Iatrogenic Neurology

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Chapter 12
Drug-Induced Movement Disorders

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Objectives

- To recognize that prescription drugs may cause tremor, parkinsonism, chorea, dystonia, myoclonus, or tics
- To emphasize the importance of reviewing all current and prior medications when evaluating patients with movement disorders
- To understand that the most common medicines that cause clinically significant and disabling movement disorders are those prescribed for psychiatric disorders such as psychosis and depression
- To gain familiarity with disorders caused by dopamine receptor–blocking agents (DRBAs), such as acute akathisia, acute dystonic reactions, neuroleptic malignant syndrome (NMS), neuroleptic-induced parkinsonism (NIP), and the tardive syndromes
- To appreciate that chronic levodopa therapy for Parkinson's disease (PD) frequently causes fluctuating chorea and dystonia
- To be aware that most drug-induced movement disorders are transient and remit with discontinuation of the offending agent; the main exceptions to this are the often permanent tardive syndromes

Abnormal, involuntary movements are a common side effect of many prescription drugs. It is imperative that the clinician review all current and prior medications when evaluating patients with movement disorders. The main categories of abnormal movements include tremor, parkinsonism, chorea, dystonia, myoclonus, and tics. Tremor is a rhythmic oscillation of a body part and may occur when the limb is at rest (resting tremor), when held in suspension (postural tremor), or when performing an action (action tremor). Parkinsonism consists of bradykinesia (slowness of movement), resting tremor, cogwheel rigidity (increase in muscle tone) and postural instability. Chorea involves brief, jerky, unpredictable movements that flit from one part of the body to another. Dystonia includes sustained muscle contractions that result in twisting repetitive movements or static abnormal postures. Myoclonus is a brief, lightning-like jerk that can involve active muscle contraction (positive myoclonus) or inhibition of ongoing muscle activity (negative myoclonus). Hiccups and sleep jerks are common examples of positive myoclonus, whereas asterixis represents negative myoclonus. Tics are brief, repetitive, stereotyped movements or sounds that occur randomly. Patients with tics often have a feeling of inner tension before a tic movement and a sense of relief once the movement has been completed. Unlike the previously described abnormal movements, which are involuntary, akathisia is a usually considered voluntary because the patient is compelled to move to relieve inner restlessness.

This chapter describes common culprits of drug-induced movement disorders. Most of the discussion

Table 12.1. Drugs that May Cause Tremor

Beta-adrenergic agonists
Theophylline
Caffeine
Nicotine
Lithium
Antiepileptic drugs (valproic acid, lamotrigine)
Tricyclic antidepressants
Monoamine oxidase inhibitors
Amphetamines
Dopamine receptor–blocking agents (antipsychotics, metoclopramide, prochlorperazine, droperidol, domperidone, promethazine)
Corticosteroids
Thyroid hormone
Cardiac antiarrhythmics (amiodarone, procainamide)
Calcium channel blockers (nimodipine, flunarizine)
Pindolol (see Chapter 20)
Cimetidine[139]
Ethanol

Source: Adapted from WC Koller. Treatment of Tremor Disorders. In R Kurlan (ed), Treatment of Movement Disorders. Philadelphia: Lippincott, 1995;407.

Table 12.3. Drugs that May Cause Chorea

Dopamine receptor–blocking agents (antipsychotics, metoclopramide, prochlorperazine, droperidol, domperidone, promethazine)
Levodopa
Antiepileptic drugs (phenytoin, carbamazepine, ethosuximide, valproate, gabapentin [in therapeutic range]; phenobarbital toxicity)
Anticholinergics[150]
Amphetamines (see Chapter 22)
Oral contraceptives
Tricyclic antidepressant
Selective serotonin reuptake inhibitors
Cimetidine[151]
Cyclosporin[152]
Theophylline[153]
Clebopride[154]
Oxymetholone (anabolic steroid)[155]
Lithium[156]

Table 12.2. Drugs that May Cause Parkinsonism

Dopamine receptor–blocking agents (antipsychotics, metoclopramide, prochlorperazine, droperidol, domperidone, promethazine)
Dopamine-depleting agents (tetrabenazine, reserpine)
Alpha-methyldopa
Meperidine[140]
Lithium
Calcium channel blockers[141–143]
Disulfiram[144]
Phenytoin
Selective serotonin reuptake inhibitors
Amiodarone (see Chapter 20)
Clebopride[145, 146]
Cephaloridine[147]
Amphotericin B (intraventricular)[148]
Manganese intoxication with parenteral nutrition[149]

Table 12.4. Drugs that May Cause Dystonia

Dopamine receptor–blocking agents (antipsychotics, metoclopramide, prochlorperazine, droperidol, promethazine, sulpiride[157] and domperidone[158])
Tetrabenazine[159]
Dopamine agonists (levodopa)
Antiepileptic drugs (phenytoin, carbamazepine, ethosuximide)
Selective serotonin reuptake inhibitors
Antimalarials (amodiaquine,[160] chloroquine[161])
Diphenhydramine[162]
Fentanyl[163]
Disulfiram[164]
Midazolam[165]
Ondansetron[166]

focuses on agents that alter brain dopamine activity such as neuroleptics and levodopa. The abnormal movements caused by antidepressants, especially the newer agents that alter serotonergic transmission, are also reviewed. Tables 12.1 through 12.6 summarize which drugs can potentially cause abnormal movements; however, not all of these drugs are discussed. Movement disorders caused by cardiovascular drugs are included in Chapter 20.

