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The nosology of tardive syndromes☆

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ABSTRACT

Since the original description of side effects of neuroleptics, different terminologies and definitions for tardive dyskinesia (TD) and tardive syndrome (TS) have been used by different authors, and often these two terms have been used interchangeably. This paper proposes a nosology designed to define and clarify various terms and phenomenologies within the TS spectrum.

We propose to use the term tardive dyskinesia to refer to the original description of repetitive and complex oral-buccal-lingual (OBL) movements, as well as to the analogous repetitive movements that can appear in the limbs, trunk, or pelvis. The repetitive, relatively rhythmic nature of the movements is the common denominator of this phenomenologic category.

The term tardive syndrome refers to the spectrum of all persistent hyperkinetic, hypokinetic and sensory phenomenologies resulting from chronic dopamine receptor blocking agents (DRBA) exposure. Thus, TS is an umbrella term.

When dystonia is the main feature of TS it is considered to be tardive dystonia (TDyst). Retrocollis appears to be the predominant form of cervical dystonia in this condition. Cranial dystonias, particularly oromandibular dystonia, are also common forms of TDyst. Tardive akathisia refers to the inability to remain still with an urge to move, giving the appearance of restlessness. It is a sensory phenomenon and a common and disabling form of TS. Unlike acute akathisia, tardive akathisia tends to occur late and persists after the drug is withdrawn. In tardive tourettism, the patient exhibits the features of Tourette syndrome with complex motor and phonic tics associated with premonitory urge and relief of tension after performing the tic behavior. Tardive tremor differs from the resting tremor seen in drug-induced parkinsonism in that it is mainly a postural and kinetic greater than resting tremor. Tardive pain has been reported in association with chronic use of DRBA's. The pain involved the mouth, tongue and the genital region. The patients tended to obsess over the pain and usually had some other form of motor tardive syndrome, either tardive dyskinesia, tardive akathisia or tardive dystonia. The term tardive parkinsonism has been proposed for those drug induced parkinsonism patients who have persistent symptoms following discontinuation of the DRBA. However, there is a strong possibility that the DRBA may have simply unmasked subclinical parkinsonism or that there is coincident Parkinson disease developing during the period the patient is taking the DRBA.

1. Introduction

Different terminologies and definitions for *tardive dyskinesia* (TD) and *tardive syndrome* (TS) have been used by different authors, and often these two terms have been used interchangeably. Unless an author defines these terms in her/his writing, the reader is left uncertain which specific abnormal movement phenomenology the author is referring to. To avoid this ambiguity we propose a nosology designed to define and clarify various terms and phenomenologies within the TS spectrum.

The reason for the ambiguity and confusion is largely attributable to the history of awareness by the medical community of TS and other

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movement and sensory disorders caused by exposure to dopamine receptor blocking agents (DRBAs), also known as neuroleptics, used chiefly to treat psychosis (antipsychotic drugs) or various gastrointestinal disorders such as nausea (anti-emetics), cough (anti-tussives) and gastroparesis (promotility drugs). It should be noted that various conditions and drugs other than DRBAs can cause abnormal movements that resemble specific tardive disorders [1].

The term “tardive dyskinesia” (TD) was initially coined [2] to describe patients with rhythmic, repetitive (stereotypic), persistent movements after long exposure to antipsychotic drugs. Over time, other phenomenological types of persistent movements after exposure to these drugs were described [3–5]. At the same time, the specialty of movement disorders evolved and those specialists recognized distinctions among the different phenomenologies induced by the antipsychotic agents and began applying specific terminologies for them. To group all of these persistent movement disorders together (i.e., the abnormal movements persist after the causative drug has been withdrawn), an umbrella term, “tardive syndrome,” began to be used. Furthermore, it is this growth of knowledge of various movement phenomenologies within the encompassing TS that requires a nosology to categorize these various distinct phenomenologies to avoid ambiguity, misunderstanding and confusion. These phenomenological distinctions become critical because treatment choices can be specific depending on the type of TS the patient has.

