Tardive syndrome: An update and mini-review from the perspective of phenomenology

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Abstract: Tardive syndrome (TS) is a group of movement disorders caused by the long-term use of dopamine receptor blocking agents. The phenotypic presentation of TS is diverse, ranging from the most well-characterized symptom of tardive dyskinesia to other symptoms, including dystonia, akathisia, myoclonus, parkinsonism, tremor, and tics. These tardive symptoms are distinct not only in their phenomenology but also in their clinical outcomes. However, our knowledge of the pathophysiology and management of TS is almost exclusively based on tardive dyskinesia. First-generation antipsychotics have a higher risk of inducing TS and have largely been replaced by second-generation antipsychotics with a lower risk of TS. However, patients with off-label use of second-generation antipsychotics are still at risk of developing TS. Thus, the management of TS remains a challenging and important issue for physicians. In this review, we update the information on the epidemiology, phenomenology, and treatment of TS from the perspective of the specific form of TS.

Keywords: Antipsychotic; Dopamine receptor blocking agents; Tardive dyskinesia; Tardive syndrome

1. INTRODUCTION

Tardive syndrome (TS) is a constellation of late-onset and usually persistent involuntary movements caused by long-term dopamine receptor blocking agent (DRBA) exposure. The name "tardive" comes from the Latin word "*Tardus*", implicating the late-onset feature of the disorder. The phenomenologies seen in TS include dyskinesia, stereotypy, dystonia, akathisia, myoclonus, tremor, tics, and pain (Table 1).[1–3] Among these, tardive dyskinesia (TD), characterized by stereotyped, involuntary movements of the face, mouth, and tongue (oral-buccal-lingual dyskinesia), with possible involvement of the extremities, was the first identified and the most common presentation of TS.[4] To date, most of the studies on TS have focused on TD, with only a few reports related to other phenomenologies. Therefore, in this review, we aim to summarize and update the pathophysiology, clinical presentations, and management of TS based on different phenomenologies.

2. PATHOPHYSIOLOGY

The most popular theory is dopamine receptor hypersensitivity. The pathophysiology of TD is proposed to result from chronic blockade of dopamine receptors (particularly D2 and possibly D3 receptors), which induces upregulation of D2 receptors and causes postsynaptic dopamine receptor hypersensitivity (Fig. 1).[5,6] D2 receptors are inhibitory receptors expressed on striatal medium spiny neurons that inhibit the inhibitory indirect pathway, so their hypersensitivity produces hyperkinetic movements.[5] In addition to dopamine receptors, rodent studies have shown that serotonin receptors (5-HT2 receptors, in particular), which are widely distributed in the striatum, interact with dopaminergic neurotransmission, and their blockade reduces D2 receptor upregulation.[6,7] Additionally, the *5-HT2* gene has been shown to be associated with susceptibility to TD in schizophrenic patients.[8] This has been proposed to be the mechanism by which second-generation antipsychotics, with a lower D2 receptor affinity but higher 5-HT2 receptor affinity, have a lower risk of inducing TD than first-generation antipsychotics. However, D2 receptor hypersensitivity and upregulation cannot explain the persistence of symptoms, potentially lasting years, after discontinuation of DRBA because theoretically, in the absence of continuous blockade, dopamine receptors would be downregulated.

Striatal parvalbumin-containing, fast-spiking GABAergic interneurons synapse on medium-spiny neurons and regulate the balance between the direct and indirect pathways.[5,6] It has been proposed that chronic neuroleptic administration impairs the antioxidant system and increases dopamine turnover, which induces free radical formation and leads to neuronal damage and subsequent degeneration of GABAergic interneurons, leading to an imbalance between the direct and indirect pathways.[6,9,10] However, the phenomological diversity of TS and the exact pathomechanism by which antipsychotics produce dystonia in some patients and dyskinesia in others remain elusive.

