In some cases, certain atypical APDs have increased the chances of TD occurrence. This phenomenon has been reported in treatments involving aripiprazole, risperidone, and amisulpride.⁴²⁻⁴⁵ A separate study showed a 16.4% prevalence of TD in patients treated with olanzapine.¹⁶

Although atypical APDs do not necessarily reduce the risk of TD, some healthcare providers suggest that switching from a typical to an atypical APD to ameliorate TD symptoms can be beneficial. However, no specific guideline identifies particular medications to switch to or from to treat TD symptoms.⁴⁵ Furthermore, atypical APDs tend to have unwanted side effects, including weight gain and sedation, that should be considered against the TD symptoms.

Anticholinergic Agents

Anticholinergics such as procyclidine are prescribed for chronic obstructive pulmonary disease, for bladder control issues, and to decrease symptoms associated with Parkinson disease. These agents have been shown to worsen the symptoms of TD and to impair cognitive function.⁴⁶ However, in a study of 20 patients for 4 weeks, 18 of the 20 patients who were weaned off treatment with anticholinergics showed improved cognitive function and good motor responses,⁴⁷ suggesting that procyclidine-induced TD is reversible.

Antidepressants

Antidepressants are prescribed for depression, anxiety, obsessive-compulsive disorder, and attention deficit disorder and are even useful in treating chronic and neuropathic pain. In general, the mechanism of action of antidepressants is to increase or stabilize levels of monoamines (dopamine, serotonin, and norepinephrine) in the brain. TD induced by antidepressants is less prevalent than TD induced by APDs. However, antidepressant-induced TD is common in elderly patients who have a greater likelihood of

comorbid conditions. Because older age is associated with changes in the absorption, distribution, metabolism, and excretion of medications, long-term antidepressant exposure may lead to increased medication accumulation and severe side effects. The efficiency of amine transmitter and receptor signaling is also decreased in older patients and can further contribute to unwanted side effects.⁴⁸ Trazodone, doxepin, clomipramine, and amitriptyline can induce TD in patients with no previous exposure to APDs.^{34,35} TD symptoms are dose-dependent and exacerbated in individuals who have previously been administered lithium.⁴⁹ Amisulpride is associated with the lowest incidence of extrapyramidal side effects.⁵⁰

As mentioned previously, SSRIs are associated with TD. Fluoxetine, in particular, can lead to TD or symptoms similar to TD, and these symptoms have been reported for up to 1 year after discontinuation and withdrawal from the medication.⁵¹ With sertraline, another SSRI associated with TD, increasing age is a significant risk factor for the development of the disorder,⁵² although TD has also been reported in adolescent patients on this medication.

Monoamine oxidase inhibitors (MAOIs) are used to treat depression and Parkinson disease. MAOIs inhibit the metabolism of monoamines that, over time, can lead to an increase or stabilization of monoamine levels. The 2 types of monoamine oxidase (MAO)—type A (MAOA) and type B (MAOB)—are expressed in the hypothalamus, hippocampus, and the cingulate cortex. A large amount of MAOB (and to a lesser extent, MAOA) is expressed in the striatum and globus pallidus. The cortex has high levels of only MAOA.⁵³ Given that MAOB is highly expressed in dopamine-rich areas of the brain (the striatum, in particular), it makes sense that MAOB-targeting drugs are associated with TD. Selegiline, a selective (only binds to MAOB) and irreversible (the drug forms a covalent bond with the enzyme that cannot be undone) MAOB inhibitor (decreases activity of the enzyme), is associated with TD when used in combination with L-DOPA.⁵⁴ Rasagiline, another selective and irreversible MAOB inhibitor, is also associated with TD, but the dyskinesias are less severe and considered to be more tolerable to the patient.⁵⁵ Phenelzine, a nonselective (binds to MAOA and MAOB) and irreversible MAOI, has a high association with TD.⁵⁴

