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Tardive Dystonia due to D2 Antagonists and Other Agents

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Abstract

Tardive dystonia due to D2 antagonists or other agents is a potentially severe extrapyramidal side effect emerging after long-term drug treatment, prevalent but not limited to psychiatric populations. Its course is often deteriorating, and available treatments are frequently far from satisfying. It presents with sustained muscle contractions, abnormal postures, and repetitive twisting movements and leads to increased psychiatric morbidity, mortality, and decline of quality of life. Inadequate clinical skill and awareness of tardive dystonia can lead to neglect or misdiagnoses, considered as conversion symptoms or of psychogenic origin. Since the syndrome is persistent and often treatment resistant, prevention should be a mainstay of clinical care. Emerging evidence supports positive effects of atypical antipsychotics, particularly quetiapine and clozapine. Therapies such as tetrabenazine, valbenazine, deutetrabenazine, anticholinergics, baclofen, benzodiazepines, vitamin E, or non-pharmacologic interventions, namely botulinum toxin A, deep-brain stimulation, have been found to be helpful in some cases of tardive dystonia. This chapter comprehensively illustrates multiple aspects of this entity, including recent advances on etiology, pathophysiology, clinical presentation, epidemiology, pharmacogenomics, and treatment, aiming to enhance and deepen clinicians' and researchers' awareness of tardive dystonia, with the final goal of ameliorating patients' prognosis and quality of life.

Keywords: tardive syndromes, tardive dyskinesia, tardive dystonia, antipsychotics, clozapine, quetiapine, diagnosis, extrapyramidal side effects, D2 antagonism, pharmacogenomics, treatment

1. Introduction

With the advent of antipsychotic drugs in the 1950s, a new era in the treatment of schizophrenia began, one that substantially altered the course of the illness and offered many benefits to patients and the society. Along with therapeutic advance, new troubles emerged, as it was soon realized that neuroleptics caused important side effects, among which drug-induced movement disorders could be seriously problematic. Tardive syndromes, largely represented by tardive dyskinesia and tardive dystonia, still remain challenging in many respects.

“Dystonia Tarda” was a term firstly used in 1973 to define a dystonia which appeared as a delayed undesirable effect in patients exposed to neuroleptic drugs [1]. Case descriptions appear in the literature even earlier, but a definition of the term “Tardive Dystonia” came from Burke et al. [2] who also implemented diagnostic criteria. The syndrome consists of involuntary, sustained muscle contraction(s), usually slow, often painful, affecting the face, neck, limbs, or trunk [3]. The involuntary muscle contractions can cause abnormal postures and twisting movements, which are often disfiguring and socially awkward.

Tardive dystonia (TDt) belongs to a constellation of persistent motor and sensory syndromes, collectively called tardive syndromes (TS), manifesting as a result of dopamine receptor blocking agents (DRBAs) or, less often, by other types of drugs (**Figure 1**). Tardive dyskinesia (TDk) was the first to be observed, in the 1950s, typically comprising rhythmic, repetitive oro-buccal-lingual involuntary movements, which, however, can also appear in trunk, limbs, and pelvis [4]. Later, TDt was also described as a distinct, frequently co-occurring or independently manifesting condition. Although the term “tardive” implicates a long exposure and

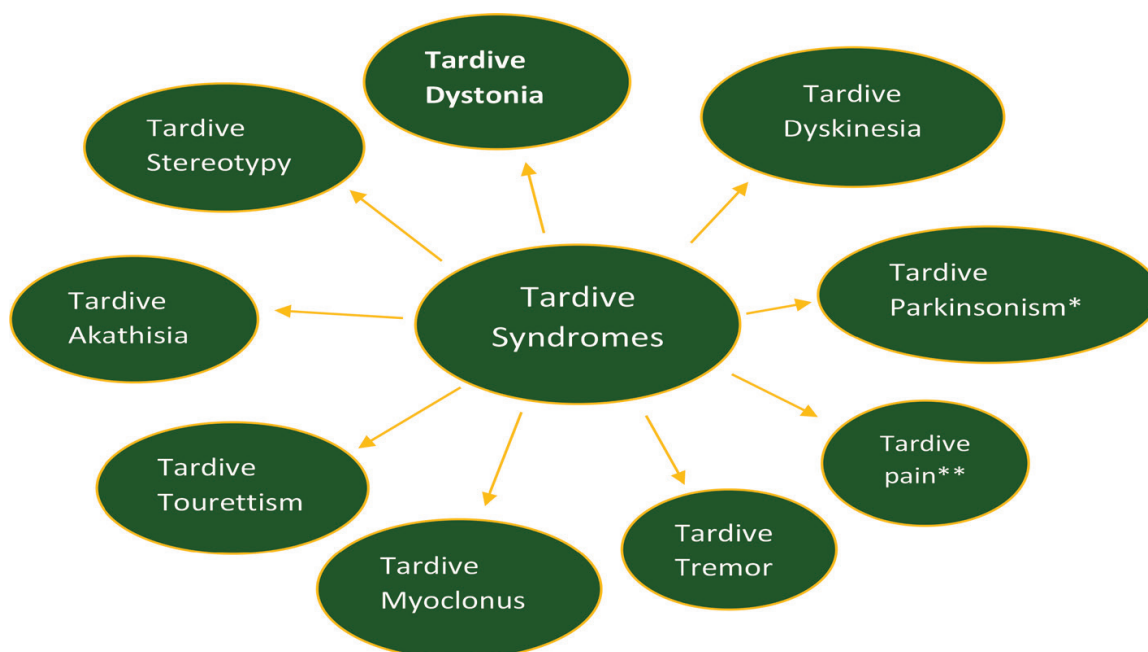


Figure 1. Tardive syndromes occurring in neuroleptic-treated patients. *Tardive parkinsonism is not solidly established, but probably signals the presence or unmasking of idiopathic parkinsonism. **Tardive pain refers to chronic oral or genital pain and is considered by some authors as a type of tardive akathisia, with a severe focal sensory discomfort.

delayed onset, tardive syndromes can actually show up even days after the administration of the offending agent, notwithstanding that risk increases with longer exposure durations. Another important feature is their persistent nature, meaning that they persist or even worsen following discontinuation of the offending drug [5].