3. TARDIVE SYNDROME

3.1. Prevalence and risk factors

A recent meta-analysis included 41 studies from 2000 to 2015, and the global mean prevalence of TD in patients taking typical and/or atypical antipsychotics was 25.3% (Table 2).[11] The rate

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Table 1

Phenomenonology of tardive syndrome

Phenomenology	Presentation
Dyskinesia	This classically manifests as oro-buccal-lingual dyskinesia, which involves stereotyped, involuntary movements of the tongue (protrusion or twisting), lips (smacking or puckering), and jaw (chewing). Involvement of the extremities, trunk or respiratory muscles is possible. Limb movements usually occur in distal segments as piano-playing movements or foot tapping. Truncal movements are rocking back and forth. When respiratory muscles are affected, it creates loud breathing, hyperventilation, or distorted speech. TD can be suppressed by voluntary action.
Dystonia	This tends to emerge focally and develops into a segmental or generalized form over time. It usually co-occurs with TD. The face and neck are the most commonly involved site, followed by the arms, trunk, and then legs. Cranial dystonia is typically blepharospasm. Cervical dystonia is primarily retrocollis. Truncal dystonia is commonly opisthotonic posturing. The appearance of dystonia is indistinguishable from idiopathic dystonia.
Akathisia	This is characterized by a feeling of inner restlessness and inability to remain still. The manifestations are typically body rocking and lower body involvement, including rocking from leg to leg, marching in place, or crossing and uncrossing legs.
Myoclonus	This is typically postural and predominantly involves the arms and hands.
Tremor	This can be kinetic, postural, or resting. It usually has a high amplitude, a frequency of 3-5 Hz, and most importantly, no parkinsonian signs.
Tics	These are indistinguishable from Tourette's syndrome by phenomenology.
Pain	This is chronic pain in the mouth and tongue or genital regions.

TD = tardive dyskinesia.

is highest with current typical antipsychotic treatment (30%), followed by current atypical antipsychotic treatment (20.7%), and lowest in patients never exposed to typical antipsychotics (7.7%).[11] In a prospective cohort study that followed 362 chronic psychiatric, TD-free outpatients for 5 years, the predicted risk of developing TD with typical neuroleptics increases with duration of exposure, from 32% for 5 years, 57% for 15 years, and 68% after 25 years.[12] According to the most recent meta-analysis, the annual incidence of TS is 3% in adults taking atypical antipsychotics and 7.7% in those taking typical antipsychotics.[13]

The nonmodifiable risk factors for TD include older age, female sex, white or African descent, genetic variants involving antipsychotic metabolism and dopamine function, longer disease duration, and preexisting mood disorders.[14,15] Older age has been consistently identified as a risk factor for TD, with a 2- to 5-fold increase in incidence in elderly adults compared with younger adults.[14] Females had a higher risk for TD (prevalence: female:male, 26.6% vs 21.6%), and their symptoms tended to be more severe.[16] In terms of ethnicity, the risk for TD was lowest in Asians and highest in African Americans.[17] Individuals with polymorphisms in *CYP2D6* (antipsychotic clearance), *COMT* (dopamine metabolism), *VMAT2* (dopamine packaging), and *DRD2* (dopamine receptor functioning) have a greater susceptibility to TD.[14] The higher risk of TD in patients with longer disease duration may be a combined effect of exposure to first-generation antipsychotics, cumulative antipsychotic dose or older age.[14] The relationship between pre-existing mood disorders and TD comes from an older literature when patients were usually treated with first-generation antipsychotics.[18]

