Neuroleptic-induced Movement Disorders: An Overview
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Movement disorders commonly are associated with many psychotropic drugs. Tricyclic antidepressants often cause a tremor in the hands and myoclonic jerks. In some patients, they result in agitation and restlessness, referred to as the jitteriness syndrome [1]. Occasional anecdotes of dyskinesia and dystonia have been reported with these drugs, but tardive dyskinesia typically is not associated with tricyclics, with the possible exception of amoxapine [2]. Movement disorders are reported somewhat more commonly with serotonin-specific reuptake inhibitors (SSRIs), including mild parkinsonian symptoms, dystonia, dyskinesia, and akathisia. There have been some reports of irreversible dyskinesia and dystonia with these drugs [3]. Lithium most commonly is associated with a peripheral tremor, which is usually a mild action tremor, but becomes coarse when toxic levels are reached. Lithium produces myoclonus less often, and is also known to exacerbate the parkinsonian adverse effects of neuroleptics. Stimulants are associated with stereotypes, dyskinesia, tremor, dystonia, and myoclonus. Anticonvulsants (eg, phenytoin or carbamazepine) are associated with dyskinesia, tremor, and tics, and in toxic doses will produce nystagmus, ataxia, and dysarthria. Anticholinergic drugs can exacerbate dyskinesias. Of course there many other drugs used in medicine that may cause disorders of movement, and the reader is referred to some recent publications on this topic [4–6].

The overwhelming concern of psychiatrists is with neuroleptic-induced movement disorders (NIMD). These may be categorized on the basis of the temporal relationship to neuroleptic use (acute and delayed or tardive) or their characteristics (hyperkinetic or hypokinetic, sometimes referred to as positive or negative). Acute NIMDs include acute dystonia, akathisia,
parkinsonism, and neuroleptic malignant syndrome. The typical tardive syndrome is tardive dyskinesia (TD), although several related syndromes have been described.

**Acute neuroleptic-induced movement disorders**

**Acute dystonia**

A dystonia is an involuntary movement in which the muscle action is sustained at the point of maximal contraction for at least a short period. The movements are typically slow, but rapid dystonia, referred to as myoclonic dystonia, has been described [7]. The disconnection between the agonist action and the reflex antagonist inhibition often results in a twisting distortion of the affected part, with sustained abnormal postures. The symptomatology is varied, with common manifestations being torticollis, retrocollis, tongue protrusion, opening or closing of the jaw, facial grimacing, limb torsion, opisthotonus, or rolling the eyes upwards, sometimes with deviation to the side (oculogyric crisis). The sudden occurrence of a muscle spasm is often very frightening to the patient, thereby presenting as a medical emergency, although it is in most cases not dangerous. The exception is the occasional occurrence of a laryngopharyngeal spasm that may compromise respiration and may even cause death. Dystonias, and in particular oculogyric crises, may be preceded by prodromal symptoms such as restlessness, anxiety, irritability, or an exacerbation of psychosis, which sometimes may be so severe that the movement disorder itself may be ignored by the patient and the clinician [8].

Although acute neuroleptic-induced dystonia is common, its incidence is determined greatly by the type of drug used, dosage, route of administration, and age of the individual. Although reported rates of acute dystonia vary from 2.3% [9] to over 90% [10], high-potency drugs such as haloperidol generally produce acute dystonia in 30% to 40% of cases. The rates are lower with atypical neuroleptics, and clozapine does not appear to produce acute dystonia. The incidence increases with dose, but this has an inverted U-shaped relationship. Most dystonias occur within 2 to 3 days of the initiation or significant increment in dose of neuroleptic, and parenteral administration increases the risk. They also may occur after the abrupt discontinuation of anticholinergic medication within the first few weeks of initiating neuroleptics. Children and young adults appear to have greater risk, and males develop it twice as often as females. Some coexisting conditions, such as hypocalcemia, hyperthyroidism, and hyperparathyroidism, or recent cocaine use have been reported as risk factors in several case series. The pathophysiology of acute dystonia is understood incompletely, with the focus having been on dopaminergic mechanisms. Arguments have been presented for acute dopamine antagonism (DA hypofunction hypothesis) and a compensatory increase in dopamine release leading to mismatch (DA hyperfunction hypothesis) [11].
Acute dystonia is generally easy to treat. In the acute situation, the parenteral administration of benztropine, benzhexol, biperiden, procyclidine or other anticholinergic drug, or the antihistaminic/anticholinergic diphenhydramine, is usually effective in 15 to 20 min, although a second treatment may be necessary after 30 min. If it is less severe, oral medication may be sufficient. This will need to be continued for a further 24 to 48 hours to avoid a recurrence. Prophylactic use of anticholinergic drugs to prevent dystonia is controversial, but in a high-risk patient, they may be used for 7 to 14 days when neuroleptics are first initiated, after which they can be discontinued slowly over a few days.

