3 days exposure

Handbook of Dystonia

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Dystonia Caused by Drugs

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I. INTRODUCTION

Sustained muscle contractions, often twisting or repetitive and leading to abnormal postures, can be the outcome of neuroleptic medications and other drugs blocking central dopamine receptors. Besides dystonia, a variety of involuntary movement disorders can evolve gradually after prolonged use of dopamine-blocking medications. Research into the etiology of these disorders and the basis for their clinical variety had engendered many controversies (1–4). As a result, many practical issues pertaining to the use of such medications still await further understanding of risk factors for these abnormal movements. Strategies for effective control of these movement disorders are needed. Even 40 years after the introduction of dopamine-blocking drugs, it is not known why only a minority of patients will go on to develop troublesome and sometimes severely disabling movement disorders (5,6). Dystonic manifestations are among the most worrisome of these long-term adverse outcomes. Acute dystonic reactions can also occur with introduction of the same drugs, but they differ in several ways from the slowly evolving disorder, as will be discussed.

Some reactions to centrally acting dopamine-blocking drugs, such as sedation or the induction of Parkinsonism, will occur as a dose-related response in virtually every patient so treated. However, the other idiosyncratic reactions (sometimes described, imprecisely, as "extrapyramidal syndromes") do not seem to evolve as a function of dose. The first of these to be recognized, orofacial-lingual dyskinesia, is the most common movement disorder resulting from chronic neuroleptic drug use. Other involuntary movements can develop from sustained use of neuroleptics and other dopamine-blocking drugs. These include

tremor (7), myoclonus (8), Tourettism (9), and akathisia (10,11). Each of these has met criteria for exemplifying a "tardive" syndrome (although the rarity of these idiosyncratic reactions makes it difficult to establish definitively the link between the drug exposure and the causation of the movement disorder). In contrast to these uncommon disorders from sustained use of dopamine-blocking medication, tardive dystonia has been recognized for more than a decade as a distinctive syndrome. Most clinical evidence suggests that tardive dystonia is a discrete entity rather than one extreme of a continuum extending to tardive dyskinesia. Against this interpretation is the pattern of involuntary movements that can evolve in primary and acquired dystonias, in which hyperkinetic movements can coexist with posturing and sustained abnormal contractions. Not infrequently, dyskinesia and dystonia are found in the same individuals exposed to neuroleptics, implying that there might also be a shared pathophysiology in the drug-induced disorder.

The term *tardive dystonia* had its origin in nomenclature used to distinguish the other pattern of motor response that can develop suddenly after use of dopamine-blocking drugs. The acute dystonia induced by a neuroleptic or an antiemetic can occur within hours after a single dose or during the first few days of buildup in drug effect. Its manifestations, although sometimes quite bizarre, tend to be stereotyped and the diagnosis is rapidly confirmed by its response to pharmacological treatment. In contrast, tardive dystonia is more heterogeneous and overlaps the clinical spectrum of dystonic disorders that can affect adults on a sporadic basis. By definition, tardive dystonia results from the exposure to a dopamine-blocking medication, although the amount of exposure to such drugs varies greatly among patients. Beyond dopaminergic blockade, only a few risk factors are known to predispose for tardive dystonia (discussed below). There is no way to distinguish unequivocally between dystonia resulting from drug exposure and dystonia that might have evolved spontaneously on a sporadic basis.

Tardive dystonia was first described as such in 1973 (12). Other cases quite typical of this disorder were also reported in the medical literature, using varied terminology (13,14). In 1982, the first retrospective series on tardive dystonia was published (15). This collection of 42 cases detailed the variety of dystonic manifestations, and contrasted the different time courses of evolution in the movement disorder to the more common entity of tardive dyskinesia (such as orolingual-buccal dyskinesia).

Tardive dystonia has achieved increasing recognition in the past decade. Whether the greater attention given to it in the medical literature is due just to increased awareness is unclear. The potent neuroleptic medications that are widely used and the extensive use of metoclopramide may be responsible in part for the increased incidence of reports. In addition, there is now a greater degree of sophistication on the part of clinicians at distinguishing tardive dystonia from

the variety of "extrapyramidal syndromes" that can be caused by these drugs. The increased recognition of tardive dystonia by the psychiatric and neurological community is warranted, since this movement disorder can impart major disability. Tardive dystonia needs to be among the considerations for informed consent given by patients receiving dopamine-blocking medications. The irreversibility and paucity of treatment options for what can be a major disability need to be emphasized with respect to the risk for tardive dystonia.

