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Review Paper

Tardive Dyskinesia in the Era of Typical and Atypical Antipsychotics. Part 1: Pathophysiology and Mechanisms of Induction

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Objective: Tardive dyskinesia (TD) is the principal adverse effect of long-term treatment with conventional antipsychotic agents. Several mechanisms may exist for this phenomenon. Mechanisms for the lower incidence of TD with atypical antipsychotics also remain to be fully understood. We undertook to explore and better understand these mechanisms.

Method: We conducted a comprehensive review of TD pathophysiology literature from January 1, 1965, to January 31, 2004, using the terms tardive dyskinesia, neuroleptics, antipsychotics, pathophysiology, and mechanisms. Additional articles were obtained by searching the bibliographies of relevant references. Articles were considered if they contributed to the current understanding of the pathophysiology of TD.

Results: Current TD vulnerability models include genetic vulnerability, disease-related vulnerability, and decreased functional reserve. Mechanisms of TD induction include prolonged blockade of postsynaptic dopamine receptors, postsynaptic dopamine hypersensitivity, damage to striatal GABA interneurons, and damage of striatal cholinergic interneurons. Atypical antipsychotics may cause less TD because they have less impact on the basal ganglia and are less likely to cause postsynaptic dopamine hypersensitivity.

Conclusion: Although the ultimate model for TD is not yet understood, it is plausible that several of these vulnerabilities and mechanisms act together to produce TD. The lower incidence of TD with atypical antipsychotics has helped to elucidate the mechanisms of TD.

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Clinical Implications

- Mechanisms of TD induction include prolonged blockade of postsynaptic dopamine receptors, postsynaptic dopamine hypersensitivity, damage to striatal GABA interneurons, and damage of striatal cholinergic interneurons.
- Atypical antipsychotics may cause less TD because they have less impact on the basal ganglia and are less likely to cause postsynaptic dopamine hypersensitivity.

Limitations

- The ultimate model for TD is not yet understood, and as a result, it remains a complex disorder.

Key Words: *antipsychotics, extrapyramidal symptoms,*

psychosis, schizophrenia, tardive dyskinesia

Résumé : La dyskinésie tardive à l'ère des antipsychotiques typiques et atypiques. 1re partie : la pathophysiologie et les mécanismes d'induction

Abbreviations used in this article

5-HT	Serotonin
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
GABA	gamma-aminobutyric acid
MRI	magnetic resonance imaging
PET	positron emission tomography
SD	spontaneous dyskinesia
TD	tardive dyskinesia

For many years, conventional antipsychotics were the standard treatment for schizophrenia, but use of these agents was often associated with the development of acute movement disorders, including parkinsonism, akathisia, and dystonia with short-term exposure and TD generally after long-term use (1). Since TD can lead to unintelligible speech (2), respiratory distress with diaphragmatic involvement, and falls, it is often associated with shame, guilt, anger, and depression. In patients whose psychosis is well controlled, TD can limit reintegration into society or the workforce (3,4). Because atypical antipsychotics have a lower propensity to cause TD, TD is less actively researched since the introduction of atypical antipsychotics; thus most of the articles included in this review date from prior to 2000. Atypical antipsychotics are, however, not benign and may lead to metabolic side effects in some patients (5). Nonetheless, atypical antipsychotics allow for effective control of schizophrenia symptoms with a lower incidence of TD.

Clinical Manifestations

TD is characterized by involuntary, repetitive, purposeless movements that vary in localization and form and occur in 8 main areas: tongue, jaw, lips, face, trunk, upper extremities, lower extremities, and respiratory system (6,7). The progression of TD varies, and although it may be persistent, the course of the disease often waxes and wanes with mild-to-moderate symptoms and thereafter has a range of mild-to-severe symptoms with possible periods of spontaneous remission (7,8).

