Parkinsonism and Related Disorders 59 (2019) 146–150

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Setting the record straight: The nosology of tardive syndromes

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ARTICLE INFO

Keywords:
Tardive syndrome
Tardive dyskinesia
Tardive dystonia
Tardive tremors
Tardive akathisia
Tardive tourettism
Tardive pain
Tardive parkinsonism
Extrapyramidal syndrome

ABSTRACT

We propose the use of the term tardive dyskinesia to refer to the original description of repetitive and complex oral-buccal-lingual (OBL) movements and the analogous repetitive movements of the limbs, trunk, or pelvis.

The term tardive syndrome is an umbrella term to be used to refer to the spectrum of all persistent hyperkinetic, hypokinetic, and sensory phenomenologies resulting from chronic dopamine receptor blocking agent (DRBA) exposure. TD is a type of TS.

The term tardive dystonia (TDyst) should be used when dystonia is the main feature of TS. Retrocollis and oromandibular dystonia appear to be the most common form of Tdyst. Tardive akathisia refers to the inability to remain still with an urge to move, giving the appearance of restlessness. In tardive tourettism, the patient has complex motor and phonic tics associated with premonitory urge and relief of tension after performing the tic behavior, thus resembling Tourette's syndrome. Tardive tremor is composed of mainly postural and kinetic tremors. It differs from the resting tremor seen in drug-induced parkinsonism. Tardive pain occurs in association with chronic use of DRBAs and involves the mouth, tongue, and genital region with no physical findings. In tardive parkinsonism, the patient has persistent parkinsonism even after discontinuation of the DRBA although this diagnosis is in question and may represent DRBA-uncovered idiopathic Parkinson's disease or coincident development of Parkinson's disease while taking DRBAs.

1. Introduction

The terms *tardive dyskinesia* (TD) and *tardive syndrome* (TS) have been used by different authors interchangeably. *Dopamine receptor blocking agents* (DRBAs), of which the most common are neuroleptics, were used chiefly to treat psychosis (antipsychotic drugs), thus their side-effects were observed by psychiatrists early on. The abnormal movements were only later defined by neurologists specializing in movement disorders. Over time it turned out that a number of drugs used to treat a variety of disorders, such as nausea (anti-emetics), cough (anti-tussives) and gastroparesis (promotility drugs) can also cause tardive disorders including TD [1]. Thus the term **DRBA** is more specific and the preferred term over neuroleptics or antipsychotics.

The term *tardive dyskinesia* (TD) was initially coined to describe rhythmic, repetitive (stereotypic), persistent movements after long exposure to antipsychotic drugs [2]. Initially, the term “tardive” was intended to denote the long duration of DRBA exposure before the persistent dyskinesias developed. However, it was soon noted that persistent dyskinesias can also develop quite early, even days after the DRBA was started, although the longer the exposure, the greater the risk of developing the condition [2].

Later, the term *tardive syndrome* began to be used as an umbrella term for different types of persistent movements seen in association with the exposure to antipsychotics [3–7]. The understanding of the movement disorder and the associated pharmacology requires further subdivision of phenomenological distinctions. We therefore had proposed a nosology designed to define and clarify various terms and phenomenologies within the TS spectrum. See Table 1 for the list of conditions that compose TS.

2. Historical aspects

After the introduction of reserpine and chlorpromazine in the early 1950s to treat psychosis and other agitated states, their association with drug-induced parkinsonism, akathisia, and acute dystonic reactions soon became known [9]. Other antipsychotic drugs were found to have similar adverse effects. Delay and Deniker introduced the term “neuroleptic” to describe the calming effect of these drugs. The side effect of causing drug-induced parkinsonism was considered a part of the definition of a neuroleptic [10–12].

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https://doi.org/10.1016/j.parkreldis.2018.11.025
Received 22 August 2018; Received in revised form 27 November 2018; Accepted 27 November 2018
1353-8020/

Table 1
List of conditions included in tardive syndrome.

Tardive Dyskinesia
Tardive Dystonia
Tardive Akathisia
Tardive Tics (tourettism)
Tardive Myoclonus
Tardive Tremors
Tardive Pain

In 1956, Cohen described 2 cases of acute dystonic reaction out of 1400 patients treated with chlorpromazine [13]. Kulenkampff and Tarnow in Germany also in 1956 reported similar dystonic reactions [14]. In a major review of the complications of neuroleptics in 1957, Hollister mentioned Cohen's two cases, calling them transient episodes of tonic spasms [15]. Referring to the publication of Cohen's paper and Hollister's review, Shanon and colleagues wrote a 1-page paper in 1957 reporting acute dystonic reactions in seven of 560 patients taking perphenazine [16]. All 7 were under the age of 23 years. In the same year, Schônecker reported a new phenomenological movement disorder, describing oral-buccal-lingual (OBL) movements in 3 patients [17]. These patients developed the symptoms after a longer exposure to antipsychotic drugs and the symptoms persisted even after the offending drugs were discontinued. As pointed out by Frei et al. [6], Schônecker's paper appeared to go unnoticed due to its position on a page between 2 other papers, one of which ended at the top of the same page, and the other beginning below. Only this bottom paper on the same page is cited in PubMed, and not Schônecker's. Crane in his 1968 review of TD was the first to cite Schônecker's paper, giving him credit for the first description of TD [18].