There are two essential ingredients for all the categories within the umbrella TS, and both must be present. 1) These abnormal movements are due to exposure to DRBAs. If there is no history of such exposure to a DRBA, the clinician should search pharmacy, medical, or hospital records for any evidence of exposure to DRBAs before considering another diagnosis. 2) The other essential feature of TS is not that they appear late after prolonged exposure to the DRBA, but that the movement disorder persists and will continue, and often worsen, after the offending drug is withdrawn. The observation of persistence was unexpected [6] and soon became a key feature distinguishing the oral-buccal-lingual (O-B-L) dyskinesias from the acute oral dystonias that fade away after the drug is stopped. Besides acute dystonic reactions, other reversible movement disorders recognized include drug-induced parkinsonism and acute akathisia. Because these disorders typically resolve over time after withdrawal of the DRBA, they fall outside the TS spectrum, and thus persistence of the movement disorder became recognized as an important complication of the DRBAs.

The long duration of DRBA exposure before the persistent dyskinesias developed was also a major factor in coining the name “tardive” [2]. But the experience of clinicians over the half-century since this labeling has led to the recognition that persistent dyskinesias can also develop quite soon, even days, after the DRBA was started, even though the longer the exposure the greater the risk of developing the condition.

For some reason, the term ‘tardive’ dyskinesia [2] was adopted, rather than the term “persistent” dyskinesia [6]. Although today's clinicians recognize the importance of the persistent, even irreversible, nature of TS, the name ‘tardive’ is now deeply ingrained and there is no attempt to change it.

2. Extrapyramidal syndrome (EPS)

The term EPS has been commonly used, particularly by psychiatrists, to refer to DRBA-induced motor side effects, including acute dystonia, akathisia, and parkinsonism, as well as TS. In addition, other movement disorders such as Parkinson disease have been wrongly called EPS. Thus, the term EPS lacks clinical precision and clarity.

Wilson [7] in his awesome 1912 description of progressive hepatolenticular degeneration used the term extrapyramidal motor system as the source of the symptoms of that disease, plus those of Parkinson disease, athetosis, chorea and hypertonia. The extrapyramidal motor system referred to the basal ganglia and to anatomical pathways other than the cortico-spinal (pyramidal) tract [7]. Unfortunately, it is not an accurate term because there are several other extrapyramidal pathways besides those emanating from the basal ganglia and because the major outflow of the basal ganglia is via the thalamus to the cerebral cortex and from there the descending pyramidal system [8]. The Editor-in-Chief of the journal *Movement Disorders* will no longer accept the term extrapyramidal in the journal [9].

The term EPS should be avoided due to lack of clarity. In place of the term EPS, a more precise nomenclature has been advised. We will use the term tardive syndrome (TS) to refer to the spectrum of all persistent hyperkinetic, hypokinetic and sensory phenomenologies resulting from chronic DRBA exposure. The tardive syndromes must be differentiated from acute onset DRBA-induced motor syndromes including acute dystonia, akathisia, neuroleptic-malignant syndrome and drug-induced parkinsonism.

3. Historical aspects

Reserpine (subsequently found to be a dopamine depletor) and chlorpromazine (now recognized to act as a dopamine receptor blocker) were introduced in Europe in the early 1950s to treat psychosis and other agitated states. Adverse neurologic effects caused by antipsychotic drugs were noted shortly after they became available, particularly drug-induced parkinsonism, akathisia and acute dystonic reactions. In 1954 these drugs were reported to induce parkinsonism and akathisia in some of the patients [10]. Other antipsychotic drugs were introduced and found to have similar adverse effects. Delay and Deniker [11–13] introduced the term “neuroleptic” to describe the calming effect of these drugs, but with the liability of causing drug-induced parkinsonism, which was considered a part of the definition of a neuroleptic.

