83 Tardive Dyskinesia and Other Neuroleptic-Induced Syndromes

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KEY POINTS

1. Dopamine receptor antagonists can produce a variety of motor and sensory abnormalities as an iatrogenic condition.
2. Dopamine receptor antagonists produce parkinsonism and other side effects associated with hypodopaminergic state that are reversible upon discontinuation of the offending medication.
3. Tardive dyskinesia syndrome usually occurs after chronic exposure to dopamine receptor antagonists and often persists even after discontinuation of the offending agent.
4. The pathophysiology of tardive dyskinesia is still poorly understood but may involve maladaptive plasticity of brain circuits.
5. The best established treatments for tardive dyskinesia are tetrabenazine derivatives that deplete monoamines.

INTRODUCTION

Neuroleptics are medications that are named for its neurologic side effects of inducing parkinsonism (called drug-induced parkinsonism), a variety of other movement disorders, sensory disorders and an altered state of consciousness with fever. The most common neuroleptic-induced movement disorders are acute dystonic reactions (involuntary sustained twisting movements and postures), parkinsonism, and tardive dyskinesia syndromes (TDS). TDS can manifest as repetitive rhythmic movements most often affecting the mouth and limbs as well as other types of movement disorders (**Table 83.1**). TDS have variable delayed onset after the initiation of the offending drugs and persists even after they are discontinued (see **Table 83.1**). The common pathophysiologic mechanisms of neuroleptics are binding to and antagonizing dopamine D_2 receptors. The dopamine receptor blocking agents (DRBAs) are used not only as antipsychotic agents, such as the phenothiazines and the butyrophenones, but also for gastrointestinal disorders, such as metoclopramide. By definition, these disorders are iatrogenic and hence can be prevented, their risk minimized, and potentially reversed by making the diagnosis early and instituting appropriate treatment. Although the second-generation antipsychotics, often also called *atypical* antipsychotics have been developed to reduce these side effects, they are not entirely free of them.

EPIDEMIOLOGY

The prevalence of neuroleptic-induced neurologic disorders ranges from 20% to 50%. Drug-induced parkinsonism is the most common form. Neuroleptic exposure increases the risk of parkinsonism by twofold, increasing with age and female gender. Acute dystonic reactions occur in about 2% to 5% of patients exposed to neuroleptics, more commonly in children and young adults and in males than females. TDS may occur in about one quarter of patients exposed to these drugs but estimation of true incidence and prevalence vary and is often confounded by the fact that DRBAs mask the clinical manifestation of TDS. Classic tardive dyskinesia involving orofacial movements is most common with an annual incidence rate of about 5% in the first 4 to 5 years. TDS increase with cumulative exposure to DRBAs factoring in the dosage and the duration of treatment. Advanced age is the most consistent demographic risk factor. Gender difference is not consistently found. Prevalence and incidence vary

TABLE 83.1 Adverse Neurologic Effects of D_2 Receptor–Blocking Agents

Clinical Syndromes	Major Features
Acute dystonic reaction	Sustained twisting movements occurring within the first few days of exposure to DRBA including oculogyric crisis
Acute akathisia	Inability to sit still with motor and sensory features within a few days or weeks of DRBA treatment
Drug-induced parkinsonism	Clinical features mimicking idiopathic Parkinson disease in the setting of DRBA
Neuroleptic malignant syndrome	An idiosyncratic combination of fever, dysautonomia, and movement disorder that can be severe and fatal
Tardive Dyskinesia Syndromes	Delayed-onset abnormal involuntary movements or sensory symptoms that persist even after discontinuation of a DRBA
• Withdrawal emergent syndrome	Choreic movements in children after stopping DRBA
• Tardive dyskinesia	The classic tardive dyskinesia consisting of orobuccolingual and limb dyskinesia
• Tardive dystonia	Focal or generalized sustained twisting movements associated with chronic DRBA treatment
• Tardive akathisia	Restlessness consisting of subjective sensation of inability to sit still and stereotypic restless movements
• Tardive pain	Painful sensation that is often a focal form of tardive akathisia
• Tardive tics	Motor and vocal tics associated with chronic DRBA
• Tardive myoclonus	Lightning like jerky movements associated with chronic DRBA
• Tardive tremor	Tremor associated with chronic DRBA

Abbreviation: DRBA, dopamine receptor blocking agent.

in different regions of the world. Genetic studies have implicated variants in genes involved in drug metabolism or dopaminergic system to influence the risk of TDS. Tardive dystonia is rarer than the classic type and is more common in younger patients. Other TDS, including tardive akathisia, accounts for about 10% of all TDS.