Dopamine Receptor–Blocking Agents

The medicines that have the most potential for causing uncomfortable, disabling, and often permanent movement disorders are the DRBAs, also referred to as neuroleptics (these terms may be used interchangeably). Although DRBA-induced neurologic dysfunction probably represents the most common iatrogenic disorder to result in liti-

Table 12.5. Drugs that May Cause Myoclonus

Antidepressants (tricyclics, monoamine oxidase inhibitors)
Levodopa
Lithium
Anti-infectious agents (penicillin, carbenicillin, ticarcillin, cephalosporins, antihelmintic agents)
Anesthetic drugs (amidate)
Bismuth subsalicylate (i.e., Pepto-Bismol)[167]
Chlorambucil
Antiepileptics (valproic acid, carbamazepine)
Sedative hypnotics (methaqualone, bromisovalum)
Fentanyl[163]
Antihistamine
Diclofenac
Water-soluble contrast media (metrizamide, myelografin, angiografin, isocarmate meglumine, iothalamate meglumine)
Nifedipine, verapamil (see Chapter 20)
Prednimustine[168]
Propafenone[169]

Source: Adapted from HL Klawans, PM Carvey, CM Tanner, et al. Drug-Induced Myoclonus. In S Fahn, CD Marsden, M Van Woert (eds), Advances in Neurology Series, Vol 43: Myoclonus. New York: Raven, 1986;251.

Table 12.6. Drugs that May Cause Tics

Stimulants
Levodopa
Dopamine receptor–blocking agents
Carbamazepine

Table 12.7. Neurologic Complications of Dopamine Receptor–Blocking Agents

Acute dystonic reactions
Acute akathisia
Neuroleptic malignant syndrome
Neuroleptic-induced parkinsonism (including "rabbit syndrome")
Tardive dyskinesia

gation, these agents remain one of the most widely used classes of drugs. The most common indication for prescribing DRBAs is for the primary treatment of psychosis and for the management of some affective and behavioral disorders. Although DRBAs are commonly prescribed for schizophrenia, these agents are often used to treat elderly demented patients with agitation, hallucinosis, or aggression. Some drugs used primarily for depression may have DRBA properties or may actually include a neuroleptic. Examples include Triavil, a combined preparation of amitriptyline and perphenazine (a neuroleptic), and amoxapine, a tricyclic with DRBA activity. Neuroleptics are often used by neurologists to treat tics and chorea. Other commonly used DRBAs include antiemetics such as metoclopramide (Reglan), prochlorperazine (Compazine), droperidol (Inapsine), and domperidone (Motilium), as well as the antivertigo agent, promethazine (Phenergan).

The abnormal involuntary movements caused by DRBAs are listed in Table 12.7. Acute dystonic reactions typically develop 23–28 hours after initiation of neuroleptic treatment,[1] with 85% of episodes occurring within 96 hours.[2] An increase in neuroleptic dose or discontinuation of anticholinergic drugs during ongoing neuroleptic treatment may also cause acute dystonia. The estimated incidence of neuroleptic-induced dystonia is approximately 10%,[3] but may vary depending on the patient population studied and the type of neuroleptic used. Risk factors for the development of acute dystonia include young age, male sex, use of high potency or depot neuroleptics (haloperidol [Haldol], fluphenazine [Prolixin]), prior vulnerability to acute dystonic reactions, recent cocaine abuse,[4] and concurrent medical conditions such as hyperthyroidism or hypoparathyroidism. The potency of a neuroleptic drug to cause extrapyramidal effects is related to its ability to bind to postsynaptic dopamine receptors in the striatum (caudate and putamen). The highest potency neuroleptics, in decreasing order of potency, are thiothixene (Navane), Prolixin, perphenazine (Trilafon), trifluoperazine (Stelazine), triflupromazine (Vesprin), and Haldol. Low-potency neuroleptics, in increasing order of potency, are clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), molindone (Moban), loxapine (Loxitane), thioridazine (Mellaril), and chlorpromazine (Thorazine). Clozapine, olanzapine, and risperidone are considered "atypical neuroleptics" because they have a weak propensity to bind dopamine receptors and probably exert antipsychotic effects by reducing serotonergic transmission.[5] Although clozapine (Clozaril) is more effective than

standard neuroleptics in the treatment of refractory psychosis and has minimal DRBA activity, its use is often limited by an approximately 1% risk of agranulocytosis, requiring patients to have weekly monitoring of the complete blood cell count and differential.[6] Clozapine has been reported to cause oculogyric crisis[7] and acute dystonia,[8] although this should be considered rare.

Little is known about the pathophysiology of acute dystonic reactions, but alterations in cholinergic, dopaminergic, gamma-aminobutyric acid (GABA), and sigma opiate receptor activity have been suggested. It is generally accepted that cholinergic transmission is excessive, but it is unclear whether dopamine activity is too low or too high. On one hand, acute dystonia may result from a reduction of dopamine activity by postsynaptic receptor blockade. However, dopamine receptor supersensitivity occurs soon after the first dose of neuroleptic agent, suggesting increased dopamine transmission as causative.[9] Symptoms of acute dystonia may be mild and only include a sensation of tongue thickness with no dysarthria. More commonly, symptoms are more severe and include opening or closing of the jaw, protrusion of the tongue, grimacing, tightness in the throat, pulling of the head to the side or backward, posturing of the limbs or torso, or oculogyric crisis where the eyes are forced upward and often to one side. Most terrifying is the rare manifestation of extreme laryngeal spasm that can compromise airway function and lead to sudden death. Adults tend to have involvement of the eyes, face, neck, and throat, whereas children tend to develop generalized dystonia. Acute neuroleptic-induced dystonia resolves spontaneously if the drug is discontinued. Because symptoms are often frightening and uncomfortable, however, parenteral treatment is usually indicated and is uniformly successful. The most effective medications include anticholinergics such as benztropine (Cogentin) and biperiden (Akineton) or the anticholinergic and antihistaminic agent diphenhydramine (Benadryl). For acute dystonia in adults with intravenous access, benztropine, 1–2 mg over 2 minutes, or diphenhydramine, 10–50 mg, should be given. Symptoms usually resolve in 2–5 minutes. If dystonia persists, the dose should be repeated. If this is unsuccessful, give diazepam, 5–10 mg. In adults without intravenous access, benztropine, 1–2 mg, may be given intramuscularly, but the response will be delayed. For acute dystonia in children, give intravenous diphenhydramine, 1–2 mg per kg up to 50 mg over 2 minutes, with a maximum of 400 mg in 24 hours.[10] For patients who require continued neuroleptic treatment, oral anticholinergic treatment to prevent recurrence should be continued for 1–2 weeks or longer for patients receiving a depot preparation. Once the acute episode has resolved, the clinician may be faced with an angry (or litigious) patient if the possibility of acute dystonia was not mentioned before starting the DRBA. Sometimes, anticholinergic prophylaxis should be considered in patients who are at high risk of developing acute dystonia or in patients for whom such a reaction would be exceptionally disturbing. This category includes children, young adult men, patients with prior acute dystonic reactions, and paranoid patients who may have delusions of an outside force controlling their body that may be reinforced by the dystonia.