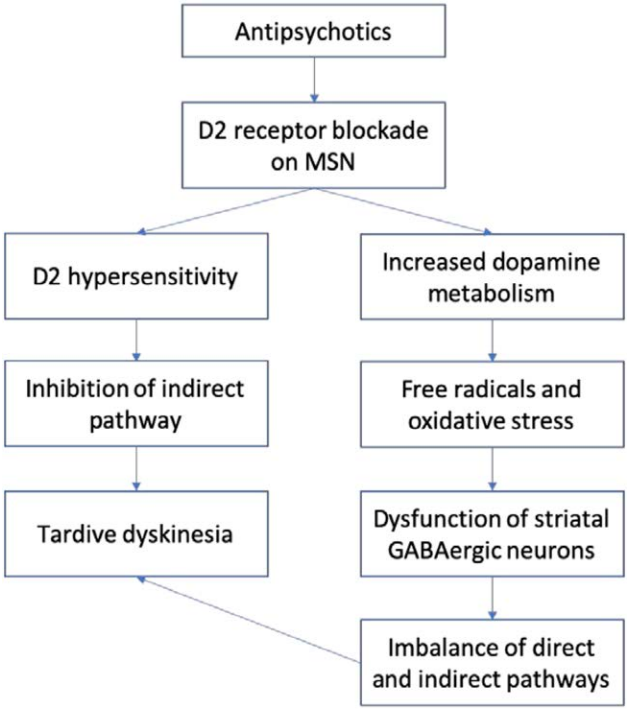

Fig. 1 Pathomechanism of tardive dyskinesia. MSN = median spiny neuron.

The modifiable risk factors for TD include first-generation antipsychotics, duration and dose of DRBA exposure, acute motor syndrome, and alcohol abuse.[19] It has been consistently shown that the annual incidence of TD is significantly lower in patients taking second-generation antipsychotics (0.8%-3%) than in those taking first-generation antipsychotics (5.4%-7.7%).[13] Longer duration of treatment and higher doses of antipsychotics have been associated with a higher risk of TD.[19] If patients have acute extrapyramidal symptoms, including parkinsonism, dystonia, akathisia, and subtle dyskinetic movements, after taking antipsychotics, they are expected to have a higher chance of developing TD.[20,21] Alcohol and substance abuse have been associated with an increased risk for TD in schizophrenic patients taking antipsychotics.[22,23]

3.2. Clinical course and phenomenology

TD is characterized by oral-buccal-lingual dyskinesia (OBLD) (Table 1). OBLD was previously classified as tardive stereotypy.[1] However, this movement lacks distractibility, which is a core feature of stereotypy. The current consensus defined tardive stereotypy as a seemingly purposeful movement pattern that is repetitive, coordinated, and distractible.[1,6] Its usual presentation is rocking, crossing legs, and rubbing hands when not feeling restless.[24]

The onset of TD typically develops after 1-2 years of DRBA exposure, but the exposure duration can be as short as 3 months.[6,25] The onset is insidious and plateaus over days to weeks. However, waxing and waning of symptom severity during the disease course is not uncommon.[3,6] In the majority of patients, TD usually persists for years or decades, even after removal of the offending drug.[6] Complete or partial remission can occur in some patients after several years with or without discontinuation of the offending drug. The reported annual spontaneous remission rate (without discontinuation of DRBAs)

Table 2

Prevalence of tardive syndrome

Phenomenology	Year	Patient number	Prevalence	Reference
Dyskinesia	2000-2015	5103	Current second-generation antipsychotics: 20.7%	11
	2000-2015	5062	Current first-genration antipsychotics: 30.0%	11
	2000-2015	346	First-generation antipsychotic naïve: 7.2%	11
	2000-2015	11 493	Pooled prevalence: 25.3%	11
Dystonia	1989	917	Psychiatric inpatients: 0.4%	66
		200	Psychiatric inpatients: 4.0%	67
		125	Particularly high prevalence using a more inclusive criteria: 21%	68
Akathisia		842	Psychiatric inpatients: 3.2%	69
		123	Elderly patients: 32.5%	70
Myoclonus		100	Patients with tardive syndrome: 1.0%	71
		60	Psychiatric inpatients: 38%	61
Tremor		123	Psychiatric outpatients: 2.4%	63
		100	Patients with tardive syndrome: 30%	71
Tics			41 cases reported in 38 case reports	62
Pain			11 cases reported in a case series	64

was 2.5%.[26,27] However, continued use of antipsychotics may suppress dyskinesia and hinder determination of the accuracy of the spontaneous remission rate. Ethnicity seems to play a role in determining prognosis. African Americans are less likely to improve than European Americans.[28] Older age and nonorofacial TD are predictors for chronic persistent TD.[29]