Antiemetics

Antiemetics are prescribed for severe nausea and acid reflux and include dopamine antagonists, serotonin (5-HT₃) receptor antagonists, neurokinin-1 antagonists, antihistamines, cannabinoids, benzodiazepines, and anticholinergics. Metoclopramide, a dopamine antagonist, has a strong correlation with the occurrence of TD.⁵⁶ Old age, female sex, history of diabetes mellitus, and taking metoclopramide for 12+ weeks are risk factors for developing metoclopramide-induced TD. Metoclopramide is associated with respiratory dyskinesia and can manifest in TD as gasping, abnormal breathing, and irregular esophageal movements.⁵⁶ Tapering metoclopramide has not been shown to decrease the risk of respiratory dyskinesia, and individuals with alterations in the *CYP2D6* gene have decreased ability to metabolize metoclopramide and are more at risk for developing TD symptoms.⁵⁷ Metoclopramide is currently the only medication that is US Food and Drug Administra-

tion (FDA) approved to treat gastroparesis, so options for preventing the onset or worsening of metoclopramide-induced TD in a patient with gastroparesis are lacking.⁵⁷

In certain clinical trials, the use of prochlorperazine, an APD that can be used to treat nausea and vertigo, has yielded a higher frequency of TD than metoclopramide.⁵⁸

Anticonvulsants

Anticonvulsant agents are prescribed to reduce epileptic seizures and do so by blocking sodium channels or enhancing GABA function. Although the incidence is rare, carbamazepine and lamotrigine are associated with TD.⁵⁹ Anticonvulsant-induced dyskinesia is considered to be underdiagnosed in patients,^{60,61} and individuals taking valproate are more likely to develop Parkinson disease compared to patients taking other anticonvulsants.⁶² Phenytoin is also implicated in dyskinesias⁶³ and has a well-documented link to TD.^{64,65} Phenytoin-induced TD is most often reported in children and young adults, with 50% of patients younger than 20 years and 20% older than 40 years.⁶⁶ The mechanism behind phenytoin-induced TD is not clear.^{66,67} However, the most widely accepted theory is that phenytoin blocks sodium channels, which can decrease the repetitive high-frequency firing of action potentials that is associated with epilepsy. A 1993 manuscript by Harrison et al hypothesized that the use of multiple anticonvulsants at once can increase the likelihood of TD.⁶⁶ They further hypothesized that phenytoin accumulates in the brain with extended administration and at supratherapeutic concentrations can decrease calcium influx and thus decrease neurotransmitter release from neurons; decrease calcium and calmodulin, thus impacting protein phosphorylation and second messenger pathways; prevent cyclic adenosine monophosphate increases; and increase GABA concentrations.⁶⁶ Recent evidence suggests that at serum concentrations and in clinical practice, phenytoin does not modify GABA (both presynaptic and postsynaptic).⁶⁸ Phenytoin is also associated with a decrease in acetylcholinesterase activity.⁶⁹ Evidence suggests that phenytoin may affect dopamine signaling because patients with Parkinson disease who have previously received phenytoin have a decreased response to L-DOPA,⁷⁰ although the exact mechanism by which this decrease in response occurs is unclear.

Antihistamines

Antihistamines treat allergy symptoms by blocking histamine receptors. TD induced by prolonged administration of antihistamines^{71,72} and facial dyskinesia after an overdose of antihistamines⁷³ have been reported. Hydroxyzine is associated with TD after prolonged use, but TD can also occur as early as 7.5 months after treatment initiation.⁷⁴ Elderly patients with previous exposure to phenothiazines (typical APDs) have a higher likelihood of developing TD after hydroxyzine treatment.⁷⁴ Although newer reports of antihistamines and TD are lacking, antihistamines are still considered medications to be used with caution for long periods. Ziprasidone, an atypical APD with high affinity for serotonin 2A and dopamine D₂ receptors and a propensity to cause TD, also has affinity for adrenergic and histamine receptors.⁷⁵ Together, this information suggests that blocking histamine receptors for long periods of time either

directly through antihistamines or indirectly through APDs can lead to TD.