Schônecker reported in the same journal also in 1957 five teenage youths' acute dystonic reaction with tonic neck, shoulder, ocular, and cranial spasms [19]. He recognized the contrast with his earlier report (lip-smacking movements in elderly people with long duration of exposure to the drug and persistence of the movements). The five teenagers had acute dystonic reactions, young age, short duration of exposure to the drug, and eventual disappearance of the movements after drug withdrawal.

Sigwald and colleagues' report of four cases of TD in 1959 [20] caught people's attention with the following description: “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 the English translation by Paulson [21]). Later, repetitive, continuous movements were observed also in the limbs [2,8,22–26]. Uhrbrand and Faurbye in 1960 raised concerns about the persistence of these abnormal movements that could result from exposure to neuroleptic antipsychotics [8]. Like Schônecker [17], Uhrbrand and Faurbye described the persistent stereotypic OBL movements even after the offending drug was discontinued and in 1964, Faurbye and colleagues proposed the term tardive dyskinesia to refer to the delayed onset of these movements [2]. A more appropriate term would have been “persistent dyskinesia” to better describe the time course of this disorder.

3. Tardive syndrome

The initial use of the term tardive dyskinesia was intended to describe the persistent stereotypic OBL movements. Later, it was recognized that in addition to the classic OBL movements, there are other movement disorders resulting from chronic neuroleptic use [4,5]. Eventually, other authors began to use other terms, such as tardive dystonia [27,28] and tardive akathisia [30,31] to distinguish phenomenologies distinct from the stereotypic OBL movements described by the early investigators.

We propose to use the term *tardive dyskinesia* (TD) for the original, classic description of repetitive and complex OBL movements and the analogous repetitive movements that can appear in the limbs, trunk, or pelvis [6] following at least 3 months of exposure to DRBAs. It is the repetitive, relatively rhythmic nature of the movements that is the common denominator of this phenomenologic category called TD. TD can develop within days of taking DRBAs, but more commonly occurs after months of DRBA exposure. The DSM IV has required one month of exposure in those over 60 years of age and three months in those younger than 60 years [32].

The term *tardive syndrome* (TS) should refer to the spectrum of all persistent hyperkinetic, hypokinetic, and sensory phenomenologies resulting from at least 3 months of DRBA exposure. For the umbrella term of TS to be used, two requirements must both be present: 1) These abnormal movements are due to exposure to DRBAs; 2) The movement disorders persist after the offending drug is withdrawn. The persistence of the symptoms becomes the key feature of TS, differentiating it from similar acute disorders resulting from DRBA use [8]. TS spectrum does not include acute disorders such as drug-induced parkinsonism (DIP), acute dystonic reaction, and acute akathisia.

Following are discussions of the various specific types of phenomenologies that make up the TS.

3.1. 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. Limb movements called “piano playing” movements can accompany the OBL movements. Truncal movements of TD may include rocking back and forth and repetitive pelvic thrusting movements. When the muscles of respiration are involved, it can create respiratory dyskinesias. The movements around the mouth are typically described as OBL and masticatory (chewing) movements, often associated with lip smacking and tongue protrusion. TD in this region of the body can affect speech, resulting in spasm in the voice, but eating is usually not impaired because the abnormal movements cease when a finger or object is touching the lips. It appears as if sensory input can modify the involuntary movements. In this respect, TD has a similar feature to the sensory trick found in dystonia [6].

TD can develop as soon as one day or as long as several years of DRBA exposure. There is no safe amount of TD exposure. Both first-generation or typical antipsychotics and second-generation or atypical antipsychotics can cause TD. TD can begin during DRBA use or after discontinuation. The DSM IV has set a requirement of three months of DRBA use, with duration of symptoms for more than 8 weeks [32]. This distinguishes TD from withdrawal-emergent syndrome, in which symptoms begin after abruptly discontinuing the DRBA but are transient, resolving within four weeks. Sudden withdrawal of a DRBA is suspected of triggering the development of TD and other tardive syndromes; therefore, the dosage of the DRBA should be tapered before stopping it.