**Acute neuroleptic-induced akathisia**

The syndrome of akathisia (from Greek, literally unable to sit) has come to refer to the development of restlessness seen most commonly as an acute adverse effect of neuroleptics, although other drugs such as the selective serotonin reuptake inhibitors (SSRIs), calcium channel antagonists also may produce it. Additionally, it may develop as a tardive syndrome [12]. Most investigators agree that there are two aspects to akathisia: a subjective report of restlessness or inner tension, particularly referring to the legs, with a consequent inability to maintain a posture for several minutes; and the objective (or observational) manifestations of restlessness in the form of semipurposeful or purposeless movements of the limbs, a tendency to shift body position in the chair while sitting, or marching on the spot while standing [13]. There is disagreement about the relative importance of these two aspects [14,15], with emphasis on the subjective component (akathisia as a mental disorder) or the objective component (akathisia as a movement disorder) by different investigators. A combination of the two has been argued as being necessary for a definite diagnosis [15] (ie, akathisia as both mental and movement disorder). A less certain diagnosis (probable or possible) of akathisia sometimes may be made if either the subjective or the objective features, but not both, are present (Box 1). Even when fairly characteristic features of akathisia are present, and the clinical situation is appropriate for the diagnosis, a clinical decision often must be made to distinguish it from anxiety or agitation or restlessness caused by other causes.

The urge to move in akathisia may be unrelenting and may preoccupy the person’s thinking. Mild cases often can be detected by asking patients if they have difficulty in checking out at supermarkets, cooking a meal while standing, or sitting to watch television. Lying down provides some relief for most patients, contrasting akathisia from restless legs syndrome. The sensations in the legs usually are localized deep inside, and paresthesia are uncommon. Akathisia first may become apparent when a patient refuses medication, and it has been recognized as an important cause of non-compliance in schizophrenic patients [16]. Some patients may experience
Box 1. Research diagnosis of drug-induced akathisia [12]

Prerequisites (necessary for all diagnoses)

A history of exposure to drugs known to cause akathisia
  (antipsychotics can cause all subtypes; nonantipsychotics can
  cause acute akathisia and chronic akathisia, acute onset)
Presence of characteristic subjective or objective features of
akathisia
Absence of other known causes of akathisia (eg, restless legs
syndrome, Parkinson’s disease, subthalamic lesion) and
absence of peripheral neuropathy, myelopathy, or myopathy

Diagnoses

Acute akathisia (antipsychotic or non-antipsychotic
drug-induced; if has a duration of at least 3 months,
categories as chronic akathisia, acute-onset)
Tardive akathisia (if has a duration of at least 3 months,
categorize as chronic akathisia, tardive onset)
Withdrawal akathisia (if has a duration of at least 3 months,
categorize as chronic akathisia, withdrawal onset)
Chronic akathisia (acute, tardive or withdrawal onset; state if
patient is not receiving antipsychotics)

* State if only subjective or objective features are present.

their internal distress in the form of apprehension, irritability, impatience, or
general unease. Others may exhibit fear, anxiety, terror, anger or rage, vague
somatic symptoms, an exacerbation of psychosis, or as sexual torment.
There has been some recent debate on the relationship between akathisia
and aggressive, self-destructive, or suicidal behavior, and case reports of
violence [17] and suicidal behavior attributed to akathisia have been
published [18].