Decongestants

Decongestants are used to treat cold and flu symptoms and are primarily comprised of pseudoephedrine, phenylephrine, or derivatives of these 2 medications. These medications are alpha-adrenergic agonists; therefore, they increase norepinephrine and epinephrine. Phenylpropanolamine is an amphetamine derivative that is used as a nasal decongestant. A 1997 manuscript reported dystonia after standard doses of medication containing phenylpropanolamine.⁷⁶ A 1982 study reported orofacial dystonia after the long-term use of an unspecified decongestant.⁷⁷ Alpha antagonists have been associated with reducing dyskinesias,^{78,79} so an alpha agonist would reasonably be expected to exacerbate movement disorders and TD.

Antimalarials

Antimalarials treat or prevent malaria, an infectious parasitic protozoan disease spread by mosquitos. The various antimalarial agents have different mechanisms of action, making their correlation with TD difficult to discern. Chloroquine is the first line of treatment for preventing and treating malaria today. Chloroquine enters the red blood cells of affected patients, diffuses into the parasitic cell and vacuole, raises the pH of the internal parasite cell, and inhibits proliferation. It can also inhibit the biosynthesis of parasitic nucleic acids. Amodiaquine is another antimalarial medication with a similar mechanism of action to chloroquine. Both of these medications are associated with TD.⁸⁰ The mechanism by which these agents cause TD is hypothesized to be via interference with the biosynthesis of neurotransmitters, although this mechanism likely does not involve RNA-dependent protein synthesis.⁸¹ Another hypothesis is that the fever associated with malaria may directly decrease brain amines (norepinephrine, dopamine, and serotonin) because of the malaria-induced spike in temperature. Spikes in temperature can disrupt brain amine function (including synthesis and signaling activity) that can be further exacerbated by exposure to the antimalarials.⁸²

Antiparkinson Agents

Antiparkinson agents are used to treat the symptoms of Parkinson disease, a long-term neurodegenerative disorder that involves loss of motor control, shaking, rigidity, and decreased mental and behavioral capacity. These medications work to either increase dopamine or decrease acetylcholine activity in the brain. L-DOPA is a dopaminergic medication and the standard of care for patients with Parkinson disease. As the precursor to dopamine, L-DOPA increases neuronal production of dopamine that then decreases the symptoms of Parkinson disease. L-DOPA-induced dyskinesias (LID) can occur in patients who take the medication, especially patients who have early-onset Parkinson disease (50% of patients 40-59 years vs 16% of patients 70+ years), suggesting an age-related phenomenon involving L-DOPA activity in the brain.⁸³ Larger doses of L-DOPA are associated with a greater incidence and more prolonged state of TD. However, not all patients on long-term, high-dose L-DOPA therapy develop LID, suggesting a genetic component to LID.⁸⁴ The mechanism by which LID

occurs is not understood, and several hypotheses address this issue. Intermittent administration of L-DOPA may lead to downstream alterations in the striatum that may promote dyskinesia.⁸⁵ Furthermore, evidence suggests that LID is a result of a disinhibition of the primary motor cortex.⁸⁶ Other hypotheses include overactivity of glutamatergic N-methyl-D-aspartate receptors,⁸⁷ abnormalities in alpha-2 adrenergic, serotonergic, cannabinoid, and opioid transmission;⁸⁸ and abnormalities in FOS proteins.⁸⁹

Anticholinergic antiparkinson agents (trihexyphenidyl and orphenadrine) block muscarinic acetylcholine receptors and decrease cholinergic nerve activity, which corrects the imbalance of dopamine and acetylcholine in the brain, particularly the striatum. A balance of dopamine and acetylcholine is necessary for normal functioning.⁹⁰ Therefore, an imbalance of either one of these neurotransmitters would have an effect on the opposing system. Experiments have demonstrated that acetylcholine may influence the severity of abnormal movements in TD.⁹¹