3.3. Treatment

Before initiating pharmacological treatments for TD, there are generally two approaches to reduce TD: withdrawal of the offending antipsychotics or switching from a first-generation antipsychotic to a second-generation antipsychotic with lower D2 receptor affinity. Withdrawal is usually not clinically feasible for patients with schizophrenia because of high rates of symptom worsening or relapse.[30] The switching approach, according to the American Academy of Neurology guideline in 2013, is not recommended because the alleviating effect supported by a number of open-label trials is contradicted by the negative finding in a single-blind crossover study.[31] However, a recent meta-analysis showed beneficial effects in reducing TD severity by switching from typical antipsychotics to clozapine.[32] Therefore, switching can be considered in clinical settings when medication withdrawal is not possible (Table 3).[33,34] Clozapine is the first second-generation antipsychotic and has been extensively studied. Its therapeutic effects in reducing TD are primarily based on the lowest D2 receptor affinity among antipsychotics, with additional potential mechanisms involving antiserotonergic ($5HT_{2A}$ and $5HT_{1C}$) and anticholinergic effects and less activity at nigrostriatal dopaminergic neurons.[35,36] Quetiapine, with high affinity for 5-HT_{2A} and lower affinity for D2 receptors, is a reasonable alternative.[33,36] Improvement of TD by switching to risperidone or olanzapine for several weeks has been observed in some trials.[31] However, there are concerns with their use beyond 48 weeks because both risperidone and olanzapine have been known to show dose-dependent increases in the risk of developing extrapyramidal side effects.[31,36]

Among the pharmacological agents, selective vesicular monoamine transporter 2 (VMAT2) inhibitors are the most effective and the only FDA approved medication to treat TD (Table 3). Tetrabenazine was the first VMAT2 inhibitor and was approved for treating Huntington chorea.[37] The beneficial effects of tetrabenazine on TD has consistently been found in several randomized controlled trials (RCTs), and the improvement can be a greater than 50% reduction in severity that is achieved in at least 50% of patients.[38,39] However, the most common side effects are drowsiness and parkinsonism.[33] In 2017, the FDA approved two newer VMAT2 inhibitors, valbenazine and deutetrabenazine, for treating TD. Two RCTs demonstrated dose-dependent reductions in dyskinesia severity in patients taking valbenazine evidenced by a much or very much improved global impression of change in approximately 60% of patients and a mean reduction in Abnormal Involuntary Movement Scale (AIMS) scores of 2.6 points.[40,41] The long half-life of valbenazine allows once daily dosing and better tolerability; only approximately 10% of participants had mild adverse effects, which included fatigue, akathisia, or dry mouth.[40,41] There were also two randomized RCTs evaluating the treatment effect of deutetrabenazine that revealed a significant treatment difference of 1.4 to 1.9 points in the AIMS score,[42,43] with a slightly higher rate of headache as the most common side effect.[43] Thus, valbenazine and deutetrabenazine are recommended as the first-line treatment for TD.[33,44]

Clonazepam should be used with caution because of its side effects of sedation and dependence (Table 3),[33] and patients with dystonic symptoms may benefit more.[38] Vitamin B6 and pyridoxal-5´-phosphate (active form of vitamin B6) are recommended only for short-term use because long-term treatment may cause sensory neuropathy (Table 3).[33] The improvement by amantadine was significant but small (approximately 15%),[31] and amatadine can be considered if more established agents fail or are contraindicated (Table 3).[33,38] If all pharmacological treatments fail, deep brain stimulation may be the last resort (Table 3). The target in most cases is the bilateral posteroventral globus pallidus internus and, in some cases, the subthalamic nucleus. The beneficial effect of pallidal deep brain stimulation has been supported by a number of case reports/series and two randomized trials, with mean improvements in AIMS scores of 38% to 63%.[33,45,46]