Progress in the field has demanded much effort, regarding the clinical recognition of the syndrome, pathophysiology, prevention, and treatment. One reason for this is that TDt often occurs simultaneously or as a component of TDk, or other tardive syndromes, and researchers have difficulties to deal with it separately. Moreover, there is often some confusion in the study, as authors may sometimes use the term tardive dyskinesia in order to refer to a variety of tardive syndromes. Much work examines tardive syndromes in general, and it is difficult to extract data referring specifically to TDt. Still, the distinction and separate examination of TDt is important, because it differs from TDk in respects of presentation, course, prognosis, and treatment; it is frequently more debilitating and treatment resistant; it is associated with a poorer quality of life, a reduced treatment compliance, and psychiatric morbidity [6–8]. Another task is to differentiate tardive dystonia from acute dystonia, emerging acutely and within days after the initial administration of anti-D2 agents, predominantly in young males, as well as from other types of dystonia. Tardive syndromes due to anti D2 agents are schematically depicted in **Figure 1**.

In their pioneering work, Adityanjee et al. had hoped that tardive dystonia together with tardive dyskinesia would in the future be a matter of historical interest, thanks to the advent of new, better antipsychotics [6]. Almost 20 years later, these movement disorders are not at all lost, not yet forgotten. Continuing to be a serious burden, they call for better understanding, prompt recognition, prevention, and optimized treatment.

2. Epidemiology

The prevalence of TDt has been estimated between 0.4 and 21.6% of neuroleptic-treated patients, in earlier studies [6], which distinguished tardive dystonia from tardive dyskinesia (**Table 1**). Most of them have included chronically ill patients. The study by Sethi et al. [13] was conducted on a veteran sample and also included mild manifestations of TDt, which is possibly the reason for the relatively high reported prevalence. Moreover, in a sample of 194 mainly Afro-Caribbean chronic psychotic patients, TDt was overall found in 13.4%, together with TDk in 9.8%, together with parkinsonism in 4.6%, and together with akathisia in 1% of patients [17]. To compare, the prevalence of TDk, which is the most frequently observed tardive syndrome, has been reported to be 20–40% by a recent review [3].

More recently, the CATIE trial examined the efficacy, tolerability, and cost-effectiveness of the first- and second-generation antipsychotics and has provided some epidemiological data for extrapyramidal side effects, including TDk and/or TDt. The proportion of patients who met modified Schooler-Kane tardive dyskinesia criteria ranged from 8.3 to 9.6% with Second Generation Antipsychotics (SGAs) and 11.8% for perphenazine. There were no statistically significant differences between treatment groups on any TD indicator [18], but TDk was not discriminated from TDt by the researchers.

Study	Number of neuroleptic exposed patients	Tardive dystonia prevalence (%)
Yassa et al. [9]	351	2
Yassa et al. [10]	558	1.6
Friedman et al. [11]	331	1.5
Chiu et al. [12]	917	0.04
Sethi et al. [13]	125	21.6
Inada et al. [14]	716	2.1
Sachdev et al. [15]	100	1
Raja [16]	200	4

Table 1. Early studies examining the prevalence of tardive dystonia.

A difficult question to answer is the differential risk of getting TDt after the administration of first- (typical) and second-generation (atypical) neuroleptics, when studies are conducted on subjects who have lifetime histories of exposure to both. A recent Korean study has attempted to deal with this issue [19]. The authors retrospectively and cross-sectionally examined the incidence and prevalence of TDt, apart from TDk, in 80 non-elderly (mean age \pm SD: 33.1 \pm 8.2) psychotic patients receiving SGAs, who were never treated with typical neuroleptics. The median time of exposure to antipsychotics was 66.8 months, 73.0, 58.8, and 88.0 months for patients without TDt or TDk, patients with only TDk, both, and only TDt, respectively. The sample was exposed at the onset of dystonia or previously to risperidone, amisulpride, olanzapine, aripiprazole, clozapine, ziprasidone, and quetiapine, with the most frequently prescribed antipsychotic being risperidone (72.5% of the subjects). Other received agents were benzodiazepines, antidepressants, and mood stabilizers. TDt was determined by applying the Burke criteria, at two separate examinations, and was observed in 13 patients, 8 of whom also had TDk. Prevalence was calculated to be 14.1% (11 out of 78 patients, since 2 were referred to the center for TDt). Tardive oculogyric crises occurred in another six. When only moderately and severely affected patients were included, prevalence dropped at 5.1%, which is similar to the prevalence estimated earlier, in the context of typical neuroleptics exposure (mean 5.3%) [20]. TDt and TDk were significantly associated ($p = 0.021$). A history of acute dystonia significantly increased the risk for TDt ($p < 0.001$). Having comorbid obsessive compulsive symptoms was also significantly associated ($p = 0.024$), but when corrected for clozapine use, which could provoke obsessive compulsive symptoms and be used for the treatment of TDt, significance weakened ($p = 0.074$).

