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Review Article

Clinical risk factors for the development of tardive dyskinesia

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ABSTRACT

Background: Tardive dyskinesia (TD) is a severe condition that can affect almost 1 out of 4 patients on current or previous antipsychotic treatment, including both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). While two novel vesicular monoamine transporter inhibitors, deutetrabenazine and valbenazine, have shown acute efficacy for TD, the majority of patients do not remit, and TD appears to recur once treatment is withdrawn. Hence, prevention of TD remains a crucial goal.

Methods: We provide a clinically oriented overview of risk factors for TD, dividing them into patient-, illness- and treatment-related variables, as well as nonmodifiable and modifiable factors.

Results: Unmodifiable patient-related and illness-related risk factors for TD include older age, female sex, white and African descent, longer illness duration, intellectual disability and brain damage, negative symptoms in schizophrenia, mood disorders, cognitive symptoms in mood disorders, and gene polymorphisms involving antipsychotic metabolism and dopamine functioning. Modifiable comorbidity-related and treatment-related factors include diabetes, smoking, and alcohol and substance abuse, FGA vs SGA treatment, higher cumulative and current antipsychotic dose or antipsychotic plasma levels, early parkinsonian side effects, anticholinergic co-treatment, akathisia, and emergent dyskinesia.

Discussion: Clinicians using dopamine antagonists need to consider risk factors for TD to minimize TD and its consequences.

1. Introduction

Tardive dyskinesia (TD) is a severe condition that can affect almost 1 out of 4 patients who are or have been on treatment with dopamine receptor blocking agents (DRBAs), in particular antipsychotic medications, including both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) [1]. TD is characterized by involuntary movements, most commonly of orofacial muscles, but also involving muscles of the extremities, trunk, hip, etc [2]. TD can be reliably assessed with rating scales, such as the Abnormal Involuntary Movement Scale (AIMS) [3], which is used to evaluate involuntary movements across 7 body regions. Other scales, such as the Extrapyramidal Symptoms Rating Scale [4], are also used and have the advantage of capturing all possible involuntary movements, yet are more complex and time consuming, and require more training than the AIMS.

While the pathophysiology of TD remains unknown, several hypotheses exist. One of the most discussed is dopamine hypersensitivity following receptor upregulation due to dopamine receptor blockade after antipsychotic use [5], or of more widely defined DRBAs, including metoclopramide. Two recently approved drugs belonging to the class of VMAT2 inhibitors, deutetrabenazine and valbenazine, have shown promising efficacy for TD in both patients with schizophrenia and mood disorders, and in acute and long-term settings [6–15]. Moreover, both deutetrabenazine and valbenazine were well tolerated and safe, without clinically relevant concern regarding depression, suicidality, QTc prolongation, and sedation/somnolence in the randomized controlled registration trials. However, despite such promising effectiveness of these 2 novel and recently FDA- approved VMAT2 inhibitors, long-term evidence suggests that after 48 weeks of treatment with valbenazine once the agent is withdrawn, symptoms consistently and rapidly recurred. Finally, TD has also been associated with poor quality of life [16] as well as increased mortality [17] in psychiatric patients.

Thus, prevention of TD, or at least minimizing its risk, is a preeminent goal. To facilitate this goal, we summarize known risk factors for the development of TD to provide clinically oriented information that can help clinicians take into account modifiable and nonmodifiable

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risk factors when managing patients with severe mental illness who need DRBA treatment.

2. Methods

We conducted a targeted literature review, searching for review articles and meta-analyses, as well as naturalistic cohort studies that reported on "risk factors" for "tardive dyskinesia" or "TD." Building upon a previously suggested categorization that focused on "non-therapeutic" risk factors [16], we divided risk factors for TD into nonmodifiable patient- and illness-related variables as well as modifiable comorbidity- and treatment-related variables.

In terms of terminology, we used the term TD (or "classic tardive dyskinesia") to refer to the original description of repetitive and complex oral-buccal-lingual movements, as well as to the analogous repetitive movements that can appear in the limbs or trunk. It is the repetitive, relatively rhythmic nature of the movements that is the common denominator of this phenomenological category called tardive dyskinesia. TD as well tardive dystonia, tardive tics, tardive akathisia, etc. are summarized under the broader term of tardive syndromes.

Furthermore, although the term extrapyramidal symptoms ("EPS") is mostly used in the psychiatric literature to denote parkinsonian side effects (i.e., akinesia, tremor, muscle rigidity), the term is also used more broadly to include all types of acute motor syndromes, such as dystonia, akathisia, withdrawal dyskinesia, etc. In this article, we attempted to be as specific as possible, denoting what type of acute motor syndrome was referred to, although this was not always possible based on lacking details in the original publications.