Akathisia is a subjective sensation of restlessness that is associated with difficulty remaining still. Movement temporarily relieves akathisia, only to return immediately once the patient is again resting. There is often a compulsion to move one's legs that results in pacing, rocking, tapping the foot, swinging one leg while sitting, or shifting from one foot to another while standing. When seated, akathisic patients appear fidgety, frequently shift position, and sometimes lift themselves off the chair. Prevalence estimates of acute akathisia range from 20% to 75%.[11] Although symptoms may begin within hours of initiating DRBA treatment, more commonly, akathisia develops after days or weeks and is more likely to occur with high-potency or depot agents. The physiologic disturbance in akathisia may be blockade of mesocortical dopamine receptors.[12] The subjective distress of akathisia is a major cause of noncompliance with antipsychotic medications and, when severe, can lead a patient to consider suicide. Treatment of akathisia includes DRBA discontinuation (if possible), dose reduction, change to a lower potency drug, or change to an atypical neuroleptic. When additional treatment of akathisia is required, beta-blockers are probably the drugs of choice (i.e., propranolol, 20–120 mg per day; metoprolol, 75–200 mg per day). When the patient has neuroleptic-induced parkinsonism (NIP) in addition to akathisia, amantadine (25–100 mg twice daily) or anticholinergics (benztropine, 1–2

mg three times per day; trihexyphenidyl, 2–5 mg three times per day; diphenhydramine, 25–50 mg three times per day; biperiden, 2–4 mg three times per day) should be used. The syrup preparation of amantadine (50 mg per teaspoon) allows the lowest therapeutic dosing. Patients resistant to these therapies may be given clonazepam or clonidine. Treatment of akathisia is usually continued for a few weeks and then stopped if possible. Even when the DRBA is discontinued, it may take 1–2 weeks for acute akathisia to resolve. A persistent form of akathisia is discussed later as tardive akathisia.

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication of DRBA treatment. Patients with PD are also at risk for NMS when dopaminergic drugs are drastically lowered or discontinued. Both situations reduce central dopaminergic transmission, especially in the hypothalamic temperature regulation area and striatum, which may lead to the development of the cardinal clinical features of NMS: (1) fever, (2) rigidity, (3) altered mental status, and (4) autonomic dysfunction. NMS occurs in approximately 1% of patients treated with standard neuroleptics.[13] Even the atypical neuroleptics, clozapine and risperidone, have on rare occasion, been reported to cause NMS,[14, 15] as has tetrabenazine, a dopamine-depletor with some DRBA activity.[16–18] Symptoms of NMS typically begin within 2 weeks of starting the DRBA but can occur hours after the first dose or after years of treatment. Patients who are dehydrated, exhausted, or severely agitated may be predisposed to developing NMS. Other risk factors include use of high-potency or depot neuroleptics. However, most patients with NMS have had prior uncomplicated exposure to neuroleptics. The diagnosis of NMS should always be considered in any patient taking a neuroleptic with new fever, confusion, and extrapyramidal symptoms. Fever is present in virtually all patients with NMS but may not appear until after the motor signs. Fever is usually in the range of 101–104°F but may be greater than 105°F.[19] Rigidity is present in approximately 90% of patients; tremor or dystonia are also common. Changes in mentation occur in 75% of patients and range from agitation to prominent reduction in consciousness. Autonomic disturbances include diaphoresis, cardiac arrhythmias, urinary incontinence, and labile blood pressure. Laboratory abnormalities that support the diagnosis of NMS include elevated creatine kinase, typically above 1,000 IU per liter, leukocytosis, elevated liver enzyme levels, low serum iron concentration, proteinuria, and myoglobinuria, although all of these are nonspecific.

Table 12.8. Differential Diagnosis of Neuroleptic Malignant Syndrome

Central nervous system infection (encephalitis, meningitis, rabies)
Acute dystonic reaction
Drug-induced parkinsonism
Heat stroke
Status epilepticus
Lethal catatonia
Drug allergy
Malignant hyperthermia
Serotonin syndrome
Diabetic ketoacidosis
Metabolic encephalopathy
Strychnine poisoning
Tetanus

The diagnosis of NMS is one of exclusion, requiring aggressive diagnostic studies to exclude other life-threatening conditions, most important, CNS infection or status epilepticus. Patients with heat stroke do not sweat, unlike patients with NMS who experience prominent diaphoresis. It is often difficult, if not impossible, to distinguish lethal catatonia from NMS; however, NMS develops over hours and days, whereas lethal catatonia often includes 1–2 weeks of prodromal symptoms of mood instability, insomnia, intense motor excitement, and confusion. Because an acute dystonic reaction may mimic NMS, a single dose of parenteral anticholinergic is often given to make this distinction. The differential diagnosis of NMS is summarized in Table 12.8.

Treatment of NMS includes rapid recognition of the diagnosis, immediate withdrawal of the DRBA, admission to an intensive care unit, and initiation of dantrolene sodium (50–100 mg every 6 hours per nasogastric tube or orally) and bromocriptine (2.5–10.0 mg three times per day).[20] When NMS is caused by reduction of Parkinson's medications, the previous doses should be restarted. NMS should be treated aggressively, given the mortality of 11%. Alkalinization of urine is recommended to prevent myoglobinuria. Symptoms should begin to resolve within 2–3 days. Treatment should be continued for

10 days if the DRBA was taken orally and for 2–3 weeks if a depot preparation was causative. Once NMS symptoms resolve, patients should not be challenged with standard neuroleptics for 2 weeks. Although clozapine, olanzapine, and risperidone may be the drugs of choice after NMS, it is also reasonable to introduce a lower potency standard neuroleptic and titrate slowly. Electroconvulsive therapy may be helpful in treating the psychosis in acute NMS during the time when neuroleptics are contraindicated.