In a similar line, Lee et al. estimated the incidence and prevalence of tardive syndromes in a sample of psychotic patients ($n = 123$, mean age \pm SD: 45.6 \pm 13.8) exposed to antipsychotics for a period of at least 6 months, excluding those receiving a long list of other agents implicated in tardive syndrome occurrence, which is antidepressants, reserpine, tetrabenazine, methyl-dopa, lithium, calcium-channel blockers, anticholinergics, and others [21]. The prevalence of TDt was 12.2%, with TDk being 21.1% and overall tardive syndrome prevalence 28.5%. The prevalence of nonremitting TDt was 7.3% and tardive syndrome 15.5%. A longer duration of

symptoms and more severe extrapyramidal symptoms (EPS) predicted nonremission of tardive syndromes in general. Risk factors for the emergence of tardive syndromes were EPS and physical illness (stroke, diabetes mellitus, hepatitis, chronic pain, cancer, and other chronic illnesses, e.g., hypertension, hyperthyroidism, renal stone, gastric ulcer, hyperlipidemia, benign tumor such as ovarian tumor and uterine myoma, and heart disease), but odd ratios were not calculated specifically for TDt. No difference in risk was found comparing first-generation antipsychotics (FGAs) to SGAs.

Moreover, in another retrospective study, Lee et al. set out to calculate the prevalence of tardive movement disorders in patients receiving antidepressants [22]. Out of 158 subjects, exposed to antidepressants for at least 6 months, but not to other agents causing tardive syndromes, 14% had at least one tardive syndrome and 10.4% manifested TDt. Non-remitted TDt was 5.1%. Notably, TDk was found at a lower rate (3.2%). Other tardive syndromes were tardive tremor (1.3%), tardive parkinsonism (1.3%), tardive tics (1.3%), tardive sensory syndrome (1.3%), and tardive myoclonus (0.6%). Patients exhibiting tardive syndromes had received SSRIs (fluoxetine, paroxetine, and escitalopram), SNRIs (venlafaxine and duloxetine), TCAs (amitriptyline and trazodone), NaSSA (mirtazapine), and NDRI (bupropion). The use of SNRIs and previous marriage significantly increased the risk of tardive syndrome occurrence, but the authors again do not differentiate between syndromes. Apart from this study, there are only few case reports linking antidepressant use with TDt [22–24], and, therefore, solid conclusions must await further studies.

The Genetic Risk and Outcome of Psychosis (GROUP) study is a prospective, naturalistic study on a large, relatively young (age: 27 ± 7 years; illness duration: 4 ± 4 years) cohort during 3 years of antipsychotic treatment. Drug-related movement disorders (DRMDs) as well as a variety of clinical outcomes were studied. The aim of the authors was to study the incidence, prevalence, and persistence rates of DRMDs at an early stage of the psychotic illness (schizophrenia and other non-affective psychoses), without prior treatment confounding [25]. Eligible patients for inclusion in the prevalence, incidence, and persistence analyses were 828 at baseline (age: 27 ± 7 , illness duration, mean: 4 ± 4 years) and 447 at follow-up. The prevalence of the DRMDs other than parkinsonism and akathisia did not differ significantly between patients treated with FGAs and SGAs, neither between olanzapine and risperidone, the two most frequently prescribed SGAs. Prevalence at baseline, 3-year follow-up, and 3-year incidence of TDt were 1.5, 1.8, and 1.6%, respectively. The incidence of TDt was low, probably due to a modest cumulative antipsychotic exposure in this population and in line with some previous reports (0–0.7%).

The rising prevalence of TDt in later retrospective and cross-sectional studies, compared to earlier ones, might reflect better recognition, the use of standardized tools and criteria, and lower symptom severity thresholds for the diagnosis. Indeed, in a study by Lee et al., when prevalence is calculated based only on moderately and severely ill patients, the estimation diminishes to 5.3%, similar to older studies reporting 0.4–4% [21]. Commenting data on FGAs and SGAs, it seems that the initial expectations in the beginning of the atypical antipsychotics era of banishing TDt and other tardive syndromes once and for all are far from being fulfilled. Still, TDt due to SGAs, albeit of similar prevalence, is possibly milder and more likely to remit (50 vs. 33% for SGAs and FGAs, respectively) [21].

Summing up risk factors for TDt, mostly established ones are younger age, male sex [20], longer duration and higher doses of antipsychotic exposure, mood disorders, brain injury, mental retardation, dental procedures, diabetes mellitus, alcohol and substance abuse, and a previous acute dystonic reaction [3, 6, 8]. It has been reported that the presence of TDk increases the risk of TDt by 8.7 times [17]. Males tend to have a younger age at onset of TDt than females [5].