Diagnosis

The diagnosis of TD is one of exclusion through an assessment of symptoms, clinical course, and diagnostic studies (9). TD must be differentiated from other neurologic disorders with similar manifestations, including Tourette syndrome, chronic motor tic disorder, Huntington's chorea, Sydenham's chorea, Wilson's disease, Meige's syndrome (for example, cranial dystonia), and the spontaneous movements in the elderly referred to as oral lingual dyskinesias and senile chorea (10).

TD is strongly associated with a history of conventional antipsychotic use and usually occurs after several years of treatment; however, TD can also occur after short-term exposure to conventional antipsychotic drugs. In fact, persistent TD can occur in patients treated with conventional antipsychotics, even at low dosages, for as few as 2 months (11,12).

Pathophysiology

The pathophysiology of TD is complex and remains to be fully elucidated (13). Multiple models have been proposed to assimilate the disparate research findings and properly evaluate the impact of atypical antipsychotics on TD.

One example that attempts to unify the wide range of clinical findings with TD is the stress–diathesis model. The stressor is the type, dosage, and duration of antipsychotic (or other medication) used; the diathesis is any condition that increases susceptibility to developing a movement disorder, including underlying motor abnormalities inherent in schizophrenia, genetic predisposition for movement disorders in general, or brain degeneration (such as the aging process) (14–16).

This paper is particularly focused on the stress component of this equation, but the diathesis merits a closer look. How can we reconcile the fact that certain patients do not develop TD despite many years of treatment with conventional antipsychotics, while others develop TD after brief exposure to low dosages of atypical antipsychotics? In this section, we discuss the factors that work synergistically to produce TD in a vulnerable subpopulation of patients with schizophrenia.

Disease-Related Vulnerability

SD is defined as abnormal involuntary movements in patients who have never been exposed

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to antipsychotics. Crane assessed 150 chronic male patients in Turkish mental hospitals (17), most of whom had schizophrenia, before antipsychotics were widely used. None of the patients had abnormal involuntary movements that were compatible with TD. However, Chatterjee and others found a high prevalence of EPS (16.9%) among antipsychotic-naive patients with schizophrenia (related to negative symptoms and poorer outcome) (18). The same researchers found that a poor response to treatment of a first episode of psychosis is an important factor in the development of TD (19). The authors proposed that there may be a disease-related vulnerability to TD revealed with antipsychotic exposure. Ismail and others examined younger patients with schizophrenia and some of their unaffected siblings and found that TD-like dyskinesia was present in 28.5% of siblings (20). This finding led the authors to conclude that TD-like dyskinesia may have neurodevelopmental antecedents. Anatomical and imaging studies to localize the relevant regions of the brain have been revealing. McCreadie and colleagues studied chronically ill patients who had schizophrenia and no previous exposure to antipsychotics and found that a significant portion had dyskinesia associated with enlargement of the left lentiform nucleus (21). The authors proposed that patients with dyskinesia and striatal pathology who have never been treated with antipsychotics may represent a subgroup of patients with schizophrenia.

PET and single-photon emission computed tomographic studies involving schizophrenia patients with no previous exposure to antipsychotic medication demonstrate elevated synthesis of dopamine in the striatum (22,23)—although Dao-Castellana and others report negative findings (23)—increased amphetamine-induced dopamine release (24–26), and increased baseline occupancy of dopamine D2 receptors (27). This line of evidence argues for a dysfunction in striatal dopaminergic transmission that precedes exposure to antipsychotics and is likely associated with the schizophrenia illness process per se or to psychosis in general (28). In this latest study, which used a standardized rating scale (the ESRS, 29), no TD was observed in drug-naive schizophrenia patients (28).

Genetic Vulnerability

Genetic vulnerability to dyskinetic movement disorders is distributed in the general population; therefore, conceivably, even a low dosage of an antipsychotic may lead patients at high genetic risk to express the dyskinesia phenotype. The search for genetic markers that predict such risk continues (30,31).

Decreased Functional Reserve

In addition to schizophrenia, other processes (for example, aging and head trauma) acting on the central nervous system increase the risk for TD. Generally speaking, these processes decrease the functional reserve of the systems involved in motor control; relatively small insults may therefore have a substantial impact. Hence, elderly patients are particularly vulnerable to the adverse effects of conventional antipsychotics (32,33).

Mechanisms of Antipsychotic Induction of TD

Many mechanisms have been proposed to explain how antipsychotics induce TD. The most prominent theory implicates postsynaptic dopamine receptor hypersensitivity. This model predicts that long-standing blockade of dopamine in the nigrostriatal pathway receptors leads to possibly permanent receptor hypersensitivity (Table 1) (34–47).

Table 1 Proposed mechanisms of TD induction by conventional antipsychotics

A. Postsynaptic dopamine receptor hypersensitivity • All antipsychotics block dopamine receptors (36,37). • Many nonantipsychotic medications that block dopamine have also been associated with TD (38). • Increasing dopaminergic blockade suppresses TD (albeit temporarily) (39). • A relation exists between long-standing EPS and the later development of TD (7,47). • PET data show that D_2 binding is increased after long-term antipsychotic treatment in humans (40). (The degree of D_2 upregulation likely corresponds to the propensity for TD to develop.)
B. Damage to striatal GABA-containing neurons • Decreased activity of glutamic acid decarboxylase in the substantia nigra, globus pallidus, and subthalamic nucleus in monkeys and rats with antipsychotic-induced oral movements (41).

- Decreased number of striatal neurons in rats after long-term antipsychotic treatment (41).
- Antipsychotic-induced degeneration of striatal-pallidal or striatal-nigral GABA-aminergic pathways, or both (42,43) .

C. Damage or degeneration of striatal cholinergic interneurons caused by prolonged overactivation of striatal cholinergic neurons when released from dopaminergic inhibition after antipsychotics are administered (44).

D. Prolonged blockade of postsynaptic dopamine receptors (36,37,45).

- Increased dopamine formation of free-radical metabolites (46).
- Increased excitatory glutaminergic transmission from prefrontal cortex to striatum (46).

Damage to striatal GABA-containing neurons has also been cited in the pathophysiology of TD, as revealed in reports that show decreased activity of glutamic acid decarboxylase in the substantia nigra, globus pallidus, and subthalamic nucleus in monkeys and rats with antipsychotic-induced oral movements and a decreased number of striatal neurons in rats after long-term antipsychotic treatment (Table 1) (41). Such findings are consistent with the degeneration of striatopallidal and striatonigral GABA-aminergic pathways that occur in response to antipsychotic therapy; however, human studies using GABA agonists have shown only minimal effects (42,43).

Miller and Chouinardproposed that TD occurs in response to the damage or degeneration of striatal cholinergic interneurons (44) (Table 1). The most direct evidence for these proposals can come only from pathologic studies of postmortem brains in appropriate clinical groups. Thus far, no published studies address these issues in a specific way. However, Holt and colleagues showed a loss of cholinergic interneurons in striata obtained from patients with schizophrenia (48). Most of the brains in this study were obtained from patients extensively treated with antipsychotics before death. Although no clinical data are available in this study indicating whether these patients displayed symptoms of TD or antipsychotic-resistant psychosis, the observed cholinergic cell loss might have given rise to one of these syndromes commonly associated with schizophrenia, rather than with psychosis or schizophrenia itself (28).

Several studies in animals have reported that cholinergic cells (or the marker enzyme choline acetyl transferase) in the striatum are lost or reduced in amount after prolonged regimes of haloperidol and fluphenazine (49,50). Recently, Grimm and others showed that prolonged haloperidol treatment in rats led to cholinergic cell loss in the specific areas of the striatum related to oral movements (51). This result may provide an animal model to explain why TD in humans is most commonly a motor disorder of orofacial musculature.

Proton magnetic resonance spectroscopy provides supporting evidence for the cholinergic hypothesis. This method allows quantification of choline, the precursor of acetylcholine, in specific brain structures. Choline reuptake leads to the accumulation of choline in cholinergic neurons before its conversion to the transmitter; an excess of choline in brain tissue will signify a loss of cholinergic neurons. Using this method, investigators have shown that, in schizophrenia, choline levels in the basal ganglia are greater than normal (52). Ando and others produced further results with this method (53), implying that choline levels in the lenticular nucleus are higher in schizophrenia patients with TD than in those without the syndrome.

Apart from such methods for assessing cholinergic processes in the striatum, clinical trials with cholinergic agents in patients with TD could provide indirect evidence related to the cholinergic hypothesis (44). Caroff and colleagues showed that the anticholinesterase donepezil was effective against the symptoms of TD (54,55). Since choline, the precursor of acetylcholine, was not effective, Caroff and others regarded their evidence as support for the hypothesis of Miller and Chouinard. However, a recent metaanalysis concluded that trials of cholinergic agents in the treatment of TD conducted to date have insufficient statistical power to reach a firm conclusion about the drugs' effectiveness (56). This area of research may be clarified when cholinergic agents effective against specific muscarinic receptors are tested in patients with TD.

Atypical Antipsychotics and TD

Although receptor-binding profiles vary among atypical antipsychotics, they all antagonize dopamine and serotonin receptors to some degree. Whether other receptor binding is involved in either TD onset or TD amelioration is not known. It is clear, however, that atypical antipsychotics are associated with the least risk of causing structural damage and provoking persistent, dynamic alterations in neurotransmitter systems involved in motor control. Atypical antipsychotics, in general, act on the mesolimbic (A10) rather than on the nigrostriatal (A9) dopamine pathways (likely mediated by 5-HT_2 antagonism) and modulate dopaminergic transmission through loose binding at the D_2 receptor. For a more thorough

review regarding mechanism of action of antipsychotics, several excellent articles exist in the literature (36,45). Atypical agents that bind loosely to D_2 receptors and block 5-HT_2 receptors will likely be associated with the lowest incidence of TD and may even demonstrate a protective effect in patients at increased risk for spontaneous dyskinesia (caused by genetic, neurodevelopmental, or age-related factors), a beneficial effect in patients with established TD and altered neurotransmitter systems (such as dopaminergic hypersensitivity), and a temporary masking of damage caused by conventional antipsychotics. This could also partly be due to spontaneous remission of TD from conventional antipsychotic withdrawal; it is difficult to determine the exact effect without placebo-controlled trials.

Clozapine, quetiapine, ziprasidone, olanzapine, and risperidone (< 6 mg daily) exert a favourable effect on TD by several possible mechanisms (57–60). It is likely that these mechanisms (such as suppression, spontaneous improvement, and direct effect on pathophysiology) act together at different periods during treatment and to differing degrees along with other yet unrecognized mechanisms. Of these mechanisms, support for direct effect against the pathophysiology of TD, possibly by decreasing dopamine receptor sensitivity, is found, because the decrease in TD over time is dosage-dependent (57,59). The theory that this is due to dosage-dependent suppression similar to that associated with conventional antipsychotics (58) is not supported, because some TD symptoms are stable or remain at a low level over time when treated with atypical antipsychotics. In addition, PET data show weak D_2 binding (for clozapine) in the nigrostriatal tract, not strong D_2 binding, as predicted by this theory (37,60).

The structural brain abnormalities seen in patients with schizophrenia and TD are poorly understood at this time (61); whereas some abnormalities are reversible, there appears to be a threshold beyond which they may be persistent, even if current management strategies are undertaken (62). The multiple receptor antagonist atypical antipsychotics seem to exert neuroprotective therapeutic effects that permit them to have superior therapeutic activity for many of our patients. Cloning of human receptors has permitted a better understanding of the mechanism of action of antipsychotics and has helped to define atypicality. The D_2 blocking effect does not permit a differentiation between antipsychotics, rather, blockade of other receptors helps to define atypicality (63). Atypicality is defined by 2 properties shared by all atypical antipsychotics: neuroprotective effects on cortical toxicity and extrapyramidal toxicity caused by classical antipsychotics and multiple receptor antagonism (64–66).

Atypical antipsychotics exert therapeutic effects by simultaneously acting at levels considered efficacious in humans on more than 10 receptors that are now directly or indirectly implicated in schizophrenia (67). There are numerous studies in both humans and animals that demonstrate neuroprotective effects of atypical antipsychotics (68–74). From this perspective, the most studied medications are clozapine, risperidone, and olanzapine. Three studies review the results obtained to date in patients with schizophrenia (68–72). Frazier and colleagues revealed that caudate volume increased after exposure to typical antipsychotics in childhood-onset schizophrenia patients (68). After 2 years of treatment with clozapine, caudate volume, which was larger on the first scan, had diminished to reveal no difference between subjects and control subjects on the second scan. Lang and colleagues failed to demonstrate a difference in first-episode schizophrenia patients among volumes of the lenticular, caudate, and front wall of the amygdala (basal ganglia), compared with healthy control subjects (69). In chronically treated patients, caudate, putamen, and globus-pallidus volumes were significantly larger than in first-episode patients and control subjects. In first-episode schizophrenia patients treated with risperidone, lenticular, caudate, and front wall of the amygdala (that is, basal ganglia) volumes were unchanged after one year of treatment (69). In the study by Gur and colleagues, no difference in subcortical volume was observed between patients treated for the first time with an antipsychotic and healthy control subjects, except on thalamus volume (70). In these same patients, changes in volumes did not correlate with the intensity of negative symptoms, whereas an augmentation in thalamus and putamen volume correlated with the intensity of positive symptoms. In this same study (70), larger putamen and pallidum volumes were observed among patients previously treated with antipsychotics, compared with healthy control subjects and first-episode patients. Among previously treated patients, high-dose classical antipsychotics led to increased caudate, putamen, and thalamus volumes, whereas high-dosage atypical antipsychotics led only to increased thalamus volume (70).

Two other MRI studies conducted among schizophrenia patients confirmed that typical antipsychotics increase basal ganglia volume, whereas atypical antipsychotics have the opposite effect (71,72). We have already described 2 postmortem studies (44) that demonstrated a glial cell reaction and loss of the largest striatal neurons (probably cholinergic neurons) among schizophrenia patients chronically treated with classical antipsychotics and, more frequently, among those with TD. These studies can help explain increased caudate volume caused by classical antipsychotics seen among approximately 10% of the patients in these MRI studies.

Conclusion

TD remains a complex disorder because its mechanism is not yet fully understood. Current TD vulnerability models, which are not mutually exclusive but rather complementary, include genetic vulnerability, disease-related vulnerability, and decreased functional reserve. Mechanisms of TD induction by typical antipsychotics include prolonged blockade of postsynaptic dopamine receptors, postsynaptic dopamine hypersensitivity, damage to striatal GABA neurons, and damage to striatal cholinergic neurons. Although one unifying theory may ultimately be discovered, current understanding suggests that several of these mechanisms may coexist to produce TD or that different mechanisms may predominate in different patients or patient populations. Atypical antipsychotics may be associated with a

lower risk of TD by decreasing striatal dopamine receptor sensitivity, either indirectly through serotonin or directly by looser binding to the D_2 receptor. Further, compared with typical antipsychotics, atypicals are less likely to cause changes in basal ganglia volume; thus, they are less likely to damage cells directly involved in the pathophysiology of TD. Understanding of the pathophysiology of TD has made significant advances with our understanding of atypical antipsychotic mechanisms of action and our exploration of their lower propensity to cause TD. However, the full elucidation of the mechanisms of TD remains to be discovered.

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