One of the earliest reports in the U.S. of drug-induced parkinsonism from chlorpromazine was in 1956 when Hall and colleagues [14] reported that 36 of 90 patients receiving the drug for up to 2 months developed the disorder; in all but six the adverse effect resolved within one month of being withdrawn from the drug. In that same year, Cohen [15] described two cases of acute dystonic reaction out of 1400 patients treated with chlorpromazine. He called them transient tonic spasms, but remarked that the movements resembled those seen in dystonia musculorum deformans. In the same report, Cohen [15] observed drug-induced parkinsonism in 4% of his cases. In a major review of the complications of neuroleptics in 1957, Hollister [16] mentioned Cohen's two cases, calling them transient episodes of tonic spasms, and Hollister apparently found no similar cases in the literature, although Kulenkampff and Tarnow [17] in German in 1956 reported similar dystonic reactions. Referring to the publication of Cohen's paper and Hollister's review, Shanon and colleagues [18] immediately wrote a one-page paper in 1957 reporting acute dystonic reactions in seven of 560 patients taking perphenazine. All seven were under the age of 23 years.

The year 1957 also saw the publication of the first description of stereotypic facial movements in a half-page letter in January 1957 by Schônecker [19]. He described a new phenomenological movement disorder of orobuccal and lingual (O-B-L) movements in 3 patients. In contrast to those drug-induced movement phenomenologies described by others earlier, Schônecker's patients developed theirs after they had been taking the antipsychotic for a longer period of time. He also noted that these O-B-L movements persisted after the medication had been discontinued and were still present at the time he submitted his paper. However, this report appeared to go unnoticed for several years; perhaps because it was positioned on a page between two papers, one that ended at the top of the same page, and the other beginning below Schônecker's. It is only this bottom paper on the same page that is cited in PubMed for that page in the journal, and not Schônecker's. The first reference we found to Schônecker's. paper was by Crane in his 1968 review of TD [20].

Schônecker published another paper [21] in the same journal later

that year, in December 1957. He reported five teenage youths with tonic neck, shoulder, ocular and cranial spasms. He recognized the contrast with his earlier report (lip-smacking movements, elderly people, long duration of exposure to drug, and persistence of the movements). The five teenagers, in contrast, had acute dystonic reactions, young age, short duration of exposure to drug and eventual disappearance of the movements after drug withdrawal.

Meanwhile, others were reporting their observations of neuroleptic complications, but none were describing stereotypic movements around the mouth. For example, in 1959 Ayd [22] reported his observations of 50 patients treated with perphenazine. Dystonic reactions (brief attacks of torticollis, retrocollis, or oculogyric crisis) were seen in 2, akathisia in 8 and parkinsonism in 4. Even Hollister's 1961 review of complications of psychiatric drugs failed to describe the O-B-L stereotypic movements [23]. Rather, it was Sigwald and colleagues' report of 1959 [24] that caught people's attention. They reported “the lips participate in this dyskinesia in the form of stereotypical suction movements, pursing, rolling, and incessant chomping in synergy with rhythmic contractions of the jaw.” (from English translation by Paulson [25]). A longer and more complete translation of the phenomenology of the movements is given by Crane [20]. In the early 1960's, reports of repetitive, continuous movements were being observed not only in the oral region, but also in the limbs [2,6,26–30].

The emphasis of persistent versus impersistent abnormal movements associated with neuroleptics was reported by Uhrbrand and Faurbye in 1960 [6]. This paper raised concerns about the fact that persistent abnormal movements could result from exposure to the neuroleptic antipsychotics. Like Schônecker [19], Uhrbrand and Faurbye described the stereotypic O-B-L movements and associated these with persistence even after the offending drug was discontinued. Similar association of persistence with stereotypic movements were then noted by other authors [24,26–30]. In 1964, Faurbye and colleagues [2] proposed the term, tardive dyskinesia, because of their perspective that these abnormal movements did not appear in the early months of exposure. This term was accepted and has been universally used by writers since. A more appropriate term would have been “persistent dyskinesia” because persistence of the movements after the drug is discontinued is the major problem with this disorder.

4. Tardive syndrome

Although the initial use of the term tardive dyskinesia was intended to describe the persistent stereotypic movements, over time it has become recognized that not only are there the classic O-B-L dyskinesias, but there are additional movement disorders resulting from neuroleptic use [4,5]. Unfortunately, the label ‘tardive dyskinesia’ was subsequently used by many authors to refer to other persistent motor phenomenologies due to the DRBAs. Eventually, other authors began to use terms such as tardive dystonia [31,32] and tardive akathisia [33–35] to distinguish phenomenologies distinct from the stereotypic O-B-L dyskinesia described by the early investigators in the 1960's described above. This separation by phenomenology allows investigators and clinicians to communicate with each other using common terminology.