The incidence of TD has been known to increase with age [33]. TD is thought to affect women preferentially, although this is controversial. Treatment with DRBAs can acutely reduce or mask the symptoms. TD is long lasting and can be permanent. It has been observed to improve and rarely resolve after a prolonged discontinuation of DRBAs. Gardos et al. (1988) reported a tendency for decline in TD symptoms after 4 years of DRBA discontinuation [34].

Although recommended in the treatment of TD, there is insufficient evidence to include the following in the AAN practice guideline: discontinue the DRBA if possible or replace a typical antipsychotic for an atypical antipsychotic. There is weak evidence for use of a vesicular monoamine transporter (VMAT) inhibitor. Tetrabenazine is a VMAT inhibitor that tends to deplete dopamine without causing TD [35].

The differential diagnosis of TD includes stereotyped movements of schizophrenia, spontaneous oral dyskinesias of senility or advanced age, edentulous dyskinesia, oromandibular dystonia or peripherally

induced oromandibular movements after dental procedures or placement of prostheses [36]. Stereotyped movements of schizophrenia, also known as spontaneous dyskinesias, were noted to be present in those with more severe schizophrenic illness never treated with antipsychotics. These movements are phenomenologically identical to those of TD, with the main difference being these movements occur in the absence of DRBA use and are thought to represent motor manifestations of underlying cerebral pathology related to schizophrenia. Fenton found the prevalence of spontaneous dyskinesias to be 14.9% in a population of antipsychotic-naïve schizophrenia patients [37].

3.2. Tardive dystonia

In tardive dystonia (TDyst), dystonia is the main feature. Burke et al. first described TDyst as a distinct entity in 1982 [28]. TDyst develops insidiously with a tendency to present as a focal dystonia, such as blepharospasm or cervical dystonia, and over time develops into a more segmental form. Retrocollis appears to be the predominant form of cervical dystonia in TDyst. Truncal dystonia can present as lordotic posturing, with the trunk bent forward, or opisthotonic posturing, occurring most commonly when the patient is walking. The appearance of TDyst can be indistinguishable from idiopathic dystonia [6]. TDyst may improve with discontinuation of DRBA and treatment with tetrabenazine, anticholinergics, botulinum toxin, and deep brain stimulation.

Acute dystonic reactions tend to occur in young men with a first episode of psychosis treated with high doses of a DRBA. It begins within hours to days after starting the DRBA. 50% start after 24 h and 90% within the first five days [29]. Acute dystonic reactions tend to occur in the craniocervical region, with oromandibular dystonia being the most common. Oculogyric crises, blepharospasm, and complex cervical dystonia with less common focal limb dystonia also occur. They respond dramatically to anticholinergics. See Table 2 for a comparison between the two disorders.

3.3. Tardive akathisia

Akathisia means the inability to remain still with an urge to move, projecting 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 [31]. Acute akathisia occurs fairly early after the neuroleptic is introduced, and dissipates when the offending drug is discontinued. TA tends to occur late and persists after the drug is withdrawn.

There are two aspects to akathisia: a subjective restlessness and inner tension and objective or motor manifestation in the form of semipurposeful or purposeless movements of the limbs. Stereotypic movements include repetitive self-touching, marching in place, rocking from one leg to the other, pumping the legs up and down, crossing and uncrossing the legs, and abducting and adducting the legs [31].

3.4. Tardive tics (tourettism)

Tardive tourettism is an uncommon form of TS presenting with features of Tourette syndrome, including complex motor and phonic tics associated with premonitory urge and relief of tension after performing the tic behavior. Klawans 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 DRBA exposure [38]. This patient did not have a history of tics or any family history of Tourette syndrome. Attention deficit/hyperactivity disorder and obsessive compulsive disorder are not usually present in patients with tardive tourettism.

3.5. Tardive tremor

Stacy and Jankovic in 1992 reported five patients with tardive tremors [39]. Since that time there have been 3 case reports and a case series of 10 patients [6,40,41]. Tardive tremor appears to be a rare occurrence and is described as resting, postural, and kinetic. It is involuntary, rhythmic, oscillatory movement occurring after treatment with DRBA, not present before treatment, and persistent, with failure to improve following discontinuation of the DRBA [35]. Additional signs of parkinsonism are absent in this disorder.

Tardive tremor tends to worsen with discontinuation of the DRBA. It does not respond to treatment for essential tremors or Parkinson disease, but tends to be responsive to tetrabenazine. The development of the tremor after DRBA exposure with persistence following discontinuation of the drug and improvement with tetrabenazine lends support to this being a form of TS.