Akathisia usually develops within a few days of the initiation or
increment in dose or change to high-potency neuroleptic, with most cases
developing in the first 2 weeks. With conventional neuroleptic drugs, rates
reported vary from 8% to as high as 76% [19]. A conservative estimate is
20% to 30%, but this rate is significantly affected by treatment-related
variables and other variables. The risk with atypical neuroleptics is lower
but not absent, and the published evidence for this is inconsistent because of
the problems of carryover effects and equivalent doses not always being
used. The risk increases with higher drug doses, rapid increment of the
dosage, and higher potency of the drug. The development of parkinsonism
also increases the likelihood of akathisia developing, although the latter may
occur first, or concurrently, with the parkinsonism. The role of sociodemo-
graphic factors and other treatment-related variables is modest. The presence of psychiatric disorder is not necessary for akathisia to develop, but certain organic brain disorders may increase the vulnerability. Although some evidence exists that iron deficiency may be a predisposing factor, this is far from established, and its role is likely to be minor. The literature on akathisia in childhood and adolescence is scant, although akathisia has been reported, especially in Tourette’s disorder patients treated with neuroleptics [20].

Akathisia is difficult to treat, and its prevention or modification through the appropriate use of neuroleptics is the most important strategy. Drugs that are used to treat akathisia include anticholinergics, β-adrenergic antagonists, and benzodiazepines, although the effect of the latter is probably nonspecific. There is a suggestion that anticholinergics may be more effective in those who have associated parkinsonian symptoms. Sometimes a combination of an anticholinergic drug and a β-blocker may be necessary. The reader is referred to a recent article for a more detailed discussion of management [21].

**Neuroleptic-induced parkinsonism**

Sometimes referred to as pseudoparkinsonism, the symptoms of neuroleptic-induced parkinsonism are clinically indistinguishable from Parkinson’s disease and comprise rigidity, bradykinesia, tremor at rest, and postural instability. Patients develop a poverty of spontaneous, generally automatic, movements. The face appears masked; there may be drooling of saliva. The posture is flexed, and speech becomes slow and lacking in intonation. The initial symptom may be a tremor or muscle stiffness, and reduce arm swing and increased muscle tone are obvious on examination. With the exception of seborrhea (and sialorrhea), autonomic symptoms are usually not present. The symptoms are usually bilateral but may be asymmetrical.

Parkinsonism develops later than dystonia or akathisia, although most people develop it in the first week of neuroleptic treatment or dose increment [9]. It is the adverse effect related most clearly to dopamine antagonism. It is therefore dose-related and more prevalent with high-potency drugs. Increasing age, and possibly female gender, are other risk factors [22]. Drugs with an intrinsic anticholinergic property have a lower propensity. The rate of dose increment is also important, suggesting the development of some tolerance with time. It is reversible with the cessation of the drug, although this may take many months, especially after the use of depot neuroleptics. In the elderly, however, persistence of parkinsonian symptoms occurs in a proportion; it was 11% at 1 year after neuroleptic cessation in one study [23].

The development of parkinsonism once was considered to be a necessary condition of antipsychotic drug action, until the introduction of so-called
atypical neuroleptics, with clozapine as the flag-bearer. What makes a neuroleptic atypical is debated, but the essential characteristic of these drugs is the lack of parkinsonian adverse effects at therapeutic doses. There appears to be more than one mechanism by which this occurs: antagonism of dopamine (D2) and serotonin (S2) receptors, rapid dissociation from binding with dopamine receptors, relative specificity for limbic rather than striatal dopamine receptors, intrinsic anticholinergic action, and other mechanisms. This atypical character is lost if the dose is increased above a certain threshold (e.g., greater than 6 mg/day in the case of risperidone). Recent neuroimaging studies have suggested that there may be a window of dopamine D2 receptor blockade at which antipsychotic effect is induced without parkinsonian symptoms. This may be between 60% and 80% of receptors. With haloperidol, at the usual therapeutic dose, more than 90% of D2 receptors are blocked; with atypical drugs, this is about 70% to 80%, with clozapine being less than 60% to 70%\[24,25\].

The emergence of neuroleptic-induced parkinsonism is managed best by a modification of the antipsychotic regimen. If this cannot be achieved, anticholinergic drugs are the main intervention. There is no clear evidence that any one anticholinergic is superior to the others, although M1 selectivity is the property that would be desirable. Drugs are to be used only if parkinsonism is clearly manifest, and their prophylactic use is best avoided. L-dopa and directly acting dopamine agonists do not appear to be effective in neuroleptic-induced parkinsonism, although data on this question are limited. Amantadine may have a role, especially if anticholinergics are unsuccessful or not tolerated.