We will use the term tardive dyskinesia (TD) to refer to the original description of repetitive and complex O-B-L movements, as well as to the analogous repetitive movements that can appear in the limbs, trunk, or pelvis. It is the repetitive, relatively rhythmic nature of the movements that is the common denominator of this phenomenologic category called TD. We will use the term tardive syndrome (TS) to refer to the spectrum of all persistent hyperkinetic, hypokinetic and sensory phenomenologies resulting from chronic DRBA exposure. Within this spectrum is TD and a number of other phenomenologies described below.

TS is, therefore, an umbrella term for a variety of delayed-onset, persistent motor and non-motor phenomenologies resulting from chronic DRBA exposure. Some authors [36] suggest using the adjective “classic” as a prefix in front of TD to refer to the stereotypical movements as an additional means to avoid ambiguity in case some authors still comingle the terms TD and TS.

5. Neuroleptics, DRBAs and dopamine depleting drugs

As noted above, Delay and Deniker [11–13] coined the term neuroleptic to describe both reserpine and antipsychotic drugs based on their ability to calm/quiet patients and for their ability to induce parkinsonism. Both reserpine and the antipsychotics create this outcome by reducing dopaminergic activity in the brain. Reserpine achieves this effect by inhibiting the enzyme vesicular monoamine transporter (VMAT). Reserpine inhibits both VMAT1 (located in the peripheral nervous system) and VMAT2 (located in the central nervous system). The result is that synaptic vesicles cannot accumulate monoamines, forcing the amines to remain in the cytosol and remain accessible to monoamine oxidase and be degraded. The net effect is a loss of monoamines in the brain. Besides reserpine, tetrabenazine and its analogs, valbenzaine and deutetrabenazine also inhibit VMAT2 (but not VMAT1) [37].

The DRBAs can cause drug-induced parkinsonism, acute akathisia, acute dystonic reactions and the TS. Although both VMAT inhibitors (dopamine depletors) and DRBAs can cause drug-induced parkinsonism (thus they are neuroleptics), the VMAT inhibitors do not cause tardive syndromes [37]. It should be mentioned that tetrabenazine has a mild DRBA action as well as a strong VMAT2 inhibition action, and perhaps the post-synaptic receptor inhibition is responsible for the acute dystonic reactions and neuroleptic malignant syndrome [38–40].

Below are discussions of the various specific types of phenomenologies comprising the TS.

5.1. Tardive dyskinesia

TD refers to the insidious onset of rhythmic, repetitive, stereotypic movements of the face, mouth and tongue, often with involvement of the trunk and extremities, that occur as a result of DRBA exposure. Even the muscles of respiration can be involved to create respiratory dyskinesias. The movements around the mouth are typically described as O-B-L and masticatory (chewing) movements, often associated with lip smacking and tongue protrusion. TD in this region of the body can affect speech, but eating is usually not impaired because the abnormal movements cease when a finger or object is touching the lips. Trunk involvement results in the body rocking back and forth and repetitive pelvic thrusting movements. Leg involvement can affect ambulation. The abnormal movements of TD are usually socially disfiguring. Some patients with TD also experience sensory phenomenon, such as burning pain and discomfort in the mouth and vaginal area.

Like other forms of TS, TD tends to occur after long exposure to the DRBA and can begin after discontinuation of the medication. However, there is no “safe” minimal period of DRBA exposure. Sudden withdrawal of a DRBA is suspected of triggering the development of TD and other tardive syndromes; thus, it is safer to taper the dosage of the DRBA before stopping it. The incidence of TD has been known to increase with age [41]. TD is thought to affect women preferentially. Treatment with DRBA's can reduce or mask the symptoms. To distinguish TD from neuroleptic withdrawal emergent syndrome, movements should persist beyond 8 weeks following discontinuation of DRBA's. TD is long lasting and can be permanent; however, it has been observed to improve and resolve in some cases after a prolonged discontinuation of DRBAs. Gardos et al. [42] reported a tendency of TD to decline over four years following discontinuation of DRBA's. However, complete and permanent remittance of symptoms is rare.