Anxiolytics

Anxiolytics is a broad term that includes several types of medications used to treat anxiety. Common anxiolytics include barbiturates, benzodiazepines, carbamates, opioids, and antidepressants such as fluoxetine and paroxetine. Barbiturates, GABA agonists that produce sedation, are used to treat seizure disorders and, of the anxiolytics, are more commonly associated with TD. GABA is an important neurotransmitter in motor function; therefore, an imbalance between GABA and dopamine could account for the incidences of TD in individuals who take anxiolytics.⁹² Benzodiazepines also increase GABA and produce sedation. The benzodiazepine clonazepam is associated with TD when patients stop taking the medication acutely.⁹³ Fast withdrawal from benzodiazepines can lead to withdrawal-emergent dyskinesia, a reversible form of TD.⁹³ Withdrawal-emergent dyskinesia is likely caused by the dopamine hypersensitivity hypothesis discussed earlier in the article. Meprobamate, a carbamate that binds to GABA receptors, is used to induce sedation and decrease or alter the perception of pain.⁹⁴ Because meprobamate binds to GABA, TD likely occurs through a mechanism similar to that of benzodiazepines.

Biogenic Amines

Biogenic amines are organic molecules derived from amino acids that are found in nearly all of the foods that we eat. This category of molecules includes monoamines such as histamine, serotonin, norepinephrine, dopamine, and epinephrine.

The biogenic amine tyramine is found in aged cheeses, cured meats, pickled or fermented foods, alcohol, and chocolate.⁹⁵ Individuals on long-term MAOI treatment for depression need to be cautious when consuming tyramine-rich foods because tyramine is metabolized by MAO. A buildup of tyramine in the blood can lead to a hypertensive crisis.⁹⁶ While TD has not been directly associated with hypertensive crisis, the stress on the body from a hypertensive crisis may be enough to induce further complications in a manner similar to the association between TD and malarial fever discussed previously. These

effects, in addition to the accumulation of monoamines in the brain from MAOI treatment, could result in TD.

Mood Stabilizers

Mood stabilizers are used to treat bipolar disorder, borderline personality disorder, and schizoaffective disorder. They include lithium, anticonvulsants, and APDs. Lithium is a naturally occurring element, but it is used in its salt form to treat these disorders. Lithium reduces excitatory neurotransmission and increases inhibitory neurotransmission, but the complex mechanisms by which lithium reduces excitatory neurotransmission is poorly understood.⁹⁷ And while there is an established link between lithium and TD, the incidence of TD is much greater when lithium is used in combination with APDs.⁹⁸ A 9-year study involving 16 patients using lithium to treat schizophrenia reported a negative association in persistence and onset of TD.⁹⁹ These data suggest that lithium, when used in combination with other APDs, is more likely to cause TD than lithium alone.

Evidence also indicates that individuals with bipolar disorder who are taking APDs are more sensitive to developing TD compared to other individuals taking APDs.¹⁰⁰ These individuals tend to take low doses of APDs, and yet TD symptoms emerge much sooner than in patients with other conditions such as schizophrenia and depression.¹⁰¹

Stimulants

Stimulants, both legal and illegal, have been associated with TD. Stimulants include caffeine, nicotine, guarana, ginseng, legal amphetamines, ephedrine, and illicit amphetamine and methamphetamine. Stimulants act through a variety of mechanisms to increase alertness, energy, and concentration. Caffeine, for example, is an adenosine receptor antagonist. Caffeine has not been shown to directly cause TD, but very high doses of caffeine (1,000+ mg) can exacerbate TD symptoms.¹⁰² Low doses (100 mg) of caffeine are reported to be effective at reducing dyskinetic and freezing gait movements.¹⁰³ Amphetamines, on the other hand, act directly on monoamines, particularly dopamine, and (1) inhibit monoamine metabolism, (2) prevent monoamine reuptake, (3) increase monoamine release from vesicles, and (4) reverse transport monoamines back into the presynaptic neuron for subsequent release.¹⁰⁴ Two patients taking the diet pill norpseudoephedrine as an appetite suppressant experienced persistent dyskinetic syndromes that persisted even after the medication was discontinued.¹⁰⁵

The association between illicit amphetamine and methamphetamine and dyskinesias and movement disorders is well documented.¹⁰⁶ This association is likely attributable to the neurotoxic effects of amphetamines on dopaminergic areas of the brain. These movement disorders can persist even after discontinuing use of amphetamines.¹⁰⁶