**Neuroleptic malignant syndrome**

Although uncommon, neuroleptic malignant syndrome (NMS) is the most serious adverse effect of neuroleptics, and it is potentially fatal. The principal features are hyperthermia, muscle rigidity, alteration in consciousness, and autonomic dysfunction [26,27]. Fever may be low-grade to higher than 42°C. Rigidity, which may be described as lead-pipe or cogwheel, is present in more than 90% of cases and may be so severe as to lead to rhabdomyolysis. Patients often are agitated, but they may become mute and catatonic. Confusion and delirium are common, and these in severe cases may progress to stupor or coma. Autonomic features commonly present are diaphoresis, pallor or flushing of the skin, tachycardia, lability of blood pressure, hypertension or hypotension, arrhythmia, tachypnea, dyspnea, and urinary incontinence. Movement disorders associated with NMS include bradykinesia, tremor, dystonia (blepharospasm, opisthotonus, oculogyric crises, trismus, chorea [including oro-buccal dyskinesia]), and myoclonus. Rarely, seizures, ataxia, nystagmus, and reflex changes may occur. The symptoms are acute in onset, and the full syndrome usually develops within 24 to 48 hours of the onset.
Laboratory findings are nonspecific but useful in supporting the diagnosis. The most important is a rise in creatine kinase (CK), which may vary from greater than 200 to several thousand IU/L. A rise in CK in the absence of clinical features of NMS is not enough to make a diagnosis. Two- to threefold rises in CK levels are not uncommon after neuroleptic administration, but rises above 1000 IU/L suggest caution, and such patients should be monitored for clinical signs of NMS. CK levels are useful in the follow-up of patients. Polymorphonuclear leukocytosis is another consistent finding. Less common findings are elevated liver cell enzymes, hypocalcemia, hypomagnesemia, hypoferremia, proteinuria, and myoglobinuria.

The diagnosis of NMS is a clinical one and relies on the exclusion of other causes of fever, rigidity, and altered sensorium, although the acute development of these symptoms in a patient on neuroleptics always should arouse the suspicion of NMS. It is not certain how many features are necessary for a diagnosis. Most sets of criteria for NMS need the presence of rigidity and fever for a definite diagnosis, but patients have been described who lacked one of more of the features. These may well be forme fruste of the syndrome, and a dimensional approach to NMS has been advocated by some authors [28]. All neuroleptic drugs, including clozapine, may cause NMS. The risk appears to be greatest in patients who are agitated and compromised medically through dehydration and malnutrition, especially if they are treated with large doses of parenterally administered neuroleptics over short periods to control their agitation [27,29]. Severely disturbed male manic patients often fit this description.

Neuroleptic malignant syndrome is not confined to psychiatric patients. Any patient treated with neuroleptics runs the risk of NMS. The reported incidence is variable, with rates varying from 0.1% to 2% [30,31]. This range may depend on the differences in the definition of the disorder and prescribing practices. Although most patients develop it at the time of initiation of neuroleptics, it may occur after a change in drug or dose, or in patients on stable medication because of an intercurrent illness or sometimes for no obvious cause. Parkinson’s disease patients on dopaminergic drugs (L-dopa or directly acting dopamine agonists) can develop a NMS-like syndrome if the drug is stopped suddenly. A similar syndrome can develop in cocaine users. NMS resembles some other disorders, which must be considered in the differential diagnosis. Malignant hyperthermia (MH), a genetically determined, myopathic disorder can be differentiated by a history of exposure to inhalant anesthetics and depolarizing muscle relaxants rather than neuroleptics. Lethal catatonia resembles NMS in its presentation but occurs in the absence of exposure to neuroleptics.

Once it develops, NMS progresses rapidly and often leads to medical complications that may be respiratory (pneumonia or pulmonary embolism), cardiovascular (arrhythmia or cardiac arrest), renal (myoglobinuria, azotemia, and failure) or neurological (movement disorders or cognitive
failure). Mortality was reported in 11% to 30% in earlier series, but this figure has decreased progressively with early detection and management. The pathogenesis of NMS is not understood fully, but a central dopamine shutdown is the most prevalent current theory [32].