Differential diagnosis of TD includes stereotyped movements of schizophrenia, spontaneous oral dyskinesias of senility or advanced

age, oral dyskinesia related to dental conditions (e.g. edentulous dyskinesia), oromandibular dystonia or peripherally-induced oromandibular movements after dental procedure or placement of prostheses [43]. Infrequently, levodopa-induced dyskinesias can mimic O-B-L dyskinesias, although head stereotypy ("head bobbing") is the most typical form of levodopa-induced dyskinesia [44].

5.2. Tardive dystonia

When dystonia is the main feature of TS it is considered to be Tardive dystonia (TDyst). TDyst was first reported to be a distinct entity in 1982 by Burke et al. [32]. Dystonic movements have been described as sustained, involuntary twisting movements, usually slow, which can affect the limbs, neck, trunk or face [45]. Retrocollis appears to be the predominant form of cervical dystonia compared to torticollis in idiopathic dystonia. Truncal dystonia, when present can be with lordotic posturing, with the trunk bent forward. A more common presentation, however, is with opisthotonic posturing, occurring most commonly when the patient is walking. Associated with this backward arching of the trunk, the arms are typically adducted and pronated, and the wrists are flexed. However, the appearance of TDyst can be indistinguishable from idiopathic dystonia, especially focal dystonias affecting the jaw or tongue. There may be an alleviating maneuver (sensory trick response, geste antagoniste) and a worsening of the dystonia with action. It appears that TDyst is insidious in onset tending to affect the face or neck first with progression over months to years from focal to segmental or generalized dystonia. In many cases TD is also present. In older patients, focal dystonias are usually the presenting pattern. In younger patients, generalized dystonia can develop. When patients with TDyst have coexisting TD or tardive akathisia, the additional phenomenology readily makes the recognition that the dystonia is that of a tardive rather than an idiopathic form of dystonia.

Three longitudinal studies of TDyst have reported consistent findings. See Table 1 for a compilation of the data from these studies. Male gender tends to have a younger age at onset compared to women. There appears to be a linear relationship between cumulative frequency and age. At onset, the dystonia was focal in the majority; however, at the time of peak severity, the majority had progressed to segmental dystonia with less focal dystonia. Remission has been reported, especially in children, but is uncommon in adults (from 11.9% to 14%) with a mean remission rate of 10% and mean follow up of 6.6 years [45,46]. Slow taper and eventual discontinuation of DRBA's appear to be important for improvement and remission.

5.3. Tardive akathisia

Akathisia means the inability to remain still with an urge to move, giving the appearance of restlessness. It is a sensory phenomenon and a common and disabling form of TS. Tardive akathisia (TA) must be distinguished from acute akathisia, a condition with identical symptoms. The latter occurs fairly early after the neuroleptic is introduced, and will dissipate when the offending drug is discontinued. TA, on the other hand, tends to occur late and, what is most important, persists after the drug is withdrawn, and often worsens on withdrawing the drug. The clinical features of both acute akathisia and TA can otherwise be indistinguishable (35). In a study of 82 schizophrenic patients 29, or 35%, were found to have akathisia and 73% of these patients had chronic akathisia [47].

There are two aspects to akathisia: a subjective restlessness and inner tension and objective or motor manifestation in the form of semipurposeful or purposeless movement of the limbs. The movements occur in patterns that make them characteristic. Typical movements of TA have included repetitive self-touching, marching in place, rocking from one leg to the other, pumping the legs up and down, crossing and uncrossing the legs or abducting and adducting the legs [35]. The onset of TA is often delayed with respect to exposure of DRBA or when DRBA is withdrawn [48], but occasionally can occur after a short exposure; in this situation, distinguishing it from acute akathisia is very difficult and depends if the akathisia dissipates or persists after drug withdrawal. TA is usually seen in combination with TD and/or TDyst [35] and can herald the onset of TD [49]. TA has been reported to persist from 2.7 months to 7 years following discontinuation of DRBA [47].