PREVENTION AND TREATMENT

No FDA-approved treatment for TD is available. Despite progress toward identifying the etiology of medication-induced TD, its cause remains uncertain. Because medications are linked to TD, the obvious solution is to stop the medication, if possible. However, abruptly stopping a

medication is likely to cause withdrawal symptoms that could facilitate the onset TD or withdrawal-emergent dyskinesia.¹

As previously mentioned, one hypothesis suggests that free radical production caused by the metabolism of APDs may be neurotoxic and influential in the development of TD.³ Therefore, consuming foods and supplements that are rich in antioxidants may prevent the onset of TD.³⁰ While positive findings concerning this theory have not yet been replicated, the anticipated increase in research surrounding the antioxidant hypothesis may lead to new information about the pathophysiology of the condition.^{30,107}

The Dyskinesia Identification System Condensed User Scale (DISCUS) is used to assess dyskinetic movement rather than diagnose it. The scale has 7 sections requiring completion: (1) assessment of facial, ocular, oral, lingual, head/neck/trunk, upper limb, and lower limb movement disorders; (2) scoring instructions for assessing movement disorders (eg, 0 [not present] to 4 [severe] or not assessed); (3) level of individual cooperation with the examination (eg, none, partial, full); (4) examination type and date (eg, baseline, annual); (5) current psychotropic medications; (6) physician's evaluation; and (7) comments. Several studies have backed the reliability of this scale and suggest that select postures and movements could be measured to predict TD using the DISCUS.¹⁰⁸

Clinically, TD is difficult to treat because of the uncertainty about what causes it. TD is commonly misdiagnosed as mental illness rather than neurologic dysfunction, resulting in the prescription of APDs that can further worsen the condition. Definitive classification of TD is necessary to prevent such treatment problems from occurring.

Overall, prevention is the best method to combat TD. Before starting patients on APDs or other TD-inducing medications, physicians should discuss the risks with patients and prescribe the lowest possible dose of a medication least associated with TD. More research is necessary to identify which medications have the least association with TD and movement disorders.

Medications and Supplements Used to Treat Tardive Dyskinesia

A number of medications and supplements have been identified that ameliorate TD symptoms.

Cholinergic Agents. Cholinergic agents are used as muscle stimulants to diagnose myasthenia gravis and to treat glaucoma. These agents can also improve the Parkinsonian features of TD. Donepezil, a reversible acetylcholinesterase inhibitor, is currently the only cholinergic medication that has shown benefit against TD.¹⁰⁹ Overall, however, cholinergic agents are not a widely accepted treatment for TD as sufficient evidence is lacking to suggest they are more helpful than other treatments.¹¹⁰

Clozapine, Quetiapine, Olanzapine, and Apomorphine.

Clozapine, a serotonin and dopamine receptor antagonist, is an atypical APD used to treat schizophrenia. Clozapine is the best current medication recommended for patients who require antipsychotics and simultaneously have TD,¹¹¹ as clozapine has been reported to reverse TD symptoms.^{112,113} Clozapine has been linked to TD; however, the incidence is much lower compared to other atypical APDs.¹¹⁴ Drugs with similar mechanisms of action such as

quetiapine, a weak striatal dopamine antagonist, and olanzapine, a dopamine and serotonin receptor antagonist, have also been shown to be effective in ameliorating TD symptoms.¹¹⁵ Apomorphine, a dopamine receptor antagonist, can be given in conjunction with L-DOPA to decrease dyskinesias.¹¹⁶

Tetrabenazine Analogs. Tetrabenazine, a vesicular monoamine transporter inhibitor, decreases the severity of TD symptoms.¹⁴ However, tetrabenazine is rapidly metabolized and therefore needs to be administered frequently.¹¹⁷ Analogs of tetrabenazine such as valbenazine, a (+)- α -isomer of tetrabenazine, have been approved for clinical trials for the treatment of TD. In a phase IIb randomized, parallel, double-blind, placebo-controlled clinical trial of patients with moderate to severe TD, 67% of patients treated with valbenazine reported a “much improved” or “very much improved” Abnormal Involuntary Movement Scale score compared with 16% of patients taking placebo.¹¹⁷