3. Results

Different types of modifiable and nonmodifiable risk factors for TD are summarized in Table 1. Additionally, Table 2 provides a checklist of actions aimed at preventing or minimizing the risk of TD that map onto each of the risk factors for TD listed in Table 1.

3.1. Nonmodifiable risk factors for TD

3.1.1. Patient-related risk factors

3.1.1.1. Older age. Evidence from solid research, including a large meta-analysis [1], supports advanced age as a risk factor for increased rates of TD and for more severe forms of TD. In particular, an approximately 2- to 5-fold increased annual incidence rate of TD has been described in elderly vs. nonelderly adults, both with FGAs (25–30% [18,19] vs. 5–6% [20]) and with SGAs (5–7% [21,22] vs 0.8%–3% [21,22]).

3.1.1.2. Female sex. Female subjects appear to be at increased risk of TD [21,22]. In an earlier review of TD prevalence in altogether 39,187 the prevalence was significantly higher in women (26.6%) than in men (21.6%) [23]. Moreover, TD severity was also greater in females, and the risk for females vs. males increased in the elderly, suggesting a possible interaction between age and sex.

3.1.1.3. White or African descent. Asian race seems to be a protective factor against TD, compared with other races [1], likely reflecting underlying racial protective factors. Additionally, elderly African American patients were at increased risk of TD compared to Caucasians [1,20,24].

3.1.1.4. Genetic variants involving antipsychotic metabolism and dopamine functioning. Six cytochrome P450 (CYP) enzymes located in the brain and the periphery are responsible for approximately 90% of all CYP activity [25]. Among these, the CYP enzymes 3A4, 2D6, and 1A2 are most important for antipsychotic metabolism. The CYP3A4 enzyme (mainly responsible for cariprazine, haloperidol, lurasidone, quetiapine, and olanzapine clearance) is relatively immune to saturation, unless very potent inhibitors are present. In contrast, the CYP2D6 enzyme (mainly responsible for aripiprazole, brexpiprazole, chlorpromazine, iloperidone, perphenazine, and risperidone clearance) is not readily inducible, but can be saturated more easily. Moreover, most known genetic polymorphisms affect CYP2D6, increasing the inter-individual variance in antipsychotic plasma levels. Finally, the CYP1A2 enzyme is also a low-affinity, high-capacity enzyme and is relevant for the clearance of clozapine and, to some degree, of asenapine and olanzapine [26–28]. Among the most replicated findings is the association between abnormal CYP2D6 metabolizer status and greater susceptibility to antipsychotic-induced TD (as well as drug-induced parkinsonism) [27,29].

There is alsoa significant relationship between TD risk and polymorphisms in genes involved in the rate of metabolism of dopamine, i.e., the Val/ValCOMT genotype [26,30], packaging of dopamine into presynaptic vesicles, i.e., the VMAT2 gene [31], and functionality of the dopamine 2 receptor, i.e., the DRD2 gene polymorphism [26].

3.1.1.5. Genetic polymorphisms that deserve further investigation. Caucasian BDNF Met allele carrier subjects were shown to have an increased mean AIMS score, but were not at an increased risk of TD [32]. Also, evidence from pooled data suggested several gene polymorphism candidates, which were potentially associated with an increased risk of TD, namely in the COMT, MAO, DRD2, DRD3, CYP1A2 and MnSOD genes [26,33–35], but clinical relevance of such associations has not been confirmed and requires further study.

3.1.2. Illness-related risk factors for TD

3.1.2.1. Longer illness duration. Longer illness duration has shown to predispose patient to TD, according to individual studies [36,37] and a meta-analysis of data from 21 studies [1]. However, it remains unclear whether such a relationship is mediated through cumulative antipsychotic dose, prior exposure to FGAs, older age, or a

Table 1
Nonmodifiable and modifiable risk factors for tardive dyskinesia.

Non-modifiable risk factors		Modifiable risk factors	
Patient-related	Illness-related	Comorbidity-related	Treatment-related
Older age	Mood disorder diagnosis	Smoking	First-generation > Second-generation antipsychotics
Female sex	Cognitive dysfunction in mood disorder	Alcohol abuse/ dependence	Acute motor syndromes (e.g. acute dystonic reactions, parkinsonism, akathisia)
African descent > Caucasian > Asian	Longer duration of severe psychiatric illness	Substance abuse/ dependence	High antipsychotic drug dose
Genetic polymorphism in genes involved in dopamine metabolism, packaging, and receptor functioning	Negative symptoms in schizophrenia	Diabetes mellitus	High antipsychotic medication plasma levels
Cytochrome P450 genetic polymorphisms/slowed antipsychotic clearance	Intellectual disability and brain damage		Intermittent antipsychotic treatment
			Co-treatment with anticholinergic medications