Study of tardive dystonia's pathophysiology is hampered by the lack of an animal model or a clear focus on what drug actions produce the movement disorder. Tardive dystonia occurs on an idiosyncratic basis, and in only a small fraction of patients so treated. Most evidence suggests that the pharmacological mechanisms underlying tardive dystonia probably differ from those producing acute dystonia with dopaminergic receptor blockade. Like the other tardive syndromes mentioned above, the pathophysiology of tardive dystonia is thought to result from postsynaptic supersensitivity induced by the sustained inhibition of dopaminergic neurotransmission (4–6). However, other properties of these drugs—such as calcium channel blockade and effects on other neurotransmitter systems (16)—may also be involved in the pathogenesis of tardive dystonia.

II. TARDIVE DYSTONIA

A. Clinical Manifestations

The 42 subjects described in the first series of tardive dystonia patients were seen at movement disorder centers in New York City, Houston, and London (15). The average exposure to the neuroleptic therapy was 3.7 years. The mean age was 34 and ranged from 13 to 60 years. Most subsequent reports of tardive dystonia have also indicated that this disorder can originate at any age. In the 1982 study, as in later reports, some of the subjects with the drug-induced dystonia had it in combination with an orobuccal-lingual dyskinesia or another pattern of tardive movement disorder (15). The criteria used for designation of tardive dystonia include a verified exposure to an appropriate drug, the exclusion of all known secondary causes, or a family history of a dystonic disorder. The clinical appearance of dystonia did not differ from the ways it might present in its idiopathic variants (whether on an inherited or sporadic basis). However, in contrast to typical torsion dystonia, which often progresses to a state of bedridden disability, in the tardive dystonia group this degree of incapacity evolved in only one of the 42 subjects (15).

Other features noted further reinforce the uniqueness of tardive dystonia among other neuroleptic-induced movement disorders. In cases that ultimately had focal, segmental, or generalized involvement, patients did not begin with lower-extremity dystonic features (in contrast to the usual picture in

torsion dystonia of early-life onset). Age seemed to have an influence on the corporal distribution of the motor disorder. For example, patients developing this problem below the age of 30 had an increased tendency for developing a generalized dystonia, while older patients were more likely to have dystonic features restricted to a segmental or a focal distribution of the face, neck, or arms. For patients with a generalized pattern of tardive dystonia, the mean age of onset was 22.5 years. In contrast, those patients with a segmental distribution of dystonia were older, with a mean age of onset of 34 years. Those patients whose dystonic involvement was strictly focal were the oldest, with a mean age of onset of 41.4 years. Unlike the picture in dystonia occurring on an idiopathic basis, gender seems to exert an influence on the chance of developing tardive dystonia. The effect of gender does not seem to govern the outcome of how severe the movement disorder might be; the female:male ratio for developing tardive dystonia was 1.6:1 in the series of Burke and colleagues (15). In women, the mean age of onset was 41.5 years, while in men the mean age of onset was 29 years.

Each of the major classes of dopamine-blocking medications was represented in the study group. In addition to neuroleptic use, one patient's exposure resulting in tardive dystonia was to promethazine in the treatment of hyperemesis gravidarum. Exposure to the drug in this case (a neurologically normal woman who developed a persisting dystonia) was for only 3 days. For most patients, however, months to years of treatment preceded the development of the drug-induced dystonia. In general, many cases indicate that exposure to dopamine-blocking medications leading to tardive dystonia can be much briefer than that usually needed to induce tardive dyskinesia. Well represented among the cases are relatively small doses of low-potency neuroleptics such as thioridazine, a drug not infrequently implicated in the development of tardive dystonia (17). Over the past decade, numerous cases of tardive dystonia associated with the use of metoclopramide have been reported (18–21). Further review of tardive dystonia cases has confirmed that this disorder can duplicate the spectrum of primary dystonias. In general, tardive dystonia is distributed predominantly in a craniocervical distribution (15,19–23). A few cases have been reported in which the disorder began focally in an arm (22). Generalized dystonia as the initial feature, although reported in one instance (22), appears to be extremely rare. Of interest has been the concomitant occurrence of tardive dystonia with tardive dyskinesia. In one series (24), more than half of a group of patients with tardive dystonia also manifested orofacial dyskinesia at some point. In another report (25), only 16% of patients with a tardive movement disorder had exclusively dystonic manifestations resulting from neuroleptic use. Surveys of chronic involuntary movements in inpatients in psychiatric hospitals have stressed the intermingling of dystonic and dyskinetic movements (24,26). Tardive akathisia is another association reported in association with tardive dystonia (25). Another difference between

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tardive dystonia and tardive dyskinesia is that, even when both are simultaneous developments in the same patient, spontaneous recovery of the dyskinetic movements is known to occur even if dystonic features persist.