When NMS is suspected, treatment should be prompt, with the immediate cessation of any neuroleptic medication, and the institution of supportive treatment for dehydration, fever, metabolic abnormalities, and any complications. Most mild cases do not need any other measures. Drugs that have been found to be useful in some cases include the dopamine agonists (bromocriptine, amantadine, or pergolide) and muscle relaxants (dantrolene sodium). Benzodiazepines are used for the management of agitation. Anticholinergic drugs are best avoided. Electroconvulsive therapy may be life-saving in severe cases, and the use of anesthetic agents and muscle relaxants (such as succinylcholine) is considered safe [33].

**Tardive neuroleptic-induced movement disorders**

The term dyskinesia (literally abnormal movement) is a generic term that refers to a range of movement abnormalities. In the case of TD, the movements are choreiform, athetoid, dystonic, stereotypic, or a combination of these. They most commonly involve the oro-buccal, lingual, and facial muscles, especially in older individuals. The lingual involvement in the form of fine vermicular movements of the tongue while it is sitting at the base of the oral cavity is a common and early feature. Dyskinetic blinking may be another early sign of TD. Lip smacking, puckering or pouting, chewing, jaw clenching or mouth opening, facial grimacing, blowing, blepharospasm, and frowning are also common features. The limbs and trunk often are involved, and the involvement of the respiratory muscles has been uncommonly reported. The fingers may display stereotypic movements, especially when held in extension, as if the patient is piano playing. Stereotypic leg movements are often present. Truncal movements are in the form of lateral, posterior or irregular neck movements, shoulder shrugging, twisting, flexion or extension of the trunk and pelvic rotation, or thrusting. Respiratory muscle involvement manifests in the form of irregular breathing, belching and grunting sounds, whistling or sucking, and aerophagia. Abdominal and pharyngeal muscles may be involved rarely [34].

The orobuccal-lingual-facial (OBLF) musculature is involved in three-quarters of affected individuals, the limbs in one-half and the trunk in up to a quarter, with all three groups being affected in about 10% [35]. The OBLF involvement is typical of the elderly, and limb-truncal (LT) involvement is more likely in the young. Although the movements are choreoathetoid, which are recognized to be characteristic of TD, neuroleptic-induced tardive movements may sometimes be dystonic, akathisic, tic-like, myoclonic, or tremorous in character. This has led to a debate between the ‘lumpers’ and ‘splitters’ (ie, those who include all these different movements within the
rubric of TD, and those who make a distinction between TD and other tardive syndromes such as tardive dystonia [TDt], tardive akathisia, tardive tics, or Tourette’s syndrome) (Box 2).

The movements of TD typically fluctuate in intensity over time, increase with emotional arousal, decrease with relaxation, and disappear during sleep. They also decrease when the affected muscles are used for voluntary activity. Distracting tasks, such as finger tapping or mental arithmetic, tend to exaggerate the movements and bring out movements that may otherwise be latent. Poor dental status may exaggerate oral movements in some patients. In mild cases, the patient may be unaware of the movements. The movements of TD have a variable response to medication. Neuroleptics, with the possible exception of clozapine, are recognized to suppress the movements. Increasing the dose of the offending drugs may, therefore, suppress the movements. Anticholinergic drugs, on the other hand, usually aggravate TD. These responses are, however, often unpredictable.

Tardive dyskinesia develops after a person has been on neuroleptics for months to years. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition requires exposure of at least 3 months, but TD may occur as early as one month in elderly individuals. The onset may be while the patient is still on neuroleptics or within a few weeks of their withdrawal. The latter (withdrawal-emergent dyskinesia) may remit spontaneously or go on to become persistent. The onset is usually gradual, and the disorder is mild except for withdrawal dyskinesias, which can be severe from the early stages.