5.4. Tardive tics (tourettism)

An uncommon form of TS is tardive tics, sometimes with phonic tics, which can then be called tardive tourettism. Tardive tourettism exhibits the features of Tourette syndrome with complex motor and phonic tics associated with premonitory urge and relief of tension after performing the tic behavior. Klawans [50] first reported a case of tardive tourettism in 1978, describing onset of tics as facial grimacing, snorting, sniffing, grunting and barking like a dog following a history of

Table 1
Summary of data tardive dystonia.

Reference	Male/Females	Age at onset (Yrs)	Types of Dystonia	Average DRBA exposure (Yrs)	Remittance (number of pts)	Mean Period of follow up (Yrs)
Burke et al., [32]	26/16	13–60	Face Neck Focal Segmental Generalized	3.7	5	3.1
Kang et al., [45]	34/44	13–72	Cranial Neck Trunk Focal Arms Legs Segmental Generalized	7.3	5	2–13
Kiriakakis et al., [46]	57/50	38.3	Face Neck Trunk Focal Arms Legs Segmental Generalized	6.2	15	8.3

DRBA exposure. This patient did not have a history of tics or any family history of Tourette syndrome. Bharucha and Sethi [51] reported one case with a review of six additional cases. Fountoulakis et al. [52] performed a systematic review of 41 cases of "tardive tourettism", but some of these cases were probably not tardive as they were associated with the use of not only DRBAs but also antiepileptics, stimulants and other medications. In contrast to Tourette syndrome, attention deficit/hyperactivity disorder and obsessive compulsive disorder are not usually present in patients with tardive tourettism. Sometimes tardive tourettism is confused with TA, however, the movements appear to differ from those of TA and resemble the motor and phonic tics associated with Tourette syndrome [51]. Concomitant TD is seen in most reported cases. Tetrabenazine and other VMAT2 inhibitors have been reported to be beneficial [53]. Behavioral therapy may also be used with some benefit.

5.5. Tardive tremor

Tardive tremor, a rare form of TS, was first described by Stacy and Jankovic in 1992 [54] who reported five patients. Since that time there have been 3 case reports [55–57] and a case series of 10 patients [58] with tardive tremor. The tremor differed from the resting tremor seen with DRBA use and parkinsonism in that it was mainly a postural and kinetic greater than resting tremor. It was described as involuntary, rhythmic, oscillatory movement occurring after treatment with DRBA, not present before treatment and persistent with failure to improve following discontinuation of the DRBA. In fact, tardive tremor tends to worsen with discontinuation of the DRBA. It did not respond to treatment for ET or PD but tends to be responsive to tetrabenazine. Clozapine was beneficial in one case [55] and another case responded to a sensory trick – placing pressure to the back of the neck ameliorated the tremor [57]. The tremor in this case was thought to be related to dystonia (dystonic tremor) as the patient also had blepharospasm. Most cases of tardive tremor have coincident TD or other forms of TS.

5.6. Tardive myoclonus

Myoclonus, defined as brief involuntary muscle contractions resulting in jerk-like movements, has also been associated with long term DRBA exposure. It appears to be a rare condition being mentioned in one report and two other reports describing it. Thirty-two patients were described with postural myoclonic movements following 3 months or greater exposure to DRBA [59]. Little and Jankovic described a single case of tardive myoclonus affecting the head and neck with associated tics and dystonia following many years of DRBA exposure [60], and two out of 42 cases of tardive dystonia had associated myoclonus [32]. Further description and information regarding treatment is not available.

5.7. Tardive pain

Pain involving the mouth and tongue as well as pain in the genital regions has been reported in association with chronic use of DRBA's. The first case of tardive pain was reported in 1989 by Hierholzer [61]. Ford and colleagues described an additional nine cases of tardive pain involving the oral and lingual regions [62], and Montagna et al. reported three cases [63]. Tschopp et al. reported one case of tardive pain [64] for a total of 14 cases. Each case described the absence of any physical findings associated with the development of the pain. Patients tended to obsess over the pain. Each of the nine patients had some other form of TS, either TD, TA or TDyst [62]. Onset of pain was reported to be within six months after TD in most cases, however some cases had the onset coincident with the onset of TD. Tetrabenazine tended to be the most efficacious agent. A single patient was reported to have benefit from ECT suggesting treatment of the underlying psychiatric condition may be helpful. Botulinum toxin injections into the genioglossus muscle were reported to improve the pain as well as the lingual movements from both tardive pain and TD [64]. Some authors [65] consider tardive pain to be a focal form of tardive akathisia in which a severe focal sensory discomfort is interpreted by the patient as pain.