NIP is caused by drugs that block striatal dopamine receptors (DRBAs) or by agents that function presynaptically by reducing dopamine stores (i.e., reserpine, tetrabenazine). NIP symptoms and signs include reduced facial expression, hypophonia, drooling, slowness of movement, rigidity, resting tremor, micrographia, reduced arm swing, flexed posture, and postural instability. NIP is clinically indistinguishable from PD, although signs are typically symmetric and bilateral in NIP compared with the asymmetric presentation and course of PD. The "rabbit syndrome" (perioral and perinasal rhythmic 4- to 6-Hz tremor that looks like a rabbit chewing) is most often a manifestation of NIP but can, on occasion, be seen in PD. The rabbit syndrome may be a restricted manifestation of NIP and, like NIP-induced tremor, responds well to anticholinergics. NIP generally occurs later than akathisia and acute dystonia, often developing weeks after initiation of neuroleptic therapy or after a dose increase during ongoing treatment. The main risk factors for development of NIP are high neuroleptic potency and high neuroleptic dose.

Treatment of NIP includes the following options: (1) withdrawal or dose reduction of the offending agent; (2) addition of antiparkinson drugs such as amantadine, anticholinergics, levodopa, or dopamine agonists; or (3) change to an atypical neuroleptic. NIP refractory to these measures may improve with electroconvulsive therapy. NIP usually resolves within a few weeks or months of stopping the DRBA but symptoms may persist for much longer. In general, the diagnosis of PD should not be given to anyone who has taken a DRBA within the past year unless there is clear evidence that the parkinsonism has worsened since the DRBA was stopped.

Whether treated or not, NIP is a transient phenomenon even during continued neuroleptic exposure. Antiparkinson drugs can usually be successfully stopped after a few weeks. On a final note, most patients with NIP receive the DRBA from their physician, and this is documented in the medical record. However, there are some patients who ingest medications belonging to a friend or relative without knowing the nature of the drug and may not admit this to their physicians. The clinician must sometimes be persistent in questioning such patients. There are rare but unusual reports of unsuspected, surreptitious neuroleptic exposure. As described by Albanese et al.,[21] three men with parkinsonism who repeatedly improved in the hospital but worsened at home were being given haloperidol by their wives. One man had the neuroleptic dissolved in his coffee. A clue that this was a drug-induced parkinsonism was the coexistence of akathisia.

Of all the drug-induced movement disorders, tardive dyskinesia (TD) is the most clinically significant and potentially disabling. TD refers to a variety of persistent (usually longer than 3 months in duration) abnormal involuntary movements caused by DRBAs. All of the standard neuroleptics have been implicated as culprits of TD. The prevalence of TD among patients on chronic neuroleptic therapy is approximately 20%.[22] Likely risk factors for the development of TD include advancing age[23] and, to a lesser extent, female sex[24] and duration of neuroleptic exposure. The risk of TD is fairly stable from ages 20 to 40 years but then increases dramatically. The risk of TD for a 20-year-old patient after 2 years of neuroleptic exposure is 10% and after 4 years is 18%. For a 40-year-old patient, the risk is 18% at 2 years and 30% at 4 years.[25] In patients older than age 45 years, the cumulative incidence of TD after neuroleptic exposure is 26%, 52%, and 60% after 1, 2, and 3 years, respectively.[26] Children and adolescents have an extremely low chance of developing persistent tardive syndromes.[27] Despite rare reports that the newer atypical neuroleptics risperidone and clozapine[28] may also cause TD, the risk with these agents is minimal compared with that of classic neuroleptics.[29] The three patients described with risperidone-associated TD all had prior exposure to standard neuroleptics, and one patient had a history of TD.[30–32]

TD typically begins insidiously after several years of ongoing DRBA treatment but can occur after only a few months (or even days) of exposure. Most strikingly, TD commonly appears acutely

after DRBA discontinuation or dose reduction. It is generally accepted that a movement disorder should begin within 3 months of stopping a DRBA for a diagnosis of TD to be considered.[33] However, there is no absolute period of time between stopping a DRBA and onset of abnormal movements that excludes the diagnosis of TD. The TD syndromes behave predictably to DRBA manipulations, and this is often of diagnostic importance. For example, TD worsens on neuroleptic dose reduction or discontinuation and improves with neuroleptic dose increase. This clinical improvement is deceiving because the TD is being masked by higher doses of neuroleptics while the underlying physiologic disturbance persists or worsens with continued exposure to the offending agent. The cause of TD remains elusive but probably includes postsynaptic striatal dopamine supersensitivity due to upregulation in response to long-standing receptor blockade as well as D_1- and D_2-receptor imbalance. Changes in GABA, acetylcholine, serotonin, and sigma opiate receptors have also been implicated. In addition, neuroleptics may be toxic to neurons in the substantia nigra and striatum by generation of free radicals or lipid peroxidation.[34, 35]

The TD syndromes are listed in Table 12.9. "Classic TD" most often refers to the repetitive, rhythmic, purposeless movements (tardive stereotypies) or sounds that most physicians recognize as TD. Tardive stereotypies typically involve the oral-buccal-lingual region and include lip pursing or smacking, tongue protrusion ("fly-catcher's tongue"), rolling the tongue within the mouth, pressing the tongue against the cheek ("bon-bon sign"), chewing, blowing, teeth clenching, side-to-side jaw movements, and puffing out the cheeks. Examples of tardive stereotypies affecting the body are "piano-playing" movements of the fingers and pelvic rocking ("copulatory dyskinesia"). TD may be manifest as respiratory dyskinesia such as irregular breathing, panting, gasping, or as vocalizations such as moaning or humming. On occasion, patients with TD may develop true choreatic movements that flow from one muscle to another in random fashion unlike the repetitive movements of tardive stereotypy.