**Box 2. Neuroleptic-induced tardive subsyndromes**

**Movement disorders**
- Tardive dyskinesia (TD)
  - Oro-buccal-lingual-facial (OBLF) syndrome
  - Limb-truncal (LT) syndrome
  - Mixed
- Tardive akathisia (TA)
- Tardive dystonia (TDt)
- Tardive tics and Tourette’s syndrome (TTS)
- Tardive myoclonus (TMyo)
- Tardive tremor (TTrem)
- Tardive parkinsonism (TPark)

**Behavioral syndromes**
- Supersensitivity psychosis (SP)
- Tardive dysmentia (TDem)
- Tardive dysbehavior (TBeh)

* The status of the behavioral syndromes is uncertain.
Spontaneous dyskinesias

Dyskinesias, in particular oro-facial movements, have been reported to occur in some individuals with no exposure to neuroleptics and no neuroleptic disorder. They are more common in the elderly, with one study reporting prevalence rates of 0.8%, 6.0%, and 7.8% in the sixth, seventh, and eighth decades of life of otherwise healthy subjects [36]. Kane et al [37] reported a rate of 4.0% in healthy elderly (mean age 73 years) subjects. The prevalence is higher in psychogeriatric patients and those in institutions who have not received neuroleptics. It is particularly high in patients with dementia [38].

Is dyskinesia a feature of schizophrenia?

The occurrence of “peculiar, sprawling, irregular, choreiform, outspreading movements” in schizophrenic patients were noted by Kraepelin [39]. Many studies have investigated neuroleptic-naive schizophrenic patients and reported rates of dyskinesia that vary from nil [40] to as high as 53% [41], with rates of 1% to 7.6% reported in first-episode schizophreniform psychosis. These movements usually are described as grimacing, tic-like, or stereotypic, but oro-facial dyskinesias and choreiform movements are observed less commonly. These findings have raised the argument that dyskinesias may be intrinsic to the pathophysiology of schizophrenia, and that neuroleptics serve to enhance the process.

Epidemiology

The prevalence of TD has been investigated extensively, and 76 published studies were reviewed by Yassa and Jeste [42]. The rates ranged from 3% to 70%, with a median rate of about 24% in patients on chronic neuroleptic treatment. The higher rates likely were reported in the elderly. Most TD is mild. The study by Woerner et al [43] is noteworthy for its attempt to address some of the methodological issues. The overall prevalence in neuroleptic-treated individuals was 23.4%, of which 3.8% had another neuro-medical illness that might have had an etiological role, thus giving a conservative prevalence rate of 19.6%. In the same study, when a group of patients with no evidence of TD was withdrawn from neuroleptic drugs and examined weekly for 3 weeks, 34% developed emergent dyskinesia. Rates of withdrawal-emergent dyskinesia of 8% [44] and 51% [45] have been reported in two studies of children on long-term neuroleptics. High rates have been reported in elderly patients on neuroleptics [46,47]. High rates also have been reported in neuroleptic-treated individuals with mental retardation [48,49].

Given the difficulties inherent in prevalence estimates, it has been much more rewarding to examine the incidence of TD in newly medicated patients followed longitudinally (Tables 1, 2). These studies suggest that the
cumulative incidence of TD increases with increasing duration of neuroleptic treatment, at a rate of about 3% to 5% per year for the first several years, to reach a plateau at about 20% to 25%, but new cases continue to occur many years after drug initiation. It is difficult to identify a point of time after which the risk decreases. The incidence is much higher in elderly individuals [50].

**Natural history**

For most people, TD does not become progressively worse, and when it does get worse, it generally tends to show a fluctuating course with some spontaneous remissions. In a 5-year follow-up study of Bergen et al [51], 24% showed a fluctuating course; 11% improved, and 7% worsened. From 5 to 10 years, about 50% of patients demonstrate a reduction in symptoms of at least 50%. The outcome is more favorable in the young, and if drug treatment can be stopped [52]. Improvement can be expected to continue for many years after neuroleptics have been ceased. The prognosis of withdrawal-emergent dyskinesia is more favorable, with over 75% showing improvement in 3 months [35].

**Risk factors**

Advancing age is the most consistently established risk factor for TD, and there appears to be a linear correlation between age and both the prevalence and severity of TD [53]. Although female gender has not emerged consistently as a risk factor in recent studies, there may be a female excess in elderly TD sufferers. Some ethnic differences, with higher rates in African Americans and lower rates in Chinese and other Asian populations, have been reported, the basis for which is not understood clearly.