3. Offending drugs

Offending drug is considered to be an agent to which a patient is exposed currently or in the past and is believed to have contributed to the provocation of TDt. Many studies deal with offending drugs associated with tardive syndromes in general, or TDk, and information for TDt has to be extracted or is confused with information for other tardive syndromes. A list of drugs that have been associated with the emergence of TDt is provided in **Table 2**. The syndrome may appear while the patient is on the drug, or after the drug's reduction or discontinuation, without being any "safe" period of exposure [7]. It is presumed that any drug exerting direct or indirect anti-D2 properties can be incriminated. Regarding antipsychotics, the emergence of the syndrome seems to be extremely rare following clozapine or quetiapine exposure, probably due to their very low D2 affinity and fast dissociation from the dopamine receptor; in fact, they represent a therapeutic option [26, 27]. Numerous case reports are found in the study for several antipsychotic drugs [28–31]. A matter of serious concern is the administration of extended release preparations, for example, paliperidone palmitate [32, 33],

Antipsychotics

Typical

Atypical

Antidepressants

Buspirone

Antiepileptics

Lithium

Antiemetics

Calcium-channel blockers

Psychostimulants

Cocaine

Pseudoephedrine

Chemotherapeutic agents

Memantine

Table 2. Offending drugs implicated in TDt.

as in this case, the responsible drug cannot be easily removed or substituted. Classes of antidepressants (SSRIs, SNRIs, NASSA, NDRI, and TCAs) probably act by overstimulating of the basal ganglia serotonin 5-HT₂ receptors, leading to dopamine antagonism, while noradrenergic hyperactivity might also play a role [22, 24]. Antiemetic and prokinetic agents centrally blocking D₂ receptors on the chemoreceptor-trigger zone are also implicated, such as substituted benzamides (metoclopramide, clebopride, and cisapride) and prochlorperazine, which is a phenothiazine [34]. Calcium-channel blockers (nifedipine, cinnarizine, and flunarizine) may alter central dopamine production through N-type calcium channels and produce tardive dystonic reactions [35, 36]. On rare occasions, antiepileptics (e.g., carbamazepine [37] and lamotrigine [38]), lithium [39, 40], psychostimulants, by altering dopamine neurotransmission (e.g., cocaine and norpseudoephedrine [41–43]), chemotherapeutic agents, possibly through a delayed toxic effect on basal ganglia (e.g., 5-fluorouracil and doxorubicin [44]), buspirone [45], and memantine administered accidentally at a double than recommended daily dose [46] have been reported. Dopamine agonists can cause dystonia in the presence of parkinsonian pathology [39]. Anticholinergics have been found to worsen symptoms of TDk [47], but, on the contrary, they seem to improve TDt [6].

4. Diagnosis, clinical presentation, and course

The criteria of TDt have been set by Burke et al. and these are the following: (1) the presence of dystonia (sustained, involuntary, usually slow-twisting movements), (2) the onset of dystonia was during ongoing treatment or within 2 months of discontinuation of antipsychotic drug treatment, (3) in the presence of other tardive syndromes such as akathisia or dyskinesia, dystonia should be the main feature, (4) clinical and laboratory evaluation should be provided to exclude other causes of dystonia, and (5) negative family history of dystonia [2]. All five are required for a definite diagnosis [2, 48]. The authors had studied a sample of 42 patients with TDt, and the onset of the symptoms began after 3 days to 11 years of antipsychotic treatment [2]. Kang et al. have used the Burke criteria with minor revisions [49]. Tardive dystonia is classified in DSM-5 under the chapter “medication induced movement disorders and other adverse effects of medication” as a diagnostic entity separate from tardive dyskinesia [50]. This represents a progress from DSM-IV-TR, where it was classified under the collective term “movement disorder not otherwise specified.” It is most probable that such a departure will aid better recognition and also enhance research. In ICD-10, it is classified as “G24.0, drug-induced dystonia.”

TDt typically presents with sustained involuntary muscle contractions, which cause abnormal postures and twisting movements especially on the upper limbs, neck, trunk, or face [5]. It is classified according to the affected body parts as focal (one body part affected), segmental (two or more body parts which are contiguous), multifocal (two or more distant body parts affected), and generalized (affects the trunk and at least two other body parts) [6]. The involvement of cranial-cervical area is described in 87% of patients [7], which is the most common in TDt, and presents with retrocollis (dystonic cervical movement where the head is drawn back), anterocollis (the head is drawn forward), and torticollis (the head is turned to the side). Opisthotonus is also a frequent manifestation, with trunk involvement, most

evident during walking. The trunk is arched backwards, with the arms at adduction and extension and the wrists flexed [6]. Other cases manifest clinically with focal or segmental dystonia such as tardive oculogyric crises (involuntary ocular deviations), or involve the jaw (jaw deviation), oromandibular area (trismus), and blepharospasm [51]. Pisa syndrome refers to a tonic flexion of the trunk to one side of the body, leading to a slight lean, whereas Meige syndrome is described as oromandibular dystonia (involuntary and often forceful contraction of the muscles of the jaw and tongue) and blepharospasm (involuntary muscle spasms and contractions of the muscles around the eyes) [52].

Pain and strange somatic symptoms were described by few patients in the early stages of TDt [7]. The involuntary movements of TDt seem to get better or vanish during sleep and worsen under stress, leading to a fluctuating picture. They can be partially controlled by simple maneuvers such as a sensory trick response, where a gentle touch on the chin or neck or a forcible one with certain amount of pressure can alleviate dystonic movements [49, 53].

All forms of dystonia, which include lower limbs only, are more common in idiopathic dystonia and not in TDt [6]. None of patients with TDt had a lower limb involvement without face or neck involvement, too [2]. As already mentioned, TDt is frequently co-occurring with other tardive syndromes, such as TDk, Tardive akathisia (TDa), Tardive myoclonous (TDM), and Tardive tourettism (TDr) (**Table 3**). Patients with TDt are more aware of their movement disorders than patients with TDk [54].

The onset of TDt is insidious, mostly at first with focal dystonia (83%), affecting most frequently the face and neck; it may be heralded by increased eye-blinking or tick-like movements, and over time, it can evolve to segmental and generalized [7]. The course is progressive for months and then persists and remains static for years [2]. Unfortunately, remission rates are low, with a mean of 10%, in a mean follow-up period of 6.6 years [2, 5, 7, 49]. Tapering and withdrawal of the offending drug is important for remission and increases this possibility fourfold [7].