The withdrawal-emergent syndrome is the transient chorea that can occur after abrupt withdrawal of a DRBA. This most often affects children, and the chorea remits within 3 months. Tardive akathisia includes the same feeling of restlessness and need to move as does acute akathisia; however, tardive akathisia begins after many months or years of treatment with a DRBA and is a persistent disorder. Tardive akathisia often includes rubbing of the face, picking at clothes, rocking, side-to-side movement of the feet with legs crossed, pacing or marching in place, and alternating sitting and standing. There is a pharmacologic distinction between acute and tardive akathisia. DRBA discontinuation or dose reduction improves acute akathisia and exacerbates tardive akathisia. There is an overlap in the types of movements seen in akathisia and classic TD, such as body rocking or repetitive hand or foot movements. In general, patients with TD are moving and therefore restless, whereas patients with akathisia are restless and therefore moving.[36] When patients taking standard neuroleptics develop disabling akathisia, a change to clozapine appears to be helpful. Surprisingly, such patients often continue to experience restlessness albeit of lesser severity.[37] It is unclear whether clozapine is causing acute akathisia or whether it is masking tardive akathisia.[38]

Tardive dystonia appears to be clinically and pharmacologically distinct from the other tardive syndromes. This form of dystonia typically affects the face, neck, and trunk, with the abnormal postures becoming more prominent during actions such as walking. Patients often have retrocollis, back arching, anterior displacement of the shoulder, and arm extension. Patients with tardive dystonia or tardive akathisia often have associated oral-buccal-lingual TD. Unlike patients with classic TD, who may not be aware of their involuntary movements, patients with tardive dystonia are usually symptomatic and often have pain and disability

Table 12.9. Tardive Dyskinesia Syndromes

Classic tardive dyskinesia
Tardive stereotypy
Tardive chorea
Withdrawal-emergent syndrome
Tardive akathisia
Tardive dystonia
Tardive myoclonus
Tardive tremor
Tardive tics
Painful oral and genital syndromes

from the dystonia. Myoclonus, tremor, and tics can be manifestations of TD but are relatively uncommon. Oral and genital tardive pain syndromes have also been described.[39]

The best treatment of classic TD is discontinuation of the DRBA if the psychiatric state allows. Anticholinergics should be stopped because they are thought to exacerbate oral-buccal-lingual dyskinesia, and, in fact, cholinergic agonists may be helpful in treating TD. During the period of DRBA withdrawal and for a short time thereafter, TD movement may temporarily worsen, sometimes requiring treatment with a benzodiazepine. After this transient worsening, the longer the patient is off neuroleptics, the greater is his or her chance of improvement. Glazer and Morgenstern reported that 40% of patients had reduction of TD signs after 6 months and 90% had improved at 1 year.[40] Some patients may continue to improve for up to 5 years.[41] Fahn reported complete remission in five of eight patients after 1.5–4.0 years of drug abstinence.[42] Unfortunately, TD is often permanent, despite DRBA discontinuation.

What is the natural history of TD when patients have had to continue standard neuroleptic treatment even though efforts are made to minimize drug exposure? Yagi and Itoh followed 20 such patients for 10 years and found that 45% experienced remission, 30% had persistent symptoms, and 25% had recurrence of TD.[43] Nowadays, patients with TD who require continued treatment for psychosis should be changed to an atypical neuroleptic or begin symptomatic TD therapy. Although the main reason to change from a standard to an atypical neuroleptic is to stop further dopamine-receptor blockade, some of these agents may have a therapeutic effect. Clozapine has been shown to improve TD symptoms in many patients, especially those with tardive dystonia.[44] Historically, treatment of TD has been difficult; however, the most effective agents have been the dopamine depletors. It is thought that reserpine masks TD symptoms while the underlying physiologic abnormality has a chance to reverse over time.[42] The reserpine dose is typically 0.75–6.00 mg per day. Theoretically, reserpine may be a better agent for TD than is tetrabenazine because although both drugs are presynaptic monoamine depletors, tetrabenazine also has DRBA properties. Although tetrabenazine may successfully mask TD symptoms, the continued postsynaptic dopamine blockade perpetuates the underlying disease process. Tetrabenazine is also more difficult to use because it is not commercially available in the United States. It is possible to get the drug by contacting the company that produces it, and the dose is typically 75–300 mg per day. The addition of alpha-methyltyrosine (metyrosine or Demser, 1–4 g per day) to either of these agents can sometimes be beneficial. The use of the dopamine depletors is often limited by side effects of depression, hypotension, and parkinsonism. Other drugs with possible efficacy in the treatment of TD include dopaminergic agents such as bromocriptine, levodopa, or apomorphine, although these may exacerbate psychosis and should be used with caution. Second-line treatment includes noradrenergic antagonists such as propranolol, the GABA agonist progabide, some calcium channel blockers (i.e., nifedipine, verapamil), vitamin E (1,600 IU per day), and clonidine. Last, when TD is refractory to other therapies and of disabling severity, reinstitution of standard neuroleptics improves TD in the majority of patients. However, patients need to be informed that such action virtually eliminates their chance for TD remission.

Tardive dystonia is usually more disabling and more difficult to treat than is classic TD; however, anticholinergics, dopamine-depleting agents,[45] clozapine,[46, 47] and local injections of botulinum toxin may be beneficial. The anticholinergic drugs often used are trihexyphenidyl (5–120 mg per day; average dose, 20 mg per day) or ethopropazine (50 mg per day). Benzodiazepines and baclofen may also be helpful. Tardive akathisia is best treated with dopamine-depleting agents and does not respond well to the drugs used to treat acute akathisia. The painful oral and genital tardive syndromes respond to dopamine depletors.

Prevention of DRBA-induced involuntary movements should be a priority for all clinicians. Unfortunately, these drugs are often used for inappropriate reasons or for longer than is medically necessary. For this reason, DRBAs should be prescribed only for conditions for which no alternative medicines are effective and should be used in the lowest therapeutic doses for the shortest required time. Informed consent should always be provided whenever a DRBA is prescribed, and this should be clearly documented in the medical record. Regard-

ing the treatment of chronic psychosis, clinicians should consider preferential use of the atypical neuroleptics, given their lower incidence of neurologic complications, and routinely monitor patients for early signs of TD.