The onset of cranial tardive dystonia appears to take on the same patterns that can be seen in primary dystonia in adults. At the beginning, patients can experience nonspecific symptoms such as jaw stiffness or tight neck muscles (27). An early manifestation is often exaggerated eye closure. The increased blinking may merge into the continuum of sustained blepharospasm (24,28). Especially common in the early stages of tardive dystonia has been a segmental pattern of cranial and cervical involvement. One series (23) found that 82% of patients had facial movements such as grimacing or blepharospasm. Another report (22) indicated that neck or cranial involvement (or both) initially occurred in more than half, and ultimately in three-fourths, of patients with tardive dystonia. Sustained jaw movements (oromandibular dystonia), disturbances of respiration (sometimes with gasping or gulping), and awkward styles of swallowing have been observed. In instances such as these, distinguishing between dystonic and dyskinetic movements can be difficult, if not arbitrary. Dystonic impairment of phonation and swallowing has been observed. Interference with respiration can be so severe as to cause major obstruction to breathing. To treat this problem, patients have had a tracheostomy that is maintained open during the daytime occurrence of hyperkinetic movements (29).

Several reports have emphasized the high incidence of neck and upper-back involvement in tardive dystonia. This generally takes the form of retrocollis, arching backward of the trunk, or axial twisting. Of seven dystonic patients found in a psychiatric hospital population of 351, six were affected with torticollis, lordosis, or opisthotonos, or combinations of these patterns (30). One series indicated that when limb dystonia occurred, the likelihood that the arms would be affected by dystonia was more than double the 17% incidence in the legs (22).

Less common patterns of tardive dystonia include sustained conjugate deviation upward of the eyes, a dystonic state resembling the oculogyric crises that can occur acutely after administration of dopamine-blocking drugs (31,32). Rarely, dystonic movements may evolve only during specific activities such as chewing or speaking. Bruxism as a chronic movement disorder with dystonic features has been described (33). Tardive dystonia does not usually lead to writer's cramp or other task-specific activities. However, any fine motor activity can be severely hindered in some individuals with tardive dystonia. Walking can take on an odd appearance, and the dystonic features may be brought out only in specific ways (such as during tandem gait, backward walking, or climbing steps). Phenomena such as "trick" maneuvers that can momentarily disrupt neck pull or other dystonic manifestations may occur. Some patients may find it beneficial to lean against firm surfaces or to flex the neck while extending the arms during manual activities.

There has been little long-term follow-up of tardive dystonia to learn how often recovery occurs. Clearly, the frequent reduction or remission in involuntary movements that characterizes tardive dyskinesia is not the usual course for tardive dystonia. Some patients have actually worsened gradually over the weeks or months following the discontinuation of the neuroleptic drug. In a retrospective analysis of 67 patients (22), the clinical course of their tardive dystonia was followed. Clinical features pertaining to the distribution and other aspects of the disorder did not seem to have an effect on the likelihood of spontaneous or medication-related improvement.

There has been relative conformity among recent studies with the original descriptions of the risk profile for tardive dystonia. The increased likelihood that younger males will develop a tardive movement disorder that is dystonic rather than dyskinetic was found in other studies (24,34,35). The increased risk for males of developing this disorder may be as high as 2.4:1 (36). It is not known to what extent a family history of dystonia or other movement disorders might add to risk for tardive dystonia. A gait abnormality may also add to the predisposition for tardive dystonia (24). Prior brain injury or electroconvulsive therapy also appear to be risk factors (22,24,37). In patients with bipolar mood disorder, a curious relationship between mood elevation or manic state and the occurrence of tardive dystonic features has been described (38,39). Psychiatric diagnosis has not been fully characterized in all the studies reporting on the overall incidence of tardive dystonia in the chronically hospitalized (a rate ranging from 0.4 to over 2%) (26,40–42). Whether prior occurrence of acute dystonic reactions or of essential tremor are actually risk factors for tardive dystonia, as has been reported in a small series of cases (43,44), remains to be confirmed. In evaluating any putative case of tardive dystonia, one needs to consider that factors predisposing to tardive dystonia might also lead directly to the causation of the movement disorder without the intervening factor of the drug (45,46).