Studies	N	Number of patients with more than one tardive syndrome	Tardive syndromes
Sachdev et al. [54]	15	9	TDt, TDk
		6	TDt, TDa
Burke et al. [2]	42	16	TDt, TDk
Wojcik et al. [55]	32	27	TDt, TDk
		2	TDt, TDM
Kang et al. [48]	67	28	TDt, TDk
		21	TDt, TDa
Kiriakakis et al. [7]	107	32	TDt, TDk
		24	TDt, TDa
		1	TDt, TDr

Table 3. Clinical overlap of TDt and other tardive syndromes.

Prognosis of TDt is poor and disability in patient's everyday activities frequent. Movement disorders and their symptoms affect social life and emotional condition too. Deterioration in speech, vision, eating habits, sitting, gait, and sexual ability have been reported [9, 56, 57]. Oculogyric crises and blepharospasm, and cranial-cervical dystonia, can gravely inhibit daily living activities, such as driving and personal grooming, for example, shaving, combing, or dressing. Muscle contraction and activity may lead to abnormal positions of the body. Sometimes, fractures occur, resulting from the way of walking or standing. A potentially painful situation can be present [52, 56]. Even though rare, the involvement of laryngeal or respiratory muscles can occur in TDk [58] and TDt [59] and can be very distressing or even life-threatening.

Social avoidance, isolation, and stigmatization concerns are common in patients with TDt, as abnormal postures and contractions impose a strange appearance. Furthermore, work productivity, finding an employment, and coping with family roles become compromised. Quality of life accordingly deteriorates, to a greater extent in patients with generalized dystonia than in those with focal [60], and is associated with anxiety and depression [61].

5. Differential diagnosis

For the unfamiliar clinician, the diagnosis of TDt can be difficult. Clinical overlap with other tardive syndromes could possibly lead to a missed diagnosis, or a misdiagnosis. Strange postures can be considered as mannerisms in a psychotic patient, and deterioration with anxiety together with amelioration with relaxation or sleep can lead to a mistaken diagnosis of conversion disorder, other psychogenic condition, or hypocrisis.

Differential diagnosis begins with differentiation from other types of movement disorder or tardive syndromes, by deciding on the dystonic kind of the symptoms. Then, it must be distinguished from other primary and secondary dystonias (**Table 4**) [2, 3, 5, 39, 54, 62].

Acute dystonia

Idiopathic torsion dystonia

Focal dystonia

Secondary dystonias due to focal brain lesions

Brain injury, tumor, vascular damage, infectious, post-infectious, paraneoplastic

Secondary dystonias due to diffuse brain damage

Ischemic, hypoxic, metabolic, toxic

Dystonia-plus syndromes

Heredodegenerative dystonia (Wilson's disease, Huntington's disease, and others)

Table 4. Differential diagnosis of TDt.

Acute dystonia appears for 48–72 h after the use of neuroleptic drugs. After discontinuation or reduction of the responsible drug, it completely resolves within 48 h [2]. Acute dystonic reactions impressively respond to the administration of anticholinergics, such as biperiden 5 mg or procyclidine 5 mg, antihistamines like promethazine 50 mg [20], and benzodiazepines like clonazepam 0.5–4 mg.

Idiopathic torsion dystonia may be clinically indistinguishable from TDt. A leg involvement would be more suggestive of idiopathic dystonia. Cervical position such as head bent toward the shoulder (laterocollis) and torticollis may be seen more frequently in idiopathic dystonia, whereas retrocollis (hyperextension of head and neck backwards) is more usually encountered in TDt [51, 62]. In a recent work, Godeiro-Junior et al. [63] compared a series of 20 patients with neuroleptic-induced tardive cervical dystonia with a group of patients suffering from idiopathic cervical dystonia and found no differences that would be able to differentiate them on phenomenological grounds. The authors concluded that previous or current neuroleptic exposure remained the critical diagnostic clue, pointing to a diagnosis of TDt. Apart from this, the presence of another tardive syndrome, for example, dyskinesia or akathisia, also supports this diagnosis. Correct assessment is crucial, not only for management but also for legal reasons, in case of a lawsuit for antipsychotic adverse event [64].

6. Pathophysiology

The pathophysiology of TDt has not yet been elucidated and remains speculative to a large extent. It has been suggested that it may share some pathophysiologic mechanisms with idiopathic dystonia. Basal ganglia seem to represent a central key player in the etiology of primary and secondary dystonias, including TDt. Cerebellar abnormalities are probably also implicated, and it has been recently demonstrated that these two structures are directly interconnected, with disynaptic loops [65]. On a receptor and neurotransmitter level, the development of tardive syndromes is thought to correlate with dopamine receptor upregulation and hypersensitivity, following their chronic excessive blockade [66, 67]. D2 blockade together with D1 lower occupancy may lead to sensitization of D1 neurotransmission and a D1/D2 imbalance output, resulting in pathological movement [68]. The production of free radicals and oxidative stress, abnormalities of GABA input to striatal neurons and altered synaptic plasticity, altered serotonin receptor signaling, upregulation of D3 receptors and degeneration of striatal cholinergic neurons are also suggested as the possible contributing mechanisms, but most relevant work again does not discriminate between TDt and TDk [69, 70].