PATHOBIOLOGY

The pathogenesis of neuroleptic-induced neurologic disorders such as parkinsonism is due to antagonization of dopamine effect at the D_2 receptors. The DRBAs that bind most tightly to the receptors are the ones most likely to induce parkinsonism and TDS. The second-generation antipsychotics are atypical in that they have less propensity to produce these complications, but most are not free of inducing these side effects. Clozapine (Clozaril), a drug that predominantly blocks the D_4 receptor and serotonin receptor subtypes, is relatively free of these complications, except for acute akathisia. The monoamine-depleting drugs, reserpine and tetrabenazine derivatives, can induce acute akathisia and drug-induced parkinsonism. Tetrabenazine has also been implicated in acute dystonic reactions and neuroleptic malignant syndrome. But none of the dopamine-depleting drugs has been convincingly implicated in causing persistent TDS. In addition, calcium channel blockers such as flunarizine and cinnarizine, and rarely selective serotonin reuptake inhibitors and lithium, produce parkinsonism and TDS, and the mechanism by which these drugs produce these complications is not known.

The pathogenesis of TDS, which can persist even after the discontinuation of the DRBAs is not well understood. Dopamine receptor upregulation occurs with the use of DRBAs, but its causality to produce TDS is not established. To explain its delayed onset and persistence, maladaptive synaptic plasticity has been proposed as an underlying mechanism. Others proposed a neurodegenerative process triggered by oxidative stress or by the drugs binding to neuromelanin with resulting internalization of the cell membrane, but all these hypotheses remain to be validated. Genetic polymorphism studies have noted association of variations of drug metabolism genes, monoamine receptors or transporters, and those associated with synaptic plasticity, but these findings need to be confirmed.

DIAGNOSIS

It is important to recognize the different phenomenologies caused by the DRBAs; each requires specific treatment.

Acute Dystonic Reaction

Acute dystonic reaction manifests as sustained, twisting movements and postures of the cranial, cervical, and other body parts. Severe sustained twisting and uncomfortable postures of limbs, trunk, neck, tongue, and face are dramatic. *Oculogyric crisis* is a form of dystonia in which the eyes are deviated conjugately in a fixed posture for minutes or hours. The diagnosis is made in the setting of recent exposure to a DRBA. Acute dystonic reaction tends to occur within the first few days of exposure to the DRBA and predominantly affects children and young adults, males more than females.

Acute Akathisia

Akathisia consists of a *subjective* sense of restlessness and the most characteristic complaint is the inability to sit still. Akathisia is associated with *motor* features of restlessness. These include frequent and repetitive stereotyped movements, such as pacing, repeatedly caressing the scalp, crossing and uncrossing the legs, and repetitive body rocking. Acute akathisia occurs within the first few days or weeks of DRBA use. It may also appear later in treatment as dosage is being increased. It can occur in subjects of any age. It is self-limiting if the offending drug is stopped.

Drug-Induced Parkinsonism

The diagnosis of drug-induced parkinsonism is based on the cardinal features of tremor at rest, bradykinesia and rigidity, plus the history of current or recently discontinuation of a neuroleptic drug.

Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome (see also Chapter 133) is a rare complication characterized by a triad of fever, signs of autonomic dysfunction (eg, pallor, diaphoresis, blood pressure instability, tachycardia, pulmonary congestion, tachypnea), and a movement disorder (usually akinesia and rigidity) with the history of recent exposure to a DRBA. The level of consciousness may be depressed with obtundation and confusion, eventually leading to stupor or coma; death may occur. Neuroleptic malignant syndrome can occur any time during DRBA treatment.

Tardive Dyskinesia Syndromes

The diagnosis of TDS depends on the recognition of a typical pattern of abnormal involuntary movements or sensory symptoms plus documented use of the offending agents. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed) criteria notes at least 1 to 3 months of exposure for the diagnosis, depending on the age of the patient. The symptoms should have either started while the patient was still taking the drug or within 3 months of discontinuing the drug and persists at least 1 month after medication change or discontinuation. The timing is a continuous spectrum, however, and TDS has been noted even after a few days of DRBA exposure. The TDS is the most feared complications of antipsychotic medications because the symptoms can be long-lasting and often permanent.

Withdrawal Emergent Syndrome

Withdrawal emergent syndrome may be a mild variant of TDS. "Emergent" implies that the symptoms emerge after abrupt cessation of the chronic use of an antipsychotic drug. The syndrome is primarily one of children and persist only for a few weeks before dissipating. The abnormal movements resemble those of Sydenham chorea; they are not stereotyped and repetitive, as seen in classic TDS.