Dopaminergic Drugs for Parkinson's Disease

The abnormal movements that occur in untreated PD are resting tremor, dystonia, and akathisia. In particular, foot dystonia may be an early manifestation of the disease, especially in young patients. Once symptomatic treatment with levodopa is initiated, patients often develop a variety of new abnormal movements (dyskinesias) that were not present in the untreated condition, such as choreoathetosis, dystonia, stereotyped movements, myoclonus, or akathisia. Nearly one-half of PD patients develop dyskinesias after 5 years of levodopa treatment.[48] Young patients with PD (disease onset before age 40) are particularly vulnerable, with the incidence of dyskinesia being 54.9%, 74.5%, and 100% at 1, 3, and 6 years of treatment, respectively.[49] Although levodopa can produce dyskinesias in patients with other forms of parkinsonism such as multiple system atrophy (including striatonigral degeneration and olivopontocerebellar atrophy), a robust therapeutic response to levodopa and the induction of dyskinesias is highly suggestive of the diagnosis of PD. The physiologic requirement for the development of dyskinesia is repeated dosing of levodopa in the context of dopaminergic denervation. One of the main reasons to consider dopamine agonist monotherapy before use of levodopa in PD is that the agonists only rarely produce dyskinesia without prior or concurrent exposure to levodopa. In a study by Lees and Stern, only 3% of patients on bromocriptine monotherapy for more than 1 year developed peak dose chorea compared with 65% of comparable patients taking maximally tolerated doses of levodopa.[50]

Of the various levodopa-induced dyskinesias, chorea is the most common, often beginning as subtle truncal rocking, head nodding, facial grimacing, or worm-like movements of the hand or foot. Over time more severe generalized chorea or ballistic movements may develop. Although dystonia may affect any or all parts of the body, painful foot inversion, plantar flexion, and curling under of the toes (or toe extension) is a distinct pattern seen in patients treated with chronic levodopa. Stereotypic movements can include kicking or a tendency to lift one leg too high when walking, giving the appearance of a "hemi-goose-step march." These levodopa-induced dyskinesias classically begin on the side of the body first affected by PD symptoms, suggesting that disease severity may be a factor in the genesis of these movements.

In general, dyskinesias are not present all day but appear and disappear or fluctuate in severity in relation to clinical levodopa response. Levodopa response does not directly correlate with plasma levodopa level but rather with striatal dopamine concentration (which cannot be monitored). It is critical to determine when dyskinesia occurs in an individual patient and make medication adjustments accordingly. Patients and their spouses usually have to be taught how to make these observations so that they can report to the doctor the relationship between levodopa dosing and the onset and duration of the dyskinesia. When the patient feels that the levodopa has taken effect and PD symptoms and signs improve, he or she is having an "on" period. After a few hours of benefit, levodopa effect begins to lessen and the patient experiences "wearing off." When there is no levodopa effect, the patient is having an "off" period, with return of rest tremor and bradykinesia.

Most dyskinesias occur at the maximum of the on period (peak-dose dyskinesia) or during wearing off (wearing-off dyskinesia). The most difficult to treat are the dyskinesias that occur as levodopa is taking effect and again when the effect is wearing off (biphasic dyskinesia). For example, peak-dose chorea may be remedied by reducing the levodopa dose and giving less drug more often or by changing from a regular release to a controlled release preparation. If dystonia occurs during wearing off, a decrease in levodopa response should be prevented—for example, by giving the next scheduled dose sooner, increasing each dose of levodopa so that it will last longer, changing to a controlled release preparation, or adding a dopamine agonist such as amantadine or deprenyl. Off-period dystonia can be unbearably painful and may require use of dissolved levodopa, benzodiazepines, botulinum toxin injection, or clozapine, which appears to have

an antidyskinetic effect.[51] When dyskinesia is severe, debilitating, and unresponsive to drug manipulations, consideration should be given to pallidotomy or thalamotomy.[52–54]

Levodopa-induced myoclonus is not as common as the other types of dyskinesia and is not linked to levodopa response fluctuations. Myoclonus in PD patients typically begins after 1 year of levodopa treatment. The myoclonic jerks are usually bilateral and symmetric but can be unilateral. Because the myoclonus occurs primarily during drowsiness or sleep, the main clinical complaint is sleep disruption of the patient or spouse. Myoclonus severity increases with higher doses of levodopa, and myoclonus improves when the levodopa dose is lowered. Anticholinergics, amantadine, and propranolol have no influence on the myoclonus whereas methysergide eliminates the myoclonus, suggesting that serotonergic mechanisms may be contributory.[55]

Akathisia may be a manifestation of either wearing off or as a peak-dose levodopa effect. This highlights the fact that levodopa fluctuations are not restricted to motor phenomena, but also include transient sensory (e.g., pain, numbness), autonomic (e.g., sweating, dyspnea, tachycardia, urinary frequency), and cognitive changes (e.g., depression, anxiety, panic, hypomania).[56]

Discussion of stimulant-induced movement disorders are covered in Chapter 22.

Tricyclic Antidepressants, Monoamine Oxidase Inhibitors, and Lithium

Tricyclic antidepressants commonly cause an action tremor that is related to plasma drug concentration.[57] This tremor disappears with dose reduction or drug discontinuation and lessens with propranolol.[58] Myoclonus occurs in up to 40% of patients taking therapeutic doses of tricyclics.[59] Although the movements are typically mild and not clinically significant, 9% of patients may have more severe myoclonus requiring drug withdrawal. Desipramine-induced jaw myoclonus and stuttering have been reported.[60] Prominent chorea and myoclonus can rarely occur in tricyclic overdose and may be temporarily relieved by physostigmine.[61] Amitriptyline and doxepin have been reported to cause dystonia or tardive-like movements; however, these are considered uncommon side effects of these drugs.[62, 63]

Tremor or myoclonus may be occasional complications of monoamine oxidase inhibitors.[64] The myoclonus is most pronounced during drowsiness or REM sleep and is frequently reported by the bed partner rather than by the patient.[65]

Lithium is a well-recognized cause of postural and action tremor, with a range of frequency of 3–15 Hz. Tremor lessens with dose reduction or with the addition of low doses of propranolol (10–20 mg three times a day). Generalized myoclonus commonly occurs as part of lithium toxicity in association with jerky eye movements and a reduced level of consciousness. The myoclonus typically remits when lithium levels return to normal. If temporary symptomatic relief is required, clonazepam or valproate may be considered. Lithium may rarely cause parkinsonism,[66] although the mechanism of this is uncertain.