3.6. 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 occurring in the arms and hands predominantly. Thirty-two patients were described with postural myoclonic movements following 3 months or longer exposure to DRBA [42]. Tardive myoclonus is associated with other tardive syndromes, including tardive dyskinesia and tardive dystonia. Two out of 42 cases of tardive dystonia were found to have associated myoclonus [28,43]. The association between tardive myoclonus and tardive dystonia is not understood.

3.7. Tardive pain

Pain involving the mouth and tongue as well as pain in the genital region has been reported in association with the chronic use of DRBAs. The first case of tardive pain was reported in 1989 by Hierholzer [44]. In total, 14 cases have been reported. A review of 11 cases of tardive pain found no physical findings associated with the development of the pain. All patients had TD, with some having TDyst or TA in addition to

Table 2
Comparison between tardive dystonia and acute dystonic reactions to DRBAs.

Tardive Dystonia	Acute Dystonic Reactions
DRBA exposure: days to years (mean 5.7 yrs)	DRBA exposure: 24 h to 5 days
Gradual onset	Sudden onset
Starts out as focal form and develops into segmental form	Starts as focal form, does not progress to other forms of dystonia
Common forms:	Common forms:
Blepharospasm	Oromandibular dystonia
Cervical dystonia – retrocollis	Blepharospasm
Trunkal dystonia – opisthotonic posturing	Oculogyric crisis
	Complex forms of cervical dystonia
Improves but rarely resolves with discontinuation of DRBA and treatment with tetrabenazine, anticholinergics, and botulinum toxin	Resolves with discontinuation of DRBA and treatment with anticholinergic

DRBA – dopamine receptor blocking agents.

Table 3
Distinguishing features between DRBA-induced parkinsonism, tardive parkinsonism, and idiopathic Parkinson's disease.

DRBA-induced parkinsonism (DIP)	Tardive parkinsonism	Idiopathic Parkinson's disease
Parkinsonian symptoms present after DRBA exposure and improve after discontinuation of DRBA up to one year	Parkinsonian symptoms present after DRBA exposure and persist after discontinuation of DRBA greater than one year	Persistent Parkinsonian symptoms in absence of DRBA exposure
No hyposmia	No hyposmia	+/− hyposmia
No autonomic dysfunction	No autonomic dysfunction	+/− autonomic dysfunction
DaT scan –	DaT scan not reported	DaT scan +
Path studies: Not performed	Path studies: reduction in SN pigmentation	Path studies: reduction in SN pigmentation
	Lewy bodies present	Lewy bodies present
	Alpha synuclein staining +	Alpha synuclein staining +

TD. Patients tended to obsess over the pain [45]. Tardive pain is a sensory phenomenon thought to be a type of TA. Tetrabenazine tended to be the most effective agent. Treatment of depression was helpful in a few patients, with botulinum toxin injections helpful in one case [45,46].

3.8. Tardive parkinsonism

Parkinsonism is a well-known side effect of DRBAs. Blockage of 75–80% of postsynaptic D2 receptors produces motor features of parkinsonism [47]. 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, but in some cases, the symptoms may persist or even progress over time, thereby making it difficult to distinguish from idiopathic Parkinson's disease. The term tardive parkinsonism has been proposed for those DIP patients who have persistent symptoms following discontinuation of the DRBA.

There are a few characteristics thought to distinguish DIP and tardive parkinsonism from Parkinson's disease (see Table 3). Nonmotor characteristics such as autonomic disorders or hyposmia appear to be more consistent with idiopathic parkinsonism [48]. MRI and dopamine transporter SPECT (DaTscan) scans have been proposed to distinguish those with simple DIP from those with neurodegenerative Parkinson disease [49–51]. Pathological studies in those with tardive parkinsonism have shown reduction in pigmentation of the substantia nigra and presence of Lewy bodies, with some showing alpha synuclein positive staining as seen in Parkinson's disease [52–54]. So it appears as if tardive parkinsonism may actually represent latent Parkinson's disease uncovered by the use of DRBAs or the coexistent development of Parkinson's disease while taking DRBAs.

4. 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 OBL 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 3 months. The DSM-IV criteria indicate that these disorders can occur after only one month of treatment 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.

Conflicts of interest

Dr. Frei has no conflict of interest to declare.

Funding

Daniel Truong has research grants from Ipsen, Merz, Auspex, Daiichi Sankyo Pharma, AbbVie, National Institute of Neurological Disorders and Stroke, Kyowa, Neurocrine, Sunovion Pharmaceuticals Inc., Acadia, Accorda, Cynapsus, Neuroderm, Prexton Therapeutics, and Intec. He received fees from Teva Pharmaceutical Industries; Alexza Pharmaceuticals, Inc.; Adamas Pharmaceuticals; and US WorldMeds.

Acknowledgement

The authors thank Spencer Kieu for his assistance.

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