A possible insight to the neurobiological processes underlying the dystonic phenomenon may be provided by the different potential of typical and atypical antipsychotics to produce more severe dystonic symptoms, and in particular by the fact that switching to very low potency agents, such as clozapine and quetiapine, seems to ameliorate or even reverse dystonic movements [26]. The concept of atypicality has been introduced early and was initially defined as (1) a drug with antipsychotic efficacy at a dose that has a low risk of producing EPS, prolactin elevation, and tardive dystonia/dyskinesia, (2) a drug that has a greater affinity for the 5HT-2A receptor than for the D2 receptor, and (3) a drug that has a greater efficacy in treating positive,

negative, and cognitive symptoms of schizophrenia. Notably, among SGAs, considered to be atypical, only clozapine has demonstrated some superior efficacy in symptoms as in (3) [71]. It is supposed that 5HT-2A antagonism permits the release of dopamine in the nigrostriatal pathway, thus preventing the emergence of motor symptoms, whereas antipsychotic efficacy by D2 blocking in the mesolimbic pathway is preserved [72]. Another aspect of atypicality refers to the rapid dissociation hypothesis, where atypicality is attributed to the property of blocking D2 receptors long enough for antipsychotic efficacy and shortly enough for avoiding EPS. Clozapine and quetiapine uniquely dissociate from D2 receptor fastest. It takes less than 60 s to dissociate from 50% of D2-cloned receptors, a tremendously faster process than haloperidol, which does so in more than 25 min [73]. In this case, endogenous dopamine can bind in D2 receptors, between antipsychotic doses, and it is hypothesized that the system is thus allowed to exert the phasic nature of normal dopamine transmission, considered to be crucial for normal physiologic actions [74]. On the contrary, typical antipsychotics bind much longer on receptors, and the normal phasic dopamine neurotransmission is distorted to a much greater extent. It has been demonstrated by PET studies that haloperidol and typical antipsychotics produce an increased D2 receptor density in the striatum of humans and animals [75, 76]. Future research is hoped to elucidate and expand our knowledge on mechanism of TDt, with the aim of finding better treatments.

7. Pharmacogenomics of drug-induced dystonia

The term “pharmacogenetics” was first introduced by Friedrich Vogel, in 1959, and refers to the association between an individual’s genes and response to a drug or else, the individualizing of treatment [77, 78]. Later, in 1997, Marshall introduced the term “Pharmacogenomics” which, due to the advances of technology and whole genome-sequencing techniques, refers to the impact of multiple genes and specific genetic variations on drug response, including maximum efficacy, but also the minimization of adverse drug reactions. This developing field is expected to contribute to optimal drug choice, in terms of efficacy and safety [78].

To select an antipsychotic drug or dose, psychiatrists take into account many factors, such as the age of the patient, the gender, exercise attitudes, smoking status, liver and renal function, other comorbidities, and co-medications, [77, 79]. Further, different genetic profiles of patients and specifically genetic variations that are associated and affect the pharmacokinetic and pharmacodynamics properties of a drug will lead to different response, including efficacy and toxicity. These genetic variations may cause decreased plasma levels, which will result in a decreased efficacy, or increased plasma levels, which may lead to the appearance of an adverse drug reaction [77]. A variety of publications aim to associate genetic variations of genes involved in pharmacokinetics and pharmacodynamics and drug-induced TDt or TDk, without discriminating between the two. Research is mainly directed toward the genes that metabolize drugs or drug transporters and receptors [79, 80].

One of the most studied and well-defined genes is *CYP2D6*. One-fourth of all drugs are primarily or secondarily metabolized through *CYP2D6*, including many antipsychotics and antidepressants. *CYP2D6* in humans is found on chromosome 22q13.1, and until today, more

than 100 allelic variants have been identified. The phenotype, depending on the alleles, can be Ultra rapid Metabolizer (UM), Extensive Metabolizer (EM), Intermediate Metabolizer (IM), and Poor Metabolizer (PM) [77, 80]. Importantly, different ethnicities have different allelic distributions and therefore their drug metabolism differs [80].

Although researchers have focused on many genetic variations located on *CYP2D6* and their association with the development of TD, results are conflicting. There are studies that failed to indicate an association between TD and *CYP2D6*1*, *CYP2D6*2*, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6*, *CYP2D6*15a*, *CYP2D6*17* (Ohmori et al. [81]; Ohmori et al. [82]; Arthur et al. [83]; Armstrong et al. [84]; Brockmüller et al. [85]; Lohmann et al. [86]), but also studies that indicated an association or at least a trend of association between the studied alleles of *CYP2D6* and TD. A study in 1998, in 100 Japanese patients with schizophrenia, indicated a statistically significant association in allelic level between *CYP2D6*10* and TD, which remained significant even after adjustment for variables by regression analysis [82]. The same year, another group focused on 45 Caucasian schizophrenic patients of Austrian origin, and the potential association between *CYP2D6*3*, *CYP2D6*4*, and *CYP2D6*5* mutations and TD. There was a trend of correlation between *CYP2D6* genotype and TD development, and, in particular, heterozygotes for one mutation presented a higher risk of TD [87]. Similarly, patients with at least one mutation, *CYP2D6*1*, *CYP2D6*3* or *CYP2D6*4*, indicated a higher incidence of TD [88]. A trend of association between PM and TD severity was also detected in the study by Andreassen et al. who conducted an investigation of *CYP2D6*1*, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6*, and *CYP2D6*7* in 100 schizophrenic patients from South-East Scotland [89]. Two other studies, which also performed a gender analysis, indicated that female schizophrenic patients with TD had a higher frequency of *CYP2D6*10* allele than men [90] and that males with a non-functional or a partially functional allele of *CYP2D6*1* to *CYP2D6*1*, *CYP2D6*10B*, *CYP2D6*14*, *CYP2D6*18*, *CYP2D6*19*, *CYP2D6*25*, *CYP2D6*26*, *CYP2D6*31*, *CYP2D6*36*, and *CYP2D6*41* had a higher risk of TD than those of wild type [91]. A significant association was also found between increased metabolism of FGAs and TD [92]. Finally, in the study by Ellingrod et al., in a cohort of 37 Americans with schizophrenia, the larger part of smokers with *CYP2D6*1/*3*, **4* suffered from TD [93].