Antidepressants with Potent Serotonin Agonist Properties

The selective serotonin reuptake inhibitors (SSRIs) differ from tricyclics because they block the reuptake of serotonin more than the reuptake of norepinephrine and dopamine. The SSRIs include fluoxetine (Prozac), sertraline (Zoloft), fluvoxamine (Luvox), paroxetine (Paxil), and citalopram. Of the tricyclics, clomipramine (Anafranil) is one of the more selective serotonin uptake inhibitors. However, the main metabolite of clomipramine, desmethyl-chlorimipramine, primarily blocks norepinephrine uptake, and its plasma level often exceeds that of the parent compound. For this reason, clomipramine is often referred to as a serotonin reuptake inhibitor. The SSRIs have become first-line agents for the treatment of depression given their equal efficacy to tricyclics and their favorable side-effect profile. There are many reports suggesting that the SSRIs may cause abnormal movements such as dystonia, chorea, parkinsonism, akathisia, and bruxism. Although it is clear that these agents do have the potential to cause a variety of dyskinesias, interpretation of the anecdotal reports is limited by polypharmacy, frequent absence of drug rechallenge, lack of medication compliance monitoring, and lack of a control

group. Many of the patients had recent or concurrent exposure to neuroleptics when SSRIs were added. SSRIs appear to potentiate the effects of neuroleptics. Because SSRIs are often highly protein bound, they may displace neuroleptics from their binding in plasma and increase the physiologic activity of the neuroleptics. The physiologic mechanism of SSRI-induced abnormal movements is unknown; however, there is some evidence that the SSRIs reduce dopamine activity in the basal ganglia. Studies suggest that serotonergic pathways exert a tonic inhibition of the dopaminergic systems of the brain.[67, 68] Drugs that increase serotonin activity, such as fluoxetine, can inhibit dopamine synthesis in the corpus striatum, nucleus accumbens, and frontal cortex as well as reduce homovanillic acid in the cerebrospinal fluid.[69, 70] Increased serotonergic transmission may inhibit nigrostriatal, tuberoinfundibular, and ventral tegmental projection dopaminergic neurons.[70, 71] In addition to these indirect actions on dopamine pathways, clomipramine may possess mild dopamine receptor-blocking activity.[72]

Early experience with fluoxetine revealed that 10–15% of patients developed "anxiety, nervousness, and insomnia" as is written on the package insert. It has been suggested that many of these patients were actually experiencing akathisia, which is considered to occur in 0.2–3.5% of patients taking fluoxetine.[73, 74] Akathisia can occur with doses as low as 5 mg per day,[75] and symptoms typically begin 12 hours to 7 days after starting the drug. Many patients report that the sensation of restlessness and anxiety experienced with fluoxetine is identical to that experienced previously with neuroleptics, and this can be so intolerable as to make a patient suicidal. It is possible that the increased suicidal impulse observed in some patients taking fluoxetine may be due to akathisia.[76] The akathisia usually remits with drug discontinuation, dose reduction, or with the addition of lorazepam. Fluoxetine may also cause dystonia, parkinsonism, rabbit syndrome, blepharospasm, or bruxism.[77–83] The dystonia may be acute, appearing in the first days of therapy or subacute with onset after several weeks. Both types of dystonia respond to anticholinergics or diphenhydramine. TD-like movements such as oral facial dyskinesia can appear, especially when fluoxetine is added to a neuroleptic,[84–86] raising the question whether fluoxetine can cause latent TD to become clinically apparent. Although fluoxetine-induced dyskinesias usually remit within days of drug discontinuation, they may persist for up to 12 weeks in a manner suggestive of TD. Another contributory factor that may explain persistence of symptoms is the long physiologic effect of norfluoxetine, the active metabolite of fluoxetine that has a half-life of 7–15 days.

Sertraline has been reported to cause akathisia, even at low doses of 25 mg per day, with onset of symptoms within 3 days to 3.5 weeks.[87–92] Symptoms abate within 2 days to 1 week of stopping the drug. Interestingly, one patient did not have akathisia with fluoxetine but did so on subsequent exposure to sertraline. Fluvoxamine may cause reversible parkinsonism, jaw dystonia, oral-facial dyskinesia, akathisia, or myoclonus at a dose of 100–200 mg per day.[93–97] Paroxetine has been reported to cause parkinsonism when added to trifluoperazine.[98] There is one description of a TD-like syndrome occurring with clomipramine treatment.[99]

If SSRIs indirectly reduce brain dopamine activity, it is not surprising that they may cause increased motor disability in patients with PD who are treated for depression. The SSRIs are theoretically attractive agents for PD depression because serotonin deficiency may be involved in the pathogenesis of the disorder.[100] Although one retrospective study indicated that fluoxetine is well tolerated in patients with PD,[101] there are other reports that conclude that tremor, bradykinesia, and dexterity may worsen.[102] Deterioration of PD signs after the addition of serotonin precursors has been demonstrated.[103, 104]

Myoclonus has been described as a rare effect of buspirone.[105] The anxiolytic effects of buspirone are mediated through serotonergic pathways, and this agent binds to the 5-HT_{1A} receptor. Buspirone has a complex pharmacologic profile, possessing both partial antagonist and agonist effects at dopamine receptors, and is thought to modulate the extrapyramidal system.[106, 107] The rare reports of buspirone-associated dystonia,[108, 109] akathisia,[110] and orofacial dyskinesia[111] suggest that buspirone may possess atypical neuroleptic properties.[112] Buspirone may also improve neuroleptic-induced akathisia,[113] TD,[114] and levodopa-induced dyskinesia.[115, 116]

Trazodone (Desyrel) has been reported to cause atypical acute dystonia.[117]