4. TARDIVE DYSTONIA

4.1. Prevalence and risk factors

The reported prevalence of tardive dystonia is variable, probably due to different assessment methods. The prevalence generally falls between 0.4% and 5% but can be as high as 21% if the criteria used are more inclusive (Table 2).[47] Compared with TD, tardive dystonia has been associated with a younger age of onset with a slight male predominance.[48] The onset age tends to be younger in male patients than female patients.[49]

Table 3

Treatment for tardive syndrome

Phenomenology	Treatment (maximum daily dose)	Mechanism of action	Comments
All	Switching from first-generation antipsychotics to clozapine[33]	Low D2 receptor affinity	Several RCTs, all done in TD, showed significant reduction in TD scores, particularly in moderate to severe TD; the strategy can be applied to other tardive movement disorders
Dyskinesia	Tetrabenazine (150 mg)[33, 44]	VMAT2 inhibition	FDA approval for Huntington disease, off-label use for TD; risk of parkinsonism
	Valbenazine (80 mg)[33, 44]		The only two FDA approved drugs for TD with a much lower risk of inducing parkinsonism but much higher cost
	Deutetrabenazine (48 mg)[33, 44]		
	Clonazepam (4.5 mg)[44, 72]	GABAergic ($GABA_A$ receptor)	One RCT showed a 37% improvement in TD scores; risk of dependence; greater benefit on dystonic symptoms
	Vitamin B6, pyridoxine (1200 mg)[44, 72]	Antioxidant	Two RCTs showed significant improvements in TD scores; risk of sensory neuropathy with long-term use
	Ginkgo biloba (240 mg)[44, 72]		One RCT showed 51.3% of patients achieving ≥30% reduction in TD scores
	Vitamin E (1600 IU)[31, 33]		Several RCTs with conflicting findings (no improvement or 24%-47% improvement on TD scores); may protect against deterioration of TD
	Levetiracetam (3000 mg)[31, 72]	SV2A inhibition (inhibition of synaptic vesicle release)	One RCT and several open-label trials showed up to 43.5% improvement in TD scores, but high dropout rate because of psychiatric deterioration
	Amantadine (400 mg)[33, 44]	Weak NMDA receptor inhibition	Several RCTs showed 15-21.8% improvement in TD scores; risk of hallucination
	Deep brain stimulation[45,46]	Stimulation of globus pallidus interna	One uncontrolled trial and one RCT showed 38%-60% improvement in TD scores; after failure of medical treatment with stable psychiatric condition
Dystonia	Botulinum toxin[52]	Decrease release of acetylcholine	One uncontrolled trial showed marked or moderate improvement in 85% of patients; for focal dystonia
	Trihexyphenidyl (30 mg)[49]	Acetylcholine receptor inhibition	Retrospective studies showed some improvement in 44% of patients; can worsen TD
	Clonazepam (6 mg)[49]	GABAergic ($GABA_A$ receptor)	Retrospective studies showed mild improvement in 53% of patients; risk of dependence
	Baclofen (40 mg)[53, 73]	Activation of $GABA_B$ receptor	Retrospective studies showed mild improvement in 56% of patients; can be given intrathecally for severe cases
	Tetrabenazine (200 mg)[49]	Vesicular monoamine transporter 2 inhibition	Retrospective studies showed some improvement in 53% of patients; risk of parkinsonism
	Deep brain stimulation[45,46]	Stimulation of globus pallidus interna	One uncontrolled trial and one RCT showed 41.5%-71% improvements in dystonia scores; after failure of medical treatment with stable psychiatric condition
Akathisia	Propranolol (80 mg)[56, 57]	β-1-adrenergic receptor inhibition	Case reports showed contradictory effects; other medication tried in case reports with contradictory effects: anticholinergics, clonazepam, lorazepam
	Tetrabenazine (175 mg)[56]	VMAT2 inhibition	Case reports showed marked improvement in 50% of patients; risk of parkinsonism
Myoclonus	Clonazepam (3 mg)[61]	GABAergic ($GABA_A$ receptor)	One retrospective study showed reduced frequency and amplitude of myoclonus in all patients; risk of dependence
Tremor	Tetrabenazine (125 mg)[65]	VMAT2 inhibition	Case reports showed improvement in all patients; risk of parkinsonism
Tics	Clonazepam (3 mg)[62]	GABAergic ($GABA_A$ receptor)	Case reports showed some improvements in two patients; risk of dependence
	Clonidine (0.8 mg)[62]	Activation of α2-adrenergic receptor	Case reports showed some improvements in two patients
	Discontinuation of offending drugs[62]		Case reports showed full recovery in 7 out of 9 cases
Pain	Tetrabenazine (75 mg)[64]	VMAT2 inhibition	Case reports showed marked improvements in 7 out of 9 cases; risk of parkinsonism