5.8. Tardive parkinsonism

Parkinsonism is a well-known side effect of DRBA's. It has been found that blockage of 75 to 80% of postsynaptic D2 receptors produces motor features of parkinsonism [66]. Patients are known to develop symptoms of parkinsonism after taking DRBA's for several months, although some have had symptoms begin earlier. DRBA induced parkinsonism (DIP) is found to be greater in women, however further clinical characteristics have not proven to distinguish DIP from idiopathic Parkinson disease. DIP patients improve once the offending agent has been discontinued with complete resolution of symptoms in most cases. This improvement can be prolonged and take place over the course of a year. Not all DIP patients have improvement of the parkinsonism, however. Symptoms may persist or progress over time. The term tardive parkinsonism has been proposed for those DIP patients who have persistent symptoms following discontinuation of the DRBA. However, there is a strong possibility that the DRBA may have simply unmasked subclinical parkinsonism or that there is coincident Parkinson disease developing during the period the patient is taking the DRBA. There is no consistent clinical characteristic that distinguishes those with DIP from idiopathic parkinsonism. However nonmotor characteristics such as autonomic disorders or hyposmia appear to be more consistent with idiopathic parkinsonism [67]. MRI and dopamine transporter SPECT (DaTscan) scans have been proposed to distinguish those with simple DIP from those with neurodegenerative Parkinson disease [68–70]. Normal SPECT scans are seen with DIP, an expected result with parkinsonism caused by dopamine receptor blockade. Pathological studies in those with DIP and persistent symptoms of parkinsonism have shown reduction in pigmentation of the substantia nigra and presence of Lewy bodies with some showing alpha synuclein positive staining [71–73]. These are findings seen in patients with Parkinson disease. Thus, all post mortem evaluations of persistent parkinsonism so far support the cause to be Parkinson disease. Because of these findings, the proof of actual *tardive parkinsonism* has not been established. Rather, individuals with persistent parkinsonism after prolonged withdrawal of the DRBA should be considered to represent cases in which there is a subclinical parkinsonism that has been unmasked by DRBA use or coincident onset of symptomatic idiopathic Parkinson disease.

6. Conclusion

TS represents a persistent motor or sensory adverse effect of treatment with DRBAs. The varied forms of TS include TD involving stereotypic movements in the O-B-L area and in the trunk and distal extremities, tardive dystonia, tardive akathisia, tardive tourettism, tardive tremor, tardive myoclonus and tardive pain. Most of these disorders initially occur after treatment with DRBA for at least three months. The DSM-5 criteria indicate that only one month may be needed in individuals 60 years of age or older. The movements can begin while taking the DRBA or within four weeks of discontinuation. Multiple forms of TS can be found in one patient, and symptoms may improve over time following discontinuation of the offending agent. VMAT2 inhibitors are considered the treatment of choice. In 2017 deutetrabenazine and valbenazine were approved for the treatment of TD [37,74–76].

Conflict of interest

Dr. Frei has no conflict of interest to declare.

Daniel Truong reports Daniel D. Truong has received research

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Dr. Fahn has served on commercial consulting capacity and as advisory board member with honoraria for Adamas Pharmaceuticals; Retrophin Inc. (DMC member); PhotoPharmics; Sun Pharma Advanced Research Co., Ltd.; Kashiv Pharma. He has received honoraria for lecture at Univ Chicago Cornell Medical College; UCSD; Movement Disorder Society. He received royalties from Springer Publishers, Elsevier Publishers. He is employed by Columbia University. He provided expert testimony for Kirkland & Ellis. He has no stock ownership in medically-related fields and is not associated with any speakers' bureau.

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