Classic Tardive Dyskinesia

Classic tardive dyskinesia consists of repetitive (stereotypic) movements. The lower part of the face is most often involved. This orobuccolingual dyskinesia resembles continual chewing movements, with the tongue intermittently darting out of the mouth. Movements of the trunk may cause a repetitive pattern of flexion and extension (body rocking). The distal parts of the limbs may show incessant flexion-extension movements.

The proximal muscles are usually spared, but respiratory dyskinesias may occur.

The classic tardive dyskinesia should be differentiated from other movement disorders affecting the face. Patients with Huntington disease show facial chorea. They are frequently treated with antipsychotic drugs; a resulting tardive dyskinesia may be superimposed on the chorea; the presence of akathisia or repetitive (stereotyped) involuntary movements suggests the additional diagnosis of tardive dyskinesia. Other differential diagnoses to be considered include chorea and stereotypies involving face from other drugs such as levodopa, anticholinergic drugs, phenytoin, antihistamines, and tricyclic antidepressants. Other neurologic disorders such as hepatocerebral degeneration and cerebellar and brainstem stroke should be considered as are the abnormal involuntary movements from edentulous malocclusion.

Several other important forms of TDS are now recognized. Unlike the classic orobuccolingual dyskinesia described earlier, these other forms can be more disabling.

Tardive Dystonia

Tardive dystonia is a chronic dystonia caused by DRBAs. Individuals of all ages are susceptible to tardive dystonia, and younger individuals are more likely to have a more severe generalized form. In older individuals, tardive dystonia is usually focal (affecting a single body part), often in the face or neck, and may remain confined to these regions or may spread to the arms and trunk. The legs are infrequently affected. Often, neck involvement consists of retrocollis and the trunk arches backward. The arms are typically rotated internally, the elbows extended, and the wrists flexed. The differential diagnosis includes all the many causes of dystonia. Oromandibular dystonia is probably the most common form of spontaneous oral dyskinesia. Often, oromandibular dystonia takes the appearance of a repetitive opening and closing of the jaw as the patient attempts to overcome the muscle pulling. To discern if the repetitive movements are volitional or spontaneous, the examiner should ask the patient not to fight the movements but to let them come out as they want to. In dystonia, there will usually be a sustained contraction, such as jaw opening or clenching. Wilson disease, in particular, must be excluded specifically in patients with psychiatric symptoms and dystonia.

Tardive Akathisia

Tardive akathisia is another important disabling variant of tardive dyskinesia. It is a chronic akathisia consisting of a subjective aversion to being still. Motor signs of restlessness include frequent, repeated, stereotyped movements, such as marching in place, crossing and uncrossing the legs, and repetitively rubbing the face or hair with the hand. Patients may make moaning sounds. Patients may not use the word "restless" to describe their symptoms, instead they may use expressions such as "going to jump out of my skin" or "jittery" or "exploding inside." In contrast to acute akathisia, the delayed type tends to become worse when antipsychotic medication is withdrawn, similar to other TDS on discontinuance of these drugs. As with other types of TDS, tardive akathisia tends to persist. Usually, tardive akathisia is associated with classic orobuccolingual dyskinesia. Classic tardive dyskinesia, tardive dystonia, and tardive akathisia may occur together. Akathisia can appear as focal discomfort, such as pain, which can be exceedingly distressing. The diagnosis of focal akathisia is challenging and is discussed further in the following text.

Other Tardive Syndromes

Less common variants of tardive dyskinesia include tardive pain, tardive tics, tardive myoclonus, and tardive tremor. Tardive pain most commonly manifests as painful or burning mouth or vagina. These may be the unpleasant symptoms of focal akathitic complaint that patients often refer to as pain. Tardive tics are rare and similar to phenomenology of chronic motor tics or Tourette syndrome. Myoclonus can occur from many different etiologies and neuroleptics may induce them as a delayed-onset tardive syndrome. Tardive tremors are distinguished from essential tremor, Parkinson disease, cerebellar tremor, and other facial tremors by its etiology. The tardive syndromes involving facial movements need to be differentiated from hemifacial spasm, myokymia, and synkinesis of facial muscles from faulty regeneration after facial nerve injury based on their difference in phenomenology.

MANAGEMENT

Efforts should be made to prevent the neuroleptic-induced complications because these are iatrogenic disorders. Antipsychotic drugs should be given only when indicated, namely, to control psychosis or a few other conditions where no other effective agent has been helpful, as in some choreic disorders or tics. These drugs should not be used indiscriminately, and when they are used, the dosage and duration should be as low and as brief as possible. If the psychosis has been controlled, the physician should attempt to reduce the dosage and even try to eliminate the drug, if possible. In nonpsychotic disorders, such as tics, other drugs should be tried first, and only if they fail should a DRBA be used.

Acute Dystonic Reaction

Acute dystonic reaction is easily reversible with parenteral administration of antihistamines (eg, diphenhydramine 50 mg intravenously), anticholinergic drugs (eg, benztropine mesylate 2 mg intramuscularly), or diazepam (5-7.5 mg intramuscularly).

Acute Akathisia

Acute akathisia disappears on discontinuance of the offending drug. Acute akathisia sometimes improves with the β-adrenergic blocker propranolol given in doses of 20 to 80 mg/d or mirtazapine (15 mg/d).

Drug-Induced Parkinsonism

Drug-induced parkinsonism has a variable response to levodopa (titrated up to 600-1,500 mg). Oral anticholinergic drugs (trihexyphenidyl 2-15 mg/d) and amantadine (up to 300 mg/d) are effective. On withdrawal of the offending antipsychotic drug, the symptoms slowly disappear in weeks or months.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome, a potentially lethal condition, treatment needs to be started immediately with hospitalization, initiating supportive therapy including intravenous hydration and cooling to address medical complications such as fever, rhabdomyolysis, and renal failure. The withdrawal of the antipsychotic medication is critical. Although controlled trials have

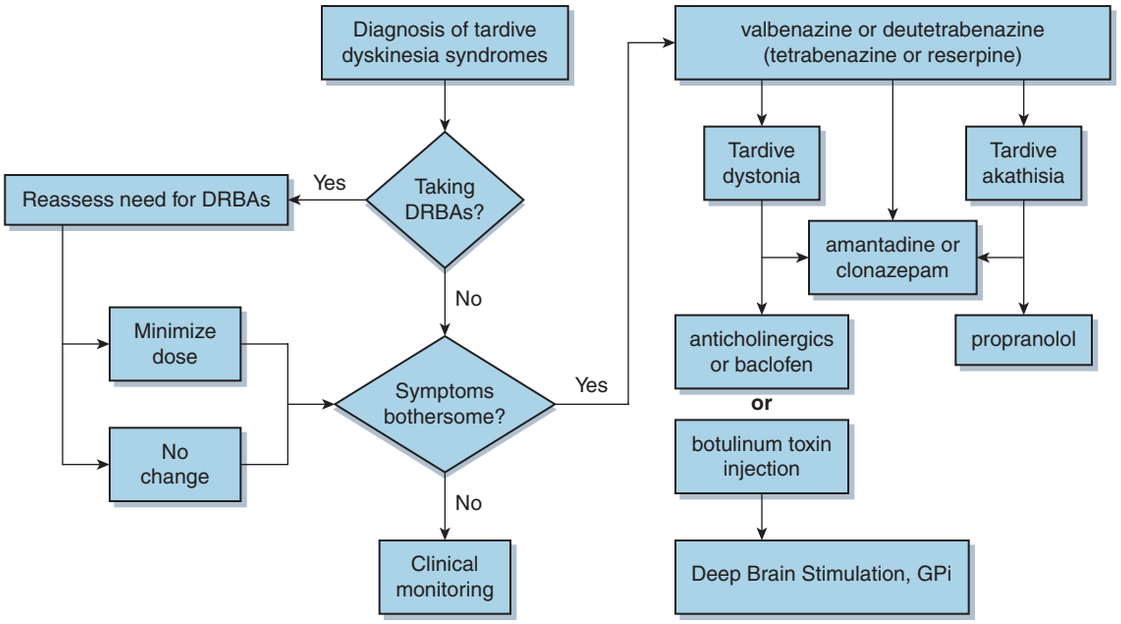

FIGURE 83.1 Treatment algorithm for tardive dyskinesia syndromes. Abbreviation: DRBAs, dopamine receptor blocking agents.

not been conducted, numerous reports suggest that dantrolene sodium, a muscle relaxant, and levodopa or direct-acting dopamine agonists, may be beneficial. Carbamazepine is also effective. In most patients, the antipsychotic medication can be restarted later without recurrence of the syndrome.