Several investigators have commented on a higher relative incidence of TD in patients with affective disorder treated long-term with neuroleptics,
## Comparative studies on risk of tardive dyskinesia among various neuroleptics

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**Abbreviation:** AIMS, Abnormal Involuntary Movements Scale.
but this finding is inconsistent, and may apply to early- and not late-onset TD. Kane et al [54] reported incidence figures of 26% for affective and schizoaffective disorders and 18% for schizophrenia. In schizophrenic patients, a family history of affective illness is reported to increase the risk. Depression may, furthermore, produce a state-dependent exacerbation of TD [55], while mania may lead to the reverse. Whether schizophrenia increases or decreases the risk for TD is not known. Within schizophrenia, those with the negative syndrome, or evidence of cognitive impairment and neurological deficits, are reported to be more at risk [56], and the presence of TD indicates a poorer prognosis for schizophrenia. The presence of brain damage (as evidenced by epilepsy, head trauma, or dementia) has been suggested as a risk factor, but the evidence is inconsistent. TD is known to develop in Tourette’s syndrome patients treated with neuroleptics, but the prevalence rate, though not well-studied, is likely to be lower than that seen in schizophrenia, possibly because of the youth of the patients and the small neuroleptic doses used [57]. There has been recent interest in variables such as smoking, alcohol abuse, and diabetes as risk factors. A recent study found that alcohol/drug abuse increased the risk of TD by threefold [58]. Diabetics have an increased risk of spontaneous dyskinetic movements (21% in the study by Ganzini et al [59]) and TD (79% in diabetics versus 53% in nondiabetics) [59]. Woerner et al [60] reported a risk ratio of 2.3 for diabetics exposed to neuroleptic compared with nondiabetics, with the risk greater in aged diabetics. Alcoholics and smokers have an increased prevalence of spontaneous dyskinesias and TD [61]. It has been suggested that patients who are more prone to develop acute extrapyramidal adverse effects with neuroleptics are also at a higher risk of TD [62]. Genetic factors have been studied. An intriguing finding is that heterozygous carriers of mutated alleles of the CYP2D6 gene have an increased susceptibility to TD [63]. An association between TD and a dopamine D3 receptor gene variant also has been reported [64].

Recent longitudinal studies have shown that drug dose and duration of exposure are very important. The prevalence increases with duration of exposure as new cases are added, but this may reach a plateau after about 5 years. Whether drug type is important has remained controversial. There is no convincing evidence that once drug dosage has been accounted for, any of the conventional neuroleptics presents a differentially smaller risk; nor is there empirical evidence that depot neuroleptics are more likely to cause TD [35]. The evidence in relation to the newer atypical drugs is still preliminary but suggests that these drugs may present a lower risk for TD. Although TD has been reported with risperidone, olanzapine, quetiapine, sulpiride, and amisulpride, there is no convincing report of TD with clozapine monotherapy, and this may indeed be the safest drug [35]. Anticholinergic drugs are known to exaggerate TD or make latent TD become manifest, but there is no convincing evidence they are risk factors for TD per se [35]. Lithium is not known to increase the risk.
Pathophysiology

The pathophysiology of TD is not understood completely. Much of the traditional conceptualization of the disorder has been guided by the causative role of antipsychotic and other dopamine (DA) antagonists. This resulted in the proposal of the dopamine supersensitivity hypothesis of TD [65], which states that the chronic administration of DA antagonists leads to the development of postsynaptic DA receptor supersensitivity, thereby producing the hyperkinetic state of TD. This hypothesis is compatible with many clinical and laboratory observations, but it has limitations. Observations in animal models do not parallel clinical observations, as DA supersensitivity in rats develops rapidly (often after a single injection) and persists for only a short period after cessation of the DA antagonist drug. Supersensitivity in animals declines after desensitization with DA agonists, but these drugs are not effective in treating TD. Moreover, supersensitivity in animals is almost invariable, whereas TD develops only in a fraction of patients. DA supersensitive rats do not exhibit a behavioral change, which has to be brought out by challenging them with dopaminomimetic drugs. Rats that do develop an analog of TD continue to show the movements after DA supersensitivity has disappeared. There is no direct evidence of DA supersensitivity in TD patients, either from postmortem studies, cerebrospinal fluid studies, or radioligand imaging studies using positron emission tomography. DA-mediated endocrine function is not different in TD subjects from non-TD controls. The effects of DA agonists and antagonists are also inconsistent in TD patients. Moreover, the DA hypothesis does not explain the spontaneous occurrence of dyskinesia in many schizophrenic and healthy subjects and the increased risk with age and many other host factors.

