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 dopaminergic 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,
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 Phenergan, 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.58

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 Phenytion is also implicated in dyskinesias63 and has a well-documented link to TD.64,65 Phenytion-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 phenytion-induced TD is not clear.66,67 However, the most widely accepted theory is that phenytion 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 phenytion 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, phenytion does not modify GABA (both presynaptic and postsynaptic).68 Phenytion is also associated with a decrease in acetylcholinesterase activity.68 Evidence suggests that phenytion may affect dopamine signaling because patients with Parkinson disease who have previously received phenytion 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 antihistamines71,72 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