B. Treatment

Strategies for lessening the severity of sustained abnormal contractions associated with tardive dystonia are essentially the same as those usually tried with primary dystonias. There has been no systematic analysis of medications for tardive dystonia, and anecdotal reports are confounded by discontinuation due to adverse effects, changes in psychiatric state leading to alterations of neuroleptic regimens, and the possibility that the disorder can change spontaneously after the dopamine blockade has been discontinued. Nevertheless, many patients have received trials of a variety of drugs and occasionally show good responses. Most experience in established movement disorder clinics indicates that benzodiazepine and anticholinergic drugs can be quite helpful for some patients. In one study, possible or definite improvement occurred in 13 of 23 patients with an anticholinergic drug

and in 16 of 23 with a benzodiazepine (28). While benztropine and trihexyphenidyl do not seem to differ in their clinical utility, clonazepam appears to be superior to other benzodiazepines in its properties to quell involuntary movements and dystonic muscle contractions. Effective clonazepam doses usually range from 1.0 to 6.0 mg/day, as tolerated. Experience with anticholinergic drugs (especially trihexyphenidyl) has indicated a wide therapeutic range for dosing, sometimes exceeding usual doses of these drugs by a factor of 10 or more if adverse effects do not preclude such dosing. The benefits achieved at such high intake raise the question that an alternative mode of action besides cholinergic blockade may be operative.

Rarely, the use of an anticholinergic can precipitate (or unmask) tardive dystonia, a paradoxical response that has also been described with tardive dyskinesia and akathisia (47). In two patients in whom typical features of tardive dystonia improved with trihexyphenidyl, 15 mg/day, choreic movements were observed to increase (48).

Other medications that have provided symptomatic relief for dystonic disorders include baclofen [sometimes in dosage exceeding that for its usual application in treating spasticity (27,49,50)] and tetrabenazine. The latter drug, which acts like reserpine in depleting dopamine from nerve terminals, can be useful for lessening both dystonia and dyskinetic movement (51,52). Among the treatments of last resort is reinstitution of neuroleptic medications. Despite the risk posed for further exacerbation of tardive dystonia, some patients do not experience any change in their dystonic or dyskinetic state with continued use of dopaminergic blockade. One report describes no effect on tardive dystonia from clozapine, 600–900 mg/day, although clonazepam was beneficial (53). In another instance, clozapine use (225 mg/day) was associated with the suppression of dystonia, although some mild lip and neck movements persisted (54). Benefits in all types of tardive movements have been seen by others (55).

Other therapeutic strategies have been used in recent years. Bromocriptine in high doses has been helpful in one case of tardive dystonia (56) and in some cases of primary dystonia (57). One case report of a double-blind placebo-controlled trial describes neck-jerking controlled with propranolol (47). Diltiazem has also been claimed to suppress tardive dystonia (58). Focal dystonias involving the face and neck can be substantially lessened by selective denervation with botulinum toxin (59). As in other forms of dystonia, in most instances both spasmodic movements and sustained pull can be controlled with a moderate to major improvement of discomfort and disability. Truncal or limb dystonias are less likely to be helped with injections of botulinum toxin. In patients with retrocollis or other torsion of the trunk, however, painful spasms or abnormal head and neck positioning can be effectively controlled.

Treatment for tardive dystonia is, at present, entirely symptomatic, and no therapy has been demonstrated that can effect an improvement in the underlying

condition. However, the discontinuation of a neuroleptic medication probably offers the best chance for improvement. Since tardive dystonia is often a progressive disorder, ceasing the dopamine-blocking medication at the earliest instance may lessen the severity and the evolution of the dystonia. Unfortunately, the likelihood for remission of tardive dystonia is far less than for other conditions such as tardive dyskinesia (22,24).

III. ACUTE DYSTONIA FROM DOPAMINERGIC BLOCKADE

The acute dystonia following the start of a dopamine-blocking drug has been much more familiar to clinicians than tardive dystonia or other tardive syndromes of movement disorder. These reactions occur in 5% or more of neuroleptic-treated patients (60,61). The condition is well known to psychiatrists. However, the unexpected occurrence of its dramatic manifestations might be regarded as a neurological "emergency" to an inexperienced clinician, who may not recognize that an antiemetic or metoclopramide can also generate these adverse effects. The cause–effect relationships between the drