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Tardive dyskinesia syndromes: current concepts

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SUMMARY

Tardive syndromes (TS) encompass a broad spectrum of abnormal movements due to chronic exposure to dopamine receptor blocking agents. This review provides a compiled update on TS, including phenomenology, epidemiology, pathophysiology, genetic correlations and therapeutics, highlighting the emerging experience with atypical antipsychotics. The advent of atypical antipsychotics, which have lower affinity for dopamine receptors and act on 5-HT_{2A} and 5-HT_{2C} serotonin receptors, was expected to dramatically reduce the prevalence and incidence of this iatrogenic problem. Recent studies have shown that the reduction has been more modest than expected and TS remains an important challenge. Recent insights on pathophysiology, risk factors and genetic correlations have raised the hope for further individualized treatment for schizophrenic patients, and more strict use of antipsychotics. Up to now, there is no definite treatment for TS, but options range from relatively innocuous low doses of propranolol to more invasive procedures such as deep brain stimulation.

1. Introduction

Tardive dyskinesia (TD) is a term historically used to refer to delayed and persistent abnormal movements caused by exposure to dopamine receptor blocking agents (DRBA). There are several distinct phenomenologies under the definition of TD justifying the term tardive syndrome (TS) to encompass the broad spectrum of symptoms that can develop after chronic use of DRBA [1].

According to the diagnostic and statistical manual of mental disorders, fourth edition (DSM IV), the spectrum of TD includes involuntary movements of the tongue, jaw, trunk, or extremities, and may be choreiform, athetoid, or stereotypic in nature. Abnormal movements should appear during exposure, or within 4 weeks of withdrawal from oral DRBA or 8 weeks from depot formulations. The minimal exposure to DRBA should be 3 months, except for patients older than 60, who can develop TD after using DRBA for 1 month. Finally, the movements should be present for at least 1 month to fulfill the criteria for TD [2].

TS have been strongly associated with antipsychotic drugs, however, several other classes of drugs, such as the antiemetic metoclopramide and the calcium channel blockers cinnarizine and flunarizine, occupy dopamine receptors and have been associated with movement disorders and TS [1,3]. The advent and widespread use of atypical antipsychotics in clinical practice had been expected to dramatically reduce the incidence and prevalence of TS, however the reduction, if any, was modest [4].

In view of this, TS is a challenging condition for neurologists and psychiatrists, due to lack of definite risk factors to predict patients who will develop this condition; complex and usually mixed presentation; suboptimal results with treatment and the common persistent, chronic course. In this review we provide a compiled update on TS, including phenomenology, epidemiology, pathophysiology, genetic correlations and therapeutics, highlighting the emerging experience with atypical antipsychotics.

2. Phenomenology of tardive syndromes

Distinct hyperkinetic movement disorders have been described as part of the TS [3]. More recently there is a tendency to reserve the term "classical tardive dyskinesia" for the oro–buccal–lingual (OBL) dyskinesia, and to apply a more specific terminology based on the phenomenology to each subtype of tardive syndrome, namely: tardive dyskinesia, tardive stereotypy, tardive dystonia, tardive tremor, tardive akathisia, tardive myoclonus and tardive tourettism [1,3]. The clinical aspects of these entities are summarized in Table 1.

TS phenomenologies may frequently occur simultaneously in the same patient, for instance, OBL dyskinesia, in association with dystonia and akathisia, increasing the likelihood of TS as the final diagnosis.

Drug-induced parkinsonism is not uncommon in patients developing TS while they remain on DRBA. Whether "tardive parkinsonism" exists or not is controversial. Interestingly, approximately 50% of patients who develop parkinsonism during exposure to DRBA are found to have underlying dopaminergic striatal denervation on neuroimaging suggestive of Parkinson's disease (PD) [5]. In addition,

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Table 1
Phenomenology of tardive syndromes

Syndrome	Phenomenology
Tardive dyskinesia	Refers to the classical oro–buccal–lingual (OBL) dyskinesia and to choreic movements in other body parts. The typical pattern is a stereotyped combination of tongue twisting and protrusion, lip smacking and puckering, and chewing movements. Many patients may not be aware of their movements. Speech is usually minimally affected because voluntary action can suppress OBL dyskinesia. When affecting limbs, manifest with piano-playing movements, grasping, flexion and extension of limbs, and foot tapping. Involvement of diaphragm and respiratory muscles may result in loud breathing, hyperventilation, grunting, groaning or distorted speech. TD is more common in elderly patients and women.
Tardive stereotypy	The concept of stereotypy has been changing over the years and has been applied to distinct conditions. We accept "*a non-goal-directed movement pattern that is repeated continuously for a period of time in the same form and on multiple occasions, and which is typically distractible*" as the most appropriate definition. Tardive stereotypy has been used to describe the classical OBL dyskinesia, due to its stereotyped fashion, however, it fails to fulfill the definition of stereotypy due to lack of distractibility and unpredictable order of movements.
Tardive akathisia	Characterized by a feeling of inner restlessness and jitteriness resulting in inability to sit or stand still. Objectively, patients are seen rocking from foot to foot, walking in place, crossing/uncrossing legs, or body rocking. Akathisia can also occur in the early phase of treatment with DRBA, known as acute akathisia. Pseudoakathisia refers to the appearance of extreme restlessness in the absence of clear subjective feeling of restless.
Tardive dystonia	Tardive dystonia can be focal, segmental or generalized. It frequently coexists with other TS, and can be reduced by voluntary movements, instead of being action induced as primary dystonia. The typical distribution involves the face and neck followed by the arms, trunk, and, less frequently, legs. The classical patterns of movement are: Face: blepharospasm, oculogyric movements, tongue protrusions, jaw closing or opening, and lip retraction; Neck: retrocollis and/or laterocollis; Trunk: hyperextension, resulting in an opisthotonic posturing; Limbs: internal rotation of the arms, extension of the elbows, and flexion of the wrists. Tardive dystonia is more common in young men.
Tardive myoclonus	Myoclonus is a common adverse effect from a variety of drugs, for instance: antidepressants, antiepileptic drugs, neuroleptics, antibiotics, and others. Tardive myoclonus appears after at least 3 months of exposure to DRBA, frequently in association with other TS. It is typically postural and affects the upper extremity.
Tardive tremor	Manifests with kinetic, postural and resting tremor, usually with high amplitude, frequency of 3–5 Hz, in the absence of parkinsonian signs.
Tardive tourettism or tardive tics	May be phenomenologically identical to Tourette syndrome, except for the age of onset and history of chronic exposure to DRBA.
Tardive pain	This is a rare form of tardive syndrome that manifests with chronic pain or other unpleasant sensations in oral or genital areas.
Withdrawal-emergent dyskinesia	Seen in children following sudden discontinuation of chronic antipsychotic drug treatment. The movements are typically choreic and resolve when the offending medication is reinstituted and/or followed by a slow drug-tapering schedule. Many patients do not develop classical OBL dyskinesia until long-term DRBA are withdrawn. If these symptoms completely resolve within a few weeks the term withdrawal emergent dyskinesia can be applied retrospectively.

a recent study in an elderly cohort showed that previous exposure to antipsychotics increased the risk of probable PD by 3.2-fold [6]; the mechanism responsible for this association remains unclear.

3. Epidemiology before and after atypical antipsychotics

The real prevalence and incidence of TS is difficult to estimate due to a variety of reasons: most patients, especially those with classical OBL dyskinesia, are not aware of their symptoms, movements may fluctuate over time and the offending drug can mask symptoms [7]. Despite this, overall, the prevalence of TD is estimated to be 30% in outpatients treated with antipsychotics, ranging from 20% to 50% [2]. The incidence has been estimated between 4% and 8%, with a cumulative 5-year incidence of 25%, with approximately 2% spontaneous remissions annually [7]. Differences may be found for distinct subtypes of TS, age, gender, and classes of drugs used.

The risk factors currently accepted for TD are older age, female gender, history of brain damage or dementia, presence of a major affective disorder and longer exposure to DRBA. In regard to the dose of DRBA used, data suggest that there is a plateau effect with moderate doses, above which the risk of TS is not further increased [7]. Patients who develop acute extrapyramidal symptoms apparently have higher risk to develop TS, as do non-Caucasians [8].

Atypical antipsychotics are expected to have less extrapyramidal side effects owing to their lower affinity to dopamine D2 receptors in the dorsal striatum, and associated antagonism of 5-$HT_{2A/2C}$ receptors [9]. Indeed, some studies have suggested an incidence of TD of 2% per year, or a risk reduction of 3.5-fold [10]. Nevertheless, a review of 12 studies involving 30,129 patients suggested a more modest difference in the incidence of TS with typical and atypical antipsychotics, 5.5% versus 3.9%, respectively [4]. Up to this time, the majority of studies searching for reduction in incidence of TS with atypical antipsychotics have been limited by short follow-up, lack of a clear definition of TS, and inclusion of patients with previous exposure to typical antipsychotics [10].

4. Changing concepts of the pathophysiology of TS

TS has been commonly attributed to hypersensitivity or up-regulation of dopamine receptors, particularly D2, following chronic blockade; however, this is unlikely to be the sole explanation [11].

It is known that normal movements require a balance between the direct and indirect pathways of the basal ganglia. Activation of the direct pathway results in facilitation of movements, whereas activation of the indirect pathway results in reduction of velocity and amplitude of movements. D2 receptors, expressed on striatal medium-spiny-neurons, are inhibitory for the indirect pathway, thus D2 hypersensitivity would cause hyperkinesia. This mechanism is supported by animal models of "vacuous chewing movements" induced by prolonged exposure to haloperidol [12], and by a study in humans showing increased D2-receptor binding in PET of patients with long-term exposure to DRBA [13].