Researchers have also studied *CYP1A2* gene. Studies concerning TD and 734C/A [94–96] as well as 2964G/A [94] of *CYP1A2* in patients with schizophrenia fail to detect any association. However, C homozygotes were found to be associated with higher AIMS scores in two independent studies performed in 200 and 2015 [97, 98].

Regarding dopamine receptor genes, *DRD1*, *DRD2*, *DRD3*, and *DRD4* receptors have been investigated by a variety of laboratories.

In a study of 2011, in which *DRD1* and specifically *rs5326*, *rs4532*, and *rs265975* polymorphisms were investigated, only *rs4532* was found to be significant, with CC genotype being associated with TD [99].

As for *DRD2*, *rs1801028*, *rs1800497*, *rs1799732* (Hori et al. [100]; Kaiser et al. [101]; Koning et al. [102]; Park et al. [103]), *rs1801028* [101, 104], *rs1799978*, *rs1079597*, Val96Ala, Leu141Leu, Pro310Ser [101], *rs1800498* [102, 103], *rs6275* [103], and *rs6277* [102] did not present any statistically

significant association either in allelic or in genotypic level. However, concerning rs1800497 on *DRD2*, there is an older study which was performed in a group of patients with schizophrenia, indicating that this polymorphism may affect the development of TD differently [105].

Many scientific groups focused on rs6280, located on *DRD3* gene. The majority of the studies indicated no association between alleles and genotypes with TD development (Utsunomiya et al. [106]; Løvlie et al. [107]; Chong et al. [104]; Gaitonde et al. [108]; Rietschel et al. [109]; Garcia-Barceló et al. [110]; Basile et al. [111]; Koning et al. [102]; Segman et al. [112]). However, there are four studies which succeed in correlating TD with either the Gly-allele [113], the Gly homozygotes [114, 115], and the heterozygotes [116]. Still, a study that studied seven candidate genes, including *DRD3* and rs9817063, rs2134655, rs963468, rs324035, rs3773678, rs167771, rs11721264, rs167770, rs7633291, rs1800828 polymorphisms, as well as *DRD4* gene and specifically, rs3758653, failed to prove any association with antipsychotic-induced movement disorders [117].

Concerning serotonergic receptors, *HTR2A*, *HTR2C*, and *HTR6* genes have been investigated. *HTR2A* gene and especially rs6313, rs6311, and rs6314 were the subject of research in many groups. According to some studies, there was no association between TD development and rs6313, rs6311, and rs6314 [102, 111, 118]. Nevertheless, a study of 2011 regarding *rs6313* showed a relation between T allele and TD development [119], whereas a study of 2001 found higher frequencies of T homozygotes in patients without TD and also allelic differences between patients with and without TD [120]. Segman and his group indicated that patients with TD had higher frequencies of 102C (rs6313) and 1438G (rs6311) alleles and also that CC (rs6313) and GG (rs6311) were associated with higher AIMS scores [121].

Proceeding to *HTR2C*, ser-allele of polymorphism *rs6318*, located in this gene, was found to be more common in patients with TD [112], but also rs6318 indicated no statistical significance in two other studies [102, 119]. Further, rs3813929 indicated no association, and rs518147 was more frequent in patient with TD than those without [102, 122]. The study of Bakker studied rs569959, rs17326429, rs12858300, rs4911871, rs5946189, and rs1801412 polymorphisms of *HTR2C* and found no association between them and TD, either in genotype or in allele level [117]. *HTR6* and rs1805054 were studied in a group of 173 Japanese schizophrenia patients, and no association was observed with TD development [123].

Summing up, there are significant genetic associations between patients with schizophrenia that suffer from drug-induced TD, implicating that dopamine and serotonin systems, as well as CYP genes, participate in TD development. All included studies performed genotyping analysis with well-established and accurate laboratory techniques, like PCR-RFLP, sequencing, and TaqMan assay, whereas studied cohorts included patients of different ethnicities and races, including Caucasians, Chinese, and Japanese patients, diagnosed according to the diagnostic criteria of the Diagnostic Statistical Manual or the International Classification of Diseases. Assessment of TD was mainly performed using the Abnormal Involuntary Movement Scale (AIMS). In many studies, the study population was not large enough to achieve a statistically significant association. For this reason, studies in larger sample sizes need to be done in order to shed more light in the contribution of genetic background in patients who face drug-induced TD.

Furthermore, the majority of studies do not distinguish the terms “dystonia” and “dyskinesia.” Most of these studies concern dyskinesia, which also includes cases of dystonia, and it is difficult to separate them. Future research with better defined studies differentiating between the two conditions is necessary for the better definition of outcomes. Also, factors such as advanced age, gender, ethnicity, dose and drug duration, symptoms, smoking status, alcohol use, co-medication, comorbidities, and family history of psychiatric disorders or TD are risk factors associated with the development of TD [124] and should be taken into consideration when investigating the correlation between TD and genetic factors.