The inadequacy of the DA hypothesis has led to the consideration of many other pathophysiological models. In relation to other neurotransmitters that are affected by neuroleptics, some attention has been given to changes in norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh), but changes in γ-amino butyric acid (GABA) are considered to be the most salient for the development of TD [66]. Reduced activity in a subgroup of striatal GABA neurones has been suggested as the basis of TD, and this is supported by evidence from work in animals and in people [67].

Finally, the neurodegeneration hypothesis of TD has been presented. Free radical and excitatory mechanisms are brought into place by the increased turnover of DA and related mechanisms because of neuroleptic action. These lead to neurotoxicity and cell death, particularly of the GABA-ergic striatal neurones, because of the high levels of catecholamine turnover and oxidative metabolism in the striatum. This leads to the disinhibition of the lateral pallidal neurones and consequently the hyperkinetic state of TD, the manifestation of which is influenced by the prevalent dopaminergic tone. Withdrawal of DA antagonism will lead to the expression of a latent
hyperkinetic state, whereas DA blockade produces the reverse. The DA receptor antagonism of neuroleptics is therefore important in the pathogenesis of TD, but the mediating mechanisms are multiple and DA receptor supersensitivity may be only one, and not the pre-eminent, aspect of this (Fig. 1).

Management

No effective treatment for TD is available, although several drugs have been tried, based on the still preliminary understanding of its pathophysiology. The primary strategy in its management remains preventative. Once TD becomes established, attempts are made to minimize its symptoms and reduce ongoing risk factors for the worsening of the disorder over time. The treatment strategies are summarized in Box 3.

Future directions

There are many lacunae in our understanding of TD, which explains why rational therapy or effective preventative strategies are not available. The increasing use of atypical neuroleptics has made it necessary that the epidemiology of TD be revisited, with the expectation that the newer drugs

Fig. 1. Pathogenetic mechanisms for tardive dyskinesia.

Abbreviations: DA, dopamine; GABA, gamma amino butyric acid; Fe, iron; Mn, manganese.
will provide new insights into its pathophysiology. TD, therefore, continues to present itself as a natural experiment to study the pathophysiology of movement disorders. Its careful study also may provide a window on the underlying neurobiology of schizophrenia. Longitudinal studies of patients who receive atypical neuroleptics as their primary treatment from the first episode of psychosis onwards are necessary to assess the incidence of TD with these drugs. The current hypotheses for its pathogenesis need further empirical support and refinement so that they can be translated into treatment strategies. The subsyndromes of TD should be investigated further for their risk factors and pharmacological properties. More antipsychotic drugs need to be developed that are devoid of extrapyramidal adverse effects and carry little or no risk of producing an irreversible neurological disorder.

**Box 3. Drugs used in the treatment of tardive dyskinesia***

*Dopaminergic:*
- Antagonists:
  - Catecholamine depleters
  - Atypical neuroleptics: clozapine, risperidone, olanzapine
  - Other catecholamine depleters: AMPT
  - Classical neuroleptics: agonists–bromocriptine, L-dopa, apomorphine, piribedil, amphetamine, L-deprenyl

*GABA-ergic drugs*
- Benzodiazepines, valproate, gamma-vinyl GABA, baclofen

*Antinoradrenergic drugs*
- Propranolol, clonidine

*Cholinergic drugs*
- Physostigmine
- Deanol, choline, lecithin

*Serotonergic drugs*
- L-tryptophan, 5-hydroxy tryptophan, cyproheptadine

*Other*
- Lithium carbonate
- Ca channel antagonists: verapamil, diltiazem, nifedipine

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* Catecholamine depleters (eg, tetrabenazine) and GABA-ergic drugs (eg, valproate, baclofen, clonazepam) are used most frequently. Dopamine agonists, cholinergic drugs and serotonergic drugs are usually ineffective. Antiadrenergic drugs have only a small role.
Acknowledgments

Angie Russell assisted with manuscript preparation.

References


