Tardive Dystonia

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Abstract

This paper provides an overview of the phenomenology, epidemiology, and treatment of tardive dystonia. Tardive dystonia is one of the extrapyramidal syndromes that starts after long-term use of dopamine receptor antagonists. The diagnosis is based on the presence of chronic dystonia, defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Furthermore, dystonia must develop either during or within 3 months of a course of antipsychotic treatment, and other causes such as Wilson's disease, acute dystonia, or a conversion reaction must be ruled out. Tardive dystonia occurs in about 3 percent of patients on long-term antipsychotic treatment. Some probable risk factors for tardive dystonia are younger age, male, and the presence of tardive dyskinesia. The treatment of tardive dystonia starts with an evaluation of the need for using the causative drug. If antipsychotics must be continued, a switch to an atypical antipsychotic, particularly clozapine, may be helpful. If the dystonia is relatively localized, botulinum toxin is an effective but not well-known treatment possibility. If tardive dystonia is more extensive, either dopamine-depleting drugs or high dosages of anticholinergics can be tried.

Key words: Extrapyramidal side effects, tardive dyskinesia, tardive dystonia, antipsychotics, review, prevalence, diagnosis, treatment, movement disorders.

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Tardive dystonia is one of the extrapyramidal syndromes that starts after long-term use of dopamine receptor antagonists. Tardive dystonia is underdiagnosed and often misdiagnosed; some of the treatment possibilities are hardly known among psychiatrists. This paper provides a survey of the diagnosis, epidemiology, and treatment of tardive dystonia. A literature search was performed via MEDLINE and EMBASE using several key terms, including tardive dystonia, movement disorder, dystonia, extrapyramidal syndromes, and tardive dyskinesia. We reviewed articles in English, German, and Dutch (and in other languages, if a detailed summary of the study was given in English). Cross-references in articles were also reviewed.

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures (Barbeau et al. 1984). The term "dystonia tarda" was coined by Keegan and Rajput in 1973. However, it was not until 1982 that Burke et al. (1982*a*) published a series of case reports on 42 patients with tardive dystonia. Since 1982 more than 300 cases have been added to the literature (Greene 1997).

Tardive dystonia should be considered distinct from tardive dyskinesia because (1) it has different phenomenological manifestations, (2) patients with tardive dystonia are younger at onset and lack the female predominance seen with tardive dyskinesia, and (3) it has different reactions to anticholinergics, which can alleviate tardive dystonia but exacerbate tardive dyskinesia (Burke 1992; Greene 1997).

Burke and colleagues (1982*a*) suggested the following diagnostic criteria: (1) the patient must have dystonia, as defined above; (2) the patient must have developed dystonia either during or within 3 months of a course of neuroleptic treatment; (3) Wilson's disease must be ruled out, and there must be no other neurological signs to suggest one of the many causes of secondary dystonia; and (4) there must be a negative family history for dystonia.

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Clinical Features

Tardive dystonia's clinical features are usually divided into four categories: focal (single body part affected), segmental (two or more contiguous body parts), multifocal (two or more noncontiguous body parts), and generalized (combined involvement of at least one leg and trunk and any other body part) (Fahn et al. 1987).

Patients develop tardive dystonia after varying periods of exposure to antipsychotics, ranging from a few days to many years (Burke et al. 1982*a*; Kang et al. 1988; Lohman et al. 1995). In contrast to tardive dyskinesia, tardive dystonia often begins after a relatively short period of exposure to antipsychotics. About one-fifth of the cases occur in the first year, and half of the cases in the first 5 years of exposure (Kang et al. 1988).

Tardive dystonia can affect every body area, including twisting of the neck musculature in all directions (torti-, retro-, latero-, or ante-collis), blepharospasm, and oromandibular, laryngeal, arm, trunk, and leg dystonia. Oculogyric crises are a well-known form of acute dystonia, but a tardive form has also been reported (FitzGerald and Jankovic 1989; Sachdev 1993*c*). The most common site for tardive dystonia is the cranial and neck region, but involvement of the arms is also common (Burke et al. 1982*a*; Kang et al. 1988).