Clonazepam. While certain benzodiazepines can cause TD, evidence suggests that some may be beneficial in treating TD.¹¹⁸ Sharma’s proposed guidelines for treating TD include clonazepam and were successful in a patient who presented with TD symptoms after long-term treatment with trifluoperazine (a typical APD), citalopram, trihexyphenidyl, and propranolol.¹¹⁹ A case report published in 2001 related that 2 mg/day of clonazepam for 1 year successfully alleviated the TD symptoms of a 66-year-old female, and she did not develop tolerance during the 1-year period.¹²⁰

Propranolol. Propranolol is a beta-adrenergic receptor antagonist used to treat high blood pressure, cardiac arrhythmias, and migraines. A retrospective study of 47 patients with TD that persisted for 17 months after discontinuation of APDs reported that low-dose propranolol appeared to be well tolerated in this patient population, and 64% of the patients saw an improvement in their TD symptoms.¹²¹

Amantadine. Amantadine is a noncompetitive glutamate receptor antagonist. It is postulated to work by increasing presynaptic release of dopamine and blocking presynaptic dopamine reuptake. Amantadine has been shown to be effective in treating L-DOPA-induced TD in patients with Parkinson disease.¹²²

Branched-Chain Amino Acids. Some evidence suggests that an inability to clear ingested forms of the amino acid phenylalanine is associated with TD. Branched-chain amino acids (BCAAs) are reported to decrease TD symptoms¹²³ because they decrease plasma phenylalanine by stimulating protein synthesis and insulin release.¹²⁴ BCAAs also decrease the accumulation of tyrosine, another amino acid and an important precursor to dopamine, that reduces overall dopamine synthesis in the nervous system.¹²⁴ Most important, BCAAs also seem to be effective at decreasing TD symptoms while an APD medication is still on board or the patient has a history of APD exposure.¹²³ BCAAs are available over the counter in a flavored powder preparation to mix with water, so they may be a promising, practical, and inexpensive treatment for TD.

Ginkgo Biloba. The American Academy of Neurology recommends clonazepam and ginkgo biloba, an extract of

the ginkgo biloba tree leaf that is used as a dietary supplement, to enhance cognitive function to treat TD.^{19,125}

Antioxidant Medications and Supplements. Because evidence suggests that oxidative stress may contribute to TD, several antioxidant medications and supplements are increasingly being used to treat TD: zonisamide, yi gan san (a Chinese herb), levetiracetam, melatonin, omega-3 fatty acids, piracetam, resveratrol, vitamin B6, and vitamin E. A comprehensive update on these medications is available in a 2015 review by Lerner et al.¹¹⁸

CONCLUSION

Medication-induced TD is a complex and unique neurologic disorder. While the reported incidence of TD seems to be less with atypical APDs compared to typical APDs, a risk of developing TD is associated with these medications, as well as others. A number of challenges with TD remain, including the ability to quantify the risk of TD caused by pharmacologic management, the difficulty of diagnosing TD even with DISCUS and other approaches, the exposure of older patients to both typical and atypical APDs, and the dyskinesia caused by other neurologic disorders. Additionally, the unclear pathophysiology of TD continues to be a problem for the successful treatment and management of the condition.

While no FDA-approved treatment for TD is available, several medication and supplement options are available to ameliorate its effects. One of the most promising options is BCAAs that appear to improve TD symptoms even for patients taking APDs. While BCAAs may not work for all patients with TD, BCAAs are inexpensive and easily acquired, making them an attractive approach to combat TD.

The best strategy against TD is prevention. Prevention of medication-induced TD is centered around clinical considerations for pharmacologic choices and altering dosages based on each patient’s variables. Healthcare providers are responsible for educating themselves and their patients on the dangers associated with APDs and other TD-inducing medications and following up on patient medication compliance. Furthermore, long-term treatment with almost all of the medications mentioned in this paper is a major risk factor for developing TD. Healthcare providers should be vigilant in reassessing the course of treatment for their patients and only allow patients to stay on these medications for long periods if absolutely necessary.

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