8. Treatment

The best pathway to care is prevention, and for a difficult to treat condition such as TDt, prevention is of paramount importance. Keeping this in mind, increased guardedness must distinguish clinical care for the selection of antipsychotic treatment. Rational use of antipsychotics, that is, using as indicated and not for doubtful reasons, caution to use in mood disorders, not using without a clear indication, not using for longer than needed, should guide clinical decisions. High dosages and polypharmacy should be avoided. Atypical antipsychotics should be preferred over typical ones, even though there is some debate concerning an increased risk for metabolic syndrome, with certain SGAs [125]. Therapeutic levels of lithium and antiepileptics should be monitored and kept within the recommended range; the use of an antiemetic that passes the blood-brain barrier at a lower extent, for example, domperidone instead of metoclopramide, would be wise [35].

When TDt has already been established, a first option would be to lower the dose or stop the offending agent, if the condition of the patient allows it, or substitute the responsible drug with another agent with better side-effect profile. Correct assessment of the patient must take into account the fluctuating course and diurnal variation of dystonia. In bipolar patients, it gets worse during depressive phases [16]. There are reports of SGAs, including clozapine (as monotherapy or administered with clonazepam), olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpiride, and perospirone, being effective as a treatment of TDt [52]. However, switching from FGAs to SGAs as a class has not been consistently proven to benefit [27]. Switching from the offending drug to quetiapine or clozapine seems to make more sense, as both drugs have very low affinity for D2 receptors and are not expected to induce dystonic reactions themselves, but only extremely rarely. Recent studies (one open label and one case series, for quetiapine and clozapine, respectively) [26, 126] have demonstrated efficacy, but evidence remains insufficient to make a strong recommendation. Choosing between the two favors quetiapine, because of the serious side effects associated with clozapine (e.g., agranulocytosis) [26].

If the above strategies are insufficient, or not possible, other options can be employed [16]. Several medications have been used to treat dystonia, and the therapeutic approaches include pharmacologic treatment and other types of interventions such as chemodenervation with botulinum toxin, surgery, deep-brain stimulation (DBS), physical, and supportive methods. There are lacking guidelines concerning the selection of dystonia treatment, so the clinical practitioner may choose between recommended therapeutic methods, often guided by personal experience and the patients' needs [127].

Botulinum toxin can be a therapeutic option, since it has been shown to be helpful in the treatment of several dystonic manifestations like blepharospasm [128], oromandibular dystonia [129], laryngeal dystonia [130], cervical dystonia [131], and writer's cramp and other limb dystonias [132].

Tetrabenazine, a dopamine-depleting agent, can also be an effective treatment for some patients with dystonia, with a starting dose of 25 mg daily, and titrated up to a target dose up to 100 mg daily. It seems that tetrabenazine is more effective in patients with TDt than those with idiopathic dystonia [133]. Adverse reactions include drowsiness, parkinsonism, depression, insomnia, agitation, anxiety, and akathisia [134]. More recent studies have examined deutetabenazine and valbenazine, which, like tetrabenazine, are also selective vesicular monoamine transporter 2 (VMAT2) inhibitors, but better tolerated than tetrabenazine. The two substances have been very recently approved for the treatment of TDK (which is considered to include TDt) by the US Food and Drug Administration [27].

Acetylcholine-related drug use is one of the most common treatment strategies in dystonia, and they are frequently prescribed for dystonic reactions (including drug-induced dystonia). Anticholinergics such as trihexyphenidyl, starting from low doses such as 2 mg daily and a final dose ranging from 6 to 40 mg daily [134], benztropine, biperiden, procyclidine, orphenadrine, and ethopropazine [135], have been broadly used in many types of dystonia, and the effectiveness seems to be quite satisfying. However, there are limitations for their use, regarding less tolerability of anticholinergic use in older adults and because high doses are demanded [136]. Their typical side effects include cognitive dysfunction, memory impairment, depression, confusion, dry mouth, constipation, urinary retention, blurred vision, and deterioration of narrow-angled glaucoma.

Baclofen has been reported to be effective in patients with TDt [137], especially in patients with blepharospasm, compared to other types of dystonic reactions. Drowsiness, dizziness, nausea, and fatigue are considered to be the drug's main adverse reactions [138].

Benzodiazepines such as alprazolam, clonazepam, chlordiazepoxide, and diazepam have been used in the treatment of dystonia, according to multiple small or retrospective studies [134]. They act as GABA receptor agonists, as they enhance GABA receptor function and GABA neurotransmission. Most common side effects include sedation, cognitive impairment, abuse, tolerance, depression, ataxia, and motor disturbances. Vitamin E has also been proposed as a potential treatment in TDt, and dystonic symptoms improvement has been reported after its administration [139].

Deep-brain stimulation (DBS) has been proposed as a safe and promising treatment for patients suffering from disabling and refractory tardive dystonia, resulting in rapid and long-term improvement in those patients [140].

9. Conclusions

Tardive dystonia is a motor tardive adverse event, resulting from exposure to anti-D2 agents, mostly antipsychotics. It is frequently debilitating and treatment resistant, and although

progress has been made regarding clinical diagnosis and recognition, the neurobiological basis of the condition remains elusive and offered treatment far from satisfactory. Pioneering work must be guided toward a better understanding of normal movement control and pathophysiological processes of abnormal and dystonic movements. Pharmacogenomic studies will be further contributing to identify genetic variations associated with the appearance of drug-induced TDt in the future and are expected to lead to more individualized selection of treatment for each patient, aiming to provide a better outcome. In total, several lines of research are ultimately hoped to usher in better care for people in need of antipsychotic treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

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