Tardive dystonia often starts insidiously, and in about two-thirds of cases onset is in the face, neck, or both. Onset in an arm is less common, and onset in a leg is rare. In about three-quarters of patients, the dystonia progresses to a segmental state, but progression to a generalized state is uncommon (Burke et al. 1982*a*; Kang et al. 1988). There seems to be a relation between the age at onset of dystonia and the final severity; patients with generalized dystonia were younger than those with focal dystonia (Burke et al. 1982*a*; Kang et al. 1988).

The onset of tardive dystonia seems to occur earlier in males than in females (Burke et al. 1982*a*; Giménez-Roldán et al. 1985; Kang et al. 1988; Yassa et al. 1989; Wojcik et al. 1991), a finding we replicated in a study we conducted in Curaçao (age at onset in males, 38.4 yrs vs. females, 59.0 yrs; $n = 22$, $F = 9.08$, $p < 0.007$, unpublished data) (van Harten et al. 1996*b*). Remarkable features of tardive dystonia are the "sensory tricks," which are tactile or proprioceptive stimuli that may relieve the severity or the subjective discomfort of the dystonia; for example, a patient with torticollis obtains relief by touching his chin (Fahn et al. 1987). The severity of tardive dystonia can increase with fatigue and stress but tends to be suppressed through relaxation, hypnosis, and sleep. Mania and psychosis can alter the severity of tardive dystonia; some authors have reported a worsening (van Harten et al. 1996*a*) and others an improvement (Lal et al. 1988; Yazici et al. 1991). Sometimes tardive dystonia can cause severe pain (Burke et al. 1982*a*; Ford et al. 1994); even a rib fracture has been reported (Szymanski et al. 1993).

All agents that block dopamine receptors in the central nervous system, such as antipsychotics, antiemetics (e.g., prochlorperazine, metoclopramide), and the antidepressant amoxapine, can cause tardive dystonia (Burke et al. 1982*a*; Bateman et al. 1985; Burke 1992; Ganzini et al. 1993). Cocaine has been reported to exacerbate existing tardive dystonia (Cardoso and Jankovic 1993).

Differential Diagnosis

Differential diagnosis starts with identification of the type of involuntary movement. Dystonia can be confused with tardive dyskinesia, myoclonus, tremor, and tics. Tardive dyskinesia is characterized by writhing, purposeless, irregular movements and is located most of the time in the face, lips, tongue, or jaw and less frequently in limbs or trunk (Task Force 1992). Myoclonus is characterized by sudden, shocklike contractions of a muscle or a group of muscles. Tremor is a rhythmic, regular, oscillating movement. Tics are sudden, stereotyped, complex, repetitive, normally coordinated but inappropriate movements (Lakke 1981).

When dystonia has been diagnosed, the first possibility to consider is acute dystonia. Acute dystonia almost always occurs within 5 days of beginning antipsychotics or after a substantial increase in dosage; it responds well to the administration of anticholinergics.

The next possibility is Wilson's disease, an inborn error in copper metabolism that can express itself as dystonia. Since Wilson's disease is treatable, it must be carefully ruled out by ascertaining a normal serum ceruloplasmin level and the absence of the Kayser-Fleischer ring (Menkes 1992).

There are numerous other neurological causes of dystonia. However, they should be ruled out only if other progressive neurological signs are present besides dystonia (Burke 1992). If dystonia is not accompanied by other neurological signs, one should consider (1) a conversion reaction, (2) dystonia caused by other compounds, and (3) idiopathic dystonia.

In tardive dystonia a patient constantly tries to redress the dystonia, whereas in a conversion reaction such attempts are seen less often. Hence, tardive dystonia has a dynamic aspect, whereas a conversion reaction looks more static. Furthermore, tardive dystonia often starts as a focal dystonia and progresses to a segmental form; a conversion reaction, on the other hand, does not progress over time and does not tend to increase during activity (Lang 1995;

Williams et al. 1995). However, in clinical practice the differentiation can be very difficult (Lesser and Fahn 1978; Lang 1995). A rule of thumb is that the presence of other tardive syndromes supports the diagnosis of tardive dystonia (Fahn et al. 1987; Burke 1992).

Dystonia can also be caused by compounds other than antipsychotics, such as levodopa (Poewe et al. 1988), carbamazepine (Crosley and Swender 1979; Jacome 1979), dextroamphetamine (Mattson and Calverley 1968), and diphenylhydantoin (Chadwick et al. 1976). Generally the dystonia disappears after the dose is reduced or the causative drug is stopped.