Antiepileptic Drugs

Cerebellar ataxia is the most common movement disorder caused by antiepileptic drugs when blood levels are in the toxic range. A variety of hyperkinetic movements can occur in patients taking therapeutic or toxic doses of antiepileptics. Patients receiving chronic valproic acid therapy develop a 6- to 15-Hz postural or action tremor of the hands. There may be a resting component to the hand tremor; the head, neck, or trunk may also be affected. Valproate-induced tremor typically develops after 1–12 months of therapy when doses exceed 750 mg per day; however, there is no close correlation between tremor severity and plasma drug level.[118, 119] Tremor improves with dose reduction and resolves quickly on drug discontinuation. For patients who require continued treatment with valproate, propranolol (20–100 mg per day) usually reduces tremor. Valproate-related chorea has been described in three children, all of whom had severe brain damage.[120] Parkinsonism may be an uncommon side effect of valproate.[121, 122]

It is well documented that phenytoin can cause a variety of involuntary movements at any stage of treatment, although the mechanism is not understood.[123] Chorea is the most common manifestation and may be associated with orofacial dyskinesia, dystonia, ballism, or asterixis. Predisposing factors include static encephalopathy, prior dyskinesia (e.g., Sydenham's chorea, TD), structural brain abnormality, or neuroleptic treatment. If there is focal brain disease, the dyskinesia can be unilateral. More than half of the patients with phenytoin-induced dyskinesias have toxic drug levels. Free phenytoin levels are often elevated when the standard level is in the therapeutic range. The addition of phenobarbital, valproic acid, or ethosuximide can increase the relative free fraction of phenytoin in the serum, causing a predisposed individual to develop dyskinesia. Stopping the second agent results in resolution of dyskinesia, as will phenytoin dose reduction or withdrawal. The chorea or dystonia sometimes seen during parenteral loading with phenytoin for status epilepticus resolves as plasma levels drop. Phenytoin has been reported to cause parkinsonism on rare occasion.[124, 125]

Carbamazepine appears to have some dopaminergic properties that may explain why this drug may cause chorea, dystonia, asterixis, akathisia, tic disorder exacerbation, and de novo tics.[126–130] Ethosuximide may cause akathisia, limb chorea, orofacial dyskinesia, and tongue protrusion early in the course of therapy, often 12 hours after ingestion of the first dose, that is relieved by intravenous diphenhydramine. This is considered a rare idiosyncratic adverse effect of ethosuximide that remits with drug withdrawal.[131, 132] Chorea and dystonia may be rare manifestations of phenobarbital toxicity.[133] Gabapentin may cause muscle twitching, chorea, or oculogyric crisis.[134] Lamotrigine has been reported to cause severe tremor in three patients who were also taking valproate.[135]

Oral Contraceptives

Chorea occasionally appears in women when they are exposed to higher than normal levels of female sex hormones such as during pregnancy (chorea gravidarum) or when taking oral contraceptives. Although both progesterone and estrogen may be responsible for the emergence of chorea, it has been suggested that estrogen may be the more important culprit.[136] Contraceptive-induced chorea usually begins within 4 months of starting the agent but the onset can be delayed for up to 3 years.[137] Chorea can be bilateral or unilateral and always resolves within 1 month of drug discontinuation. In most instances, there is a history of prior Sydenham's chorea or rheumatic fever. It is generally believed that hormone-induced chorea occurs in women who have had prior striatal injury, even though this may not have been clinically apparent. All patients should be evaluated for rheumatic fever. However, serologic study results documenting exposure to beta-hemolytic streptococcus are positive only if the patient has had recent streptococcal infection. A cardiac examination is indicated to look for rheumatic valve disease, and echocardiography should be considered. Guidelines for the use of prophylactic penicillin in rheumatic fever have been clearly outlined.[138] New-onset chorea may be a manifestation of systemic lupus erythematosus or other collagen vas-

cular disease, anticardiolipin-antibody syndrome, Huntington's disease, cerebral infarction, hyperthyroidism, and polycythemia rubra vera, all of which need to be excluded.

Conclusion

Prescription drugs can potentially cause a variety of involuntary movements such as tremor, parkinsonism, chorea, dystonia, myoclonus, and tics. The most important culprits of drug-induced movement disorders are the neuroleptics (DRBAs). Such agents should be used only after informed consent with full disclosure of the potential side effects (unless required for management of acute psychosis). The reversible side effects of neuroleptics include acute akathisia, acute dystonia, NMS, and parkinsonism. TD syndromes are often permanent sequelae of long-term neuroleptic exposure. The new atypical neuroleptics such as clozapine, olanzapine, and risperidone are significantly less likely to cause extrapyramidal effects.

Treatment of PD with dopaminergic drugs is frequently associated with development of choreatic movements that tend to occur at times of peak levodopa effect. Tricyclic antidepressants, MAO inhibitors, and lithium may cause a dose-related hand tremor. The myoclonus reported from tricyclics is usually not clinically bothersome. SSRIs may cause a variety of involuntary movements as well as akathisia. Because most patients with SSRI-associated abnormal movements have recent or concurrent neuroleptic exposure, it may be that neuroleptics increase striatal sensitivity to SSRI effects or that SSRIs displace neuroleptics from protein binding sites and thereby increase the physiologic effects of the neuroleptic agent. Buspirone has complex and poorly understood effects on the dopaminergic system and can sometimes cause dystonia, chorea, or akathisia. Of the antiepileptic agents, phenytoin, carbamazepine, ethosuximide, and possibly gabapentin may cause chorea, especially in patients with prior brain injury or in patients taking more than one antiepileptic drug. Valproate frequently causes a postural and action hand tremor that remits with dose reduction or by the addition of low-dose propranolol. Higher than normal levels of female sex hormone (especially estrogen) may cause chorea, especially in women with prior striatal insult.

The vast majority of drug-induced movement disorders remit with dose reduction or drug discontinuation, with the exception of some of the permanent tardive syndromes. A thorough drug history should be performed on all patients who present with abnormal movements. Even if the abnormal movement is not a documented adverse effect, one needs to be open minded to such a possibility. When there exists a temporal relationship between drug exposure and onset of new symptoms, one should attempt dose reduction and if necessary drug withdrawal (and even drug rechallenge when it is safe to do so) to determine if such a relationship exists. In addition to referencing well-recognized drug-induced movement disorders, a number of case reports were included. Although single case reports often lack scientific rigor and are not peer reviewed, they may alert physicians to possible drug effects not previously recognized and may prompt prospective controlled studies to determine the validity of such observations.

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