Tardive Dyskinesia Syndromes

Once TDS have appeared, the logical treatment approach calls for eliminating or reducing the dosage of the causative agents, DRBAs, especially in cases where alternative approaches are available and the indication was a short-term relief of gastrointestinal or psychiatric problems (**Fig. 83.1**). It is prudent to taper DRBAs slowly to avoid worsening of the original indication and TDS. Reducing the dosage or discontinuing the offending drug can worsen the disorder in the first few weeks after withdrawal or even unmask the TDS that were not noticed. Switching from the first-generation antipsychotic medication to the newer antipsychotics is also reasonable because the incidence of TDS is less with many of the newer antipsychotics, but there is no evidence that such a switch improves TDS once it started. Paradoxically, starting or increasing the dose of DRBAs can reduce TDS, by masking the movements. Because DRBAs are the offending agents, such approach is used as the last resort and temporarily. The withdrawal emergent syndrome is self-limiting but may take weeks to resolve. Reintroducing the antipsychotic drug and then slowly tapering the dosage can eliminate the choreic movements of withdrawal emergent syndrome.

If the TDS symptoms are too distressing, treatment with vesicular monoamine transporter (VMAT) inhibitors that depletes monoamines may suppress the TDS (see **Table 83.2** and **Fig. 83.1**). Reserpine (0.75-1.5 mg/d) is a nonspecific VMAT inhibitor and tetrabenazine (25-150 mg/d) and its analogs are more selective inhibitors for VMAT2, which is present preferentially in the central nervous system, and therefore produce less side effects. Deutetrabenazine is a modified form of tetrabenazine that has slower metabolism and can be started at 6 mg twice a day and increased by 6 mg a day up to 24 mg twice a day. Most patients improve on 24 to 36 mg/d. A short-term trial up to 3 months did not show significant side effects LEVEL 1.[1,2] Valbenazine is another selective VMAT2 inhibitor that can be used at 40 to 80 mg once daily LEVEL 1.[3] Side effects of these VMAT inhibitors may consist of worsening or producing parkinsonism, depression, sedation, akathisia, dry mouth, and lowered blood pressure. The dosage should be increased gradually to minimize the side effects. Tardive dystonia may also be treated by anticholinergic drugs such as trihexyphenidyl, baclofen, or botulinum toxin injections if focal tardive dystonia is the predominant concern (see **Table 83.2** and **Fig. 83.1**). Deep brain stimulation targeted to globus pallidus interna can be considered when medication therapy fails. For tardive akathisia, propranolol may be tried (see **Table 83.2** and **Fig. 83.1**).

OUTCOME

Neuroleptic-induced movement disorders can be a diagnostic challenge and difficult to manage. In general, they improve with reduction or discontinuation of the neuroleptics, but TDS can persist despite discontinuation of the offending drugs. There are only a few published data on remission of TDS after complete withdrawal of DRBAs; the prevalence of the remission is surprisingly low, ranging from 2% to 13% although improvement is seen in about 20% to 30%. For those who remain on the DRBAs may also show apparent disappearance of tardive dyskinesia in up to 60% of cases, but their symptoms are likely masked by DRBAs because their improvement is often associated with worsening of parkinsonism. The best outcome we should aim for is to minimize the risk of this iatrogenic disorder by judicious use of neuroleptics.

Videos can be found in the companion e-book edition. For a full list of video legends, please see the front matter.

TABLE 83.2 Treatment Options for Tardive Dyskinesia Syndromes

Medication	Dose Range	Side Effects
Valbenazine	6-24 mg twice a day	QT prolongation, somnolence, akathisia
Deutetrabenazine	40-80 mg once daily	Depression, QT prolongation, akathisia, neuroleptic malignant syndrome, parkinsonism
Tetrabenazine	25-150 mg/d divided in three or four doses	Depression, QT prolongation, akathisia, neuroleptic malignant syndrome, parkinsonism
Reserpine	0.75-1.5 mg/d divided in three or four doses	Depression, hypotension, akathisia
Clonazepam	0.25-6 mg/d divided in three or four doses	Drowsiness, dizziness, fatigue, irritability
Amantadine	100-400 mg/d divided in three or four doses	Hallucinations, dizziness, peripheral edema, nausea
Ginkgo biloba	80-240 mg/d divided in three doses	Bleeding disorders, headache, dizziness, constipation
Deep brain stimulation	Globus pallidus interna	Infection, intracerebral hemorrhage, gait and speech disturbances, paresis, confusion
For Tardive Dystonia Only		
Trihexyphenidyl	1-40 mg/d divided in three or four doses	Blurred vision, dizziness, confusion, drowsiness, constipation, urinary retention
Baclofen	10-100 mg/d divided in three or four doses	Drowsiness, dizziness, weakness, confusion, fatigue
Botulinum toxin	Local injection	Excessive weakness of injected muscles
For Tardive Akathisia Only		
Propranolol	20-160 mg/d divided in three or four doses	Fatigue, dizziness, bradycardia, hypotension, depression

LEVEL 1 EVIDENCE

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