Idiopathic or primary dystonia can often be distinguished from tardive dystonia by taking a careful history about the time of onset of the dystonia in relation to start of antipsychotics. Furthermore, the prevalence of idiopathic dystonia in the general population is only 0.03 percent, which is much lower than the prevalence of tardive dystonia (Nutt et al. 1988).

Etiology

The pathophysiology of tardive dystonia is not clear. It is thought to result from postsynaptic supersensitivity induced by sustained inhibition of dopaminergic neurotransmission (LeWitt 1995). The antinoradrenergic action of the antipsychotics may also play an important role, because in idiopathic torsion dystonia, a reduction was found in the amount of noradrenaline in the hypothalamus, mammillary body, subthalamic nucleus, and locus ceruleus (Hornykiewicz et al. 1986). Furthermore, antipsychotics have strong affinities to sigma receptors, and there is a relationship between the sigma receptors and dystonia (Walker et al. 1988).

A search for a genetic cause of tardive dystonia was done on the *DYT1* gene on chromosome 9q34; early-onset primary dystonia in most Ashkenazi Jews is caused by a single founder mutation in this gene. However, there was no evidence that the *DYT1* founder mutation contributes to tardive dystonia (Bressman et al. 1997).

Prevalence and Risk Factors

Prevalence. Prevalence rates come from population-based studies and are highly dependent on the patient characteristics of the population involved and the method of case finding. Our research discovered 13 prevalence studies on tardive dystonia (see table 1). Only one study was conducted in an outpatient setting (Sachdev 1991); all other studies were conducted in a psychiatric hospital. Nine studies used the diagnostic criteria of Burke et al. (1982*a*), and some added a cutoff point on a rating scale

Table 1. Prevalence studies of tardive dystonia

Study	*n*	Prevalence (%)
Owens et al. 1982	411	2.7
Yassa et al. 1986[1]	351	2.0
Friedman et al. 1987[1]	331	1.5
Yassa et al. 1989[1]	555	1.4
Sethi et al. 1990	125	21.6
Inada et al. 1991[1]	716	2.1
Sachdev 1991[1]	100	1.0
Chiu et al. 1992[1]	917	0.4
Micheli et al. 1993[1]	878	0.9
Hoffman et al. 1994	119	11.0
Pourcher et al. 1995	64	6.3
Raja 1995[1]	200	4.0
van Harten et al. 1996*b*[1]	194	13.4

Note.— Mean prevalence of the nine studies using Burke's (Burke et al. 1982*a*) criteria = 3.0%, SD = 4.0; mean prevalence of all 13 studies = 5.3%, SD = 6.4.

[1] Used Burke's criteria for case definition.

(Friedman et al. 1987; Hoffman et al. 1994; van Harten et al. 1996*b*). About half the studies used rating scales (Yassa et al. 1986, 1989; Friedman et al. 1987; Sethi et al. 1990; Hoffman et al. 1994; Pourcher et al. 1995; van Harten et al. 1996*b*). The diversity of the rating scales used and the lack of consensus about a cutoff point makes it difficult to compare the prevalence rates. The prevalence figures reported in earlier studies (Owens et al. 1982; Yassa et al. 1986, 1989; Friedman et al. 1987) tended to be lower than those reported in more recent studies (Sethi et al. 1990; Hoffman et al. 1994; Pourcher et al. 1995; Raja 1995; van Harten et al. 1996*b*). A possible reason for this difference is that in earlier studies only patients with moderate to severe forms of tardive dystonia were considered as cases, whereas in later studies the diagnosis was also applied to mild cases. Our own study supports this explanation; we reported a prevalence of 13.4 percent when mild cases were included and a prevalence of 2.9 percent when only moderate to severe cases of tardive dystonia were considered (van Harten et al. 1996*b*). Also, the high prevalence found by Sethi et al. (1990) results from inclusion of very mild cases; only 20 percent of cases were symptomatic.

An estimate of the prevalence of tardive dystonia, calculated by taking the mean of all 13 prevalence rates, would be 5.3 percent. However, since not all studies used the same criteria for defining tardive dystonia, combining these data was inappropriate. When Burke's criteria (1982*a*) for defining tardive dystonia are used, nine studies can be combined to give a mean prevalence of 3.0 per-

cent. In these calculations each study is given equal weight; this method was also used in a review that estimated the prevalence of tardive dyskinesia (Kane and Smith 1982).

Risk Factors. To predict individual susceptibility and to develop preventive strategies, one needs to be able to identify risk factors. Since a risk factor must precede the occurrence of the illness, the most valid way to establish risk factors would be to conduct a prospective longitudinal study in a population without tardive dystonia and measure the risk factors in that population (Kraemer et al. 1997). Such a study could distinguish between factors that cause tardive dystonia and factors that affect the course of tardive dystonia once it has occurred. However, since no such study has been carried out for tardive dystonia, we have to derive our evidence from cross-sectional studies and case series. Therefore, the risk factors shown in table 2 must be interpreted with caution.

Treatment

The treatment strategy for tardive dystonia starts with an evaluation of the need for causative drugs, because antipsychotics are often prescribed for nonpsychotic conditions (Burke et al. 1982*a*, 1982*b*). However, if antipsychotics must be continued one can lower the dose as much as possible. Alternatively, a switch to an atypical antipsychotic can be considered. Of the atypical antipsychotics available, only clozapine has been reported—in several case reports and one open clinical trial—to have a beneficial effect on patients with tardive dystonia (van Putten et al. 1990; Lieberman et al. 1991; Friedman 1994; Trugman et al. 1994; van Harten et al. 1996*a*). No data exist about the relationship between the other atypical antipsychotics and tardive dystonia.

At the moment, clozapine is the first choice in the treatment of a psychotic patient with tardive dystonia; if clozapine is not tolerated, no other atypical antipsychotic can be recommended because of a lack of data. Treatment

Table 2. Risk factors for tardive dystonia derived from case studies and cross-sectional studies

Risk factors	Comment
Age	Patients with tardive dystonia are younger than patients with tardive dyskinesia (Gardos et al. 1987[1]; Yassa et al. 1989[2], 1990[2]; Chiu et al. 1992[2]; Sachdev 1993*b*[1]; Raja 1995[2]; van Harten et al. 1996*b*[2])
	Age at onset of tardive dystonia is lower than age at onset of tardive dyskinesia (Giménez-Roldán et al. 1985[1]; Yassa et al. 1989[2]; Miller and Jankovic 1990[1]; Inada et al. 1991[2]; Sachdev 1993*b*[1])
Sex	Male preponderance (Burke et al. 1982*a*[1]; Gardos et al. 1987[1]; Wojcik et al. 1991[1]) No difference in sexes[3] (Giménez-Roldán et al. 1985[1]; Yassa et al. 1986[2],1989[2], 1990[2]; Friedman et al. 1987[2]; Kang et al. 1988[1]; Miller and Jankovic 1990[1]; Inada et al. 1991[2]; Chiu et al. 1992[2]; Pourcher et al. 1995[2]; Raja 1995[2]; van Harten et al. 1996*b*[2])
Race	Extremely low prevalence in a Hong-Kong Chinese inpatient population (Chiu et al. 1992[2]) A Japanese study found rates similar to those in western studies (Inada et al. 1991[2]) No difference in prevalence rates between Afro-Americans and white patients (Sethi et al. 1990[2])
Other extrapyramidal syndrome	Increased risk (statistically significant) of tardive dystonia in patients with tardive dyskinesia (Hoffman et al. 1994[2]; van Harten et al. 1997[2]). One study found no significant relationship (Sethi et al. 1990[2]).
Other factors that may increase the risk	History of acute dystonia or essential tremor (Sachdev 1993*a*[1]). Affective disorder (Kang et al. 1988[1]; Wojcik et al. 1991[1]) Mental retardation, history of electroconvulsive therapy (Friedman et al. 1987[2])

[1] Case studies
[2] Cross-sectional studies
[3] The male/female ratio could be computed in 10 cross-sectional studies (Yassa et al. 1986, 1989, 1990; Friedman et al. 1987; Inada et al. 1991; Sachdev 1991; Chiu et al. 1992; Pourcher et al. 1995; Raja 1995; van Harten et al. 1996*b*). Five (Yassa et al. 1986, 1989, 1990; Friedman et al. 1987; and Raja 1995) of these 10 studies showed a male preponderance but none reached statistical significance (χ^2 test). However, if all data of the 10 prevalence studies are combined, the difference between males and females is highly significant. Of the 2,130 male patients, 60 had tardive dystonia, and of the 1,856 female patients, 27 had tardive dystonia; $\chi^2 = 8.62$, $p < 0.003$, relative risk 1.9.

with olanzapine was associated with a lower incidence of tardive dyskinesia and may be useful in the prevention of tardive syndromes (Tollefson et al. 1997).