FDA = Food and Drug Administration; RCT = randomized controlled trial; TD = tardive dyskinesia; VMAT2 = vesicular monoamine transporter 2.

4.2. Clinical course and phenomenology

Tardive dystonia often begins after a shorter period of exposure to antipsychotics than does TD, with a mean duration of exposure from 3.3 to 6.6 years vs 5.4 to 15.4 years for TD.[47] It tends to begin with focal dystonia and may evolve to a segmental or even generalized form over time (Table 1). The most frequently involved muscles are cervical and cranial muscles (approximately two-thirds of patients).[47] When blepharospasm and oromandibular dystonia coexist, it can be termed tardive Meige syndrome.[50] In a long-term follow-up study (Table 2), it was observed that patients with tardive dystonia more frequently had retrocollis and antecollis and less torticollis.[49] Tardive dystonia and TD often coexist (84% in one series).[47] In comparison to TD, tardive dystonia has a more unfavorable prognosis: the remission rate ranges from 7.5% to 14% after 3.1-8.5 years.[49] The removal of all offending drugs permanently or only for a certain period of time increases the chance of remission. The duration of antipsychotic exposure is also important. Patients with less than 10 years of exposure are five times more likely to remit than those exposed for more than 10 years.[49,51]

4.3. Treatment

Local injection of botulinum toxin can be the first treatment of choice for focal dystonias, particularly blepharospasm and torticollis (Table 3).[52,53] Anticholinergics and dopamine depletors (reserpine or tetrabenazine) are other options (Table 3).[53,54] If pharmacological therapies fail, deep brain stimulation targeting the globus pallidus internus should be considered (Table 3). The beneficial effect of pallidal deep brain stimulation has been supported by a number of case reports/series and two randomized trials, revealing a range of improvements from 41.5% to 71%.[33,45,46]

5. TARDIVE AKATHISIA

5.1. Prevalence and risk factors

The reported prevalence for tardive akathisia is from 20% to 30% (Table 2).[55] However, tardive akathisia may be overlooked if limb movements are present in TD.[55] Compared with TD, patients with tardive akathisia are slightly younger.[55] Among older patients with tardive akathisia, females are more prevalent than males (1.9:1).[56]

5.2. Clinical course and phenomenology

Akathisia is a subjective feeling of restlessness, accompanied by motor presentations of an inability to stay still. Tardive akathisia primarily involves the lower body (Table 1).[1] According to an early report with 45 patients, almost all patients with tardive akathisia concurrently had typical TD (99%), and many had tardive dystonia (35%).[56] Patients with the coexistence of tardive akathisia and tardive dystonia had the earliest onset. Tardive akathisia most frequently affects the legs, followed by the trunk and then the arms.[56] Patients with well-controlled or remitted akathisia were exposed to DRBAs at a younger age and had their DRBAs discontinued at a younger age than those with persistent akathisia.[56]

5.3. Treatment

For tardive akathisia, withdrawal of offending antipsychotics can be tried, or they can be replaced by clozapine.[57,58] Propranolol, lorazepam, and anticholinergics have been effective based on case reports (Table 3).[56,57] Tetrabenazine was reported to be effective in 58% of 12 patients in a therapeutic trial (Table 3).[56]

6. OTHER TARDIVE MOVEMENT DISORDERS

6.1. Prevalence and risk factors

Epidemiological data on tardive myoclonus are limited, and isolated tardive myoclonus is rare.[59,60] A study found that 38% of patients with long-term antipsychotic exposure had postural myoclonus, although the majority also had other concomitant involuntary movements (Table 2).[61] Tardive tremor, tics and pain are rare.[25,62] The prevalence of tardive tremor was reported to be 2.4% in patients receiving antipsychotics (Table 2).[63] To date, only 41 cases of tardive Tourette-like syndrome have been reported.[62] Similarly, only one case series reported 11 patients with TD or tardive akathisia with oral or genital pain.[64]

A survey found that myoclonic patients were exposed to higher daily and cumulative doses of antipsychotics than nonmyoclonic patients.[61] According to a case series, 10 out of the 11 patients reported to have tardive pain were female.[64] There are no known risk factors for the development of tardive tremor and tics.

6.2. Clinical course and phenomenology

Tardive myoclonus is primarily postural and affects the arms and shoulders more frequently than other body parts.[1,61] Head and neck involvement was described in a single case report.[60] In general, the movements are not severe, and most patients are unaware of the movements.[16] Tardive tremor is either postural or resting, with a frequency of 3 to 5 Hz and high amplitude. It usually emerges after prolonged exposure to DRBAs and persists for an average of 6 years after their discontinuation.[65] Tremor can be a frequent manifestation of antipsychotic-induced parkinsonism, but tardive tremor differs by its persistence after discontinuation of the offending drugs and unresponsiveness to parkinsonian or essential tremor therapies.[25]

The main difference between tardive tics and Tourette's syndrome is the age of onset. Tourette's syndrome typically begins before the age of 15 years, whereas tardive tics begin at an older age.[1] For most patients, symptoms develop after months to years (up to 24 years) of DRBA exposure; in some patients, tics emerge within 2 weeks to 1 year after discontinuation of DRBA.[62] In a review involving 38 case reports and 41 patients, approximately 25% of the patients also had TD.[62] The prognosis is generally good: 17 out of 41 patients had full remission, and 11 had partial remission.[62]

Tardive pain is typically a burning or lacerating sensation in the mouth or pelvis.[64] The pain typically develops after 1-6 years of DRBA exposure.[64] Tests for pain, including gynecologic evaluations, dental examinations, and imaging studies, fail to find an organic lesion. Tardive pain is always accompanied by tardive movement symptoms (dyskinesia, dystonia, or akathisia), so the diagnosis should not be made in the absence of a tardive movement disorder.[24]

6.3. Treatment

Benzodiazepines may be beneficial (clonazepam) for tardive myoclonus (Table 3).[1] Tardive tremor usually has a poor response to conventional antitremor therapy and may benefit from tetrabenazine (Table 3).[65] According to case reports, tardive tics can be improved in most cases by switching to second-generation antipsychotics (such as aripiprazole, clozapine, quetiapine, risperidone, or amisulpride), discontinuation of the offending drugs or treatment with clonazepam or clonidine (Table 3).[62] Finally, in a case series of patients with tardive pain, seven out of nine patients had marked improvement or even resolution of pain after treatment with reserpine and/or tetrabenazine (Table 3).[64]

In conclusion, TS leads to reduced quality of life and even disability but is inevitable for some patients who require long-term use of antipsychotics. Over the past decade, the most important advancement in treatment has been the development of valbenazine and deutetrabenazine, which provide favorable outcomes but fewer side effects than conventional tetrabenazine. On the contrary, the belief that second-generation antipsychotics may possess a lower risk of developing TS, which has not been consistently demonstrated, may promote their off-label use and can lead to an increased prevalence of TS. The best treatment for TS continues to be the prevention of its occurrence.

In conclusion, TS is diverse not only in its phenomenology but also in its clinical outcomes. The pathophysiology of the syndrome is still unclear and warrants further research. Future studies including patients with well-classified phenomenology may provide additional insights into the understanding of the disorder as well as treatment.

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