If tardive dystonia does not improve after a switch to clozapine, adding a benzodiazepine such as diazepam, clonazepam, or lorazepam may be beneficial (Blake et al. 1991; Shapleske et al. 1996).

If the dystonia is relatively localized, as in focal or mild segmental forms, botulinum toxin should be considered. Botulinum toxin, the most potent biological poison known, is an important development in the treatment of dystonic features. Injected in minute quantities into the contorted muscles, it causes a permanent blockade of neurotransmission at the motor endplates by inhibiting acetylcholine release from nerve endings. This induces prolonged muscle weakness without systemic toxicity. The paralytic effect of botulinum toxin subsides over 8 to 12 weeks as new nerve terminals develop. Reinjecting the muscles restores the original beneficial effect (Moore 1995). According to several controlled clinical trials, botulinum toxin is the treatment of choice in idiopathic focal dystonias such as blepharospasm, cervical dystonia, oromandibular dystonia, laryngeal dystonia, and limb dystonia (Moore 1995). Although these trials were promising, they did not include patients with tardive dystonia. Recently, an open-label study showed that botulinum toxin is also effective in tardive dystonia. Thirty-four patients with relatively localized forms of tardive dystonia unresponsive to oral medications were injected with botulinum toxin. Cervical dystonia was the most frequent manifestation in this group of patients. Of the 34 patients, 29 showed marked or moderate improvement (Tarsy et al. 1997). A few case reports of patients with tardive dystonia support this treatment option (Stip et al. 1992; Kaufman 1994; Bharucha et al. 1995; Shulman et al. 1996). One study compared the treatment of tardive cervical dystonia and idiopathic cervical dystonia with botulinum toxin and, despite a difference in dosage, the results were similar (Brashear et al. 1998). If the dystonia is too comprehensive to use botulinum toxin, a trial can be conducted with either dopamine-depleting drugs (reserpine, metyrosine, or tetrabenazine) or high dosages of anticholinergics. However, the results are often disappointing (Burke et al. 1982*a*; Kang et al. 1988). Lisuride was studied in 42 patients with various types of dystonia. Eight patients improved, and the response was confirmed by double-blind placebo substitution (Quinn et al. 1985).

Other agents that have been described as helpful in case reports are bromocriptine (Luchins and Goldman 1985), deanol (McLean and Casey 1978), baclofen (Rosse et al. 1986), ceruletide (Sugawara et al. 1992), and verapamil (Abad and Ovsiew 1993). Some case reports describe a dramatic improvement after electroconvulsion therapy (Kwentus et al. 1984; Adityanjee et al. 1990; Jayaswal et al. 1990; Kaplan et al. 1991); one case report, however, described a worsening of the dystonia (Hanin et al. 1995).

Although classical antipsychotics should be avoided, they have the ability to suppress dystonia and are used in patients for whom all treatment strategies have failed or in patients in whom the dystonia causes severe pain or muscle damage (Kang et al. 1988; Burke 1992).

Peripheral and brain-surgical methods have been used in idiopathic or torsion dystonia (Fahn and Marsden 1987) but are seldom used in tardive dystonia (Burke et al. 1982*a*).

Discussion

About 3 percent of the patients on long-term treatment with dopamine receptor antagonists develop tardive dystonia, a syndrome that often causes substantial distress. Although the treatment of tardive dystonia substantially overlaps with the treatment of tardive dyskinesia, tardive dystonia benefits more from high doses of anticholinergics, and patients with relatively localized forms of dystonia may be treated with botulinum toxin.

If classical antipsychotics are continued, tardive dystonia probably will not disappear (Burke et al.1982*a*; Burke 1992). Therefore, as mentioned, a switch from a classical antipsychotic to an atypical antipsychotic, particularly clozapine, may alleviate the dystonia. However, because atypical antipsychotics are available only in oral form, such a switch may induce noncompliance in patients with limited motivation for taking medication.

Future studies should focus on the incidence and identification of risk factors in a longitudinal study. Furthermore, double-blind randomized trials with the atypical antipsychotics are needed to find out how effective a switch to an atypical antipsychotic would be for psychiatric patients suffering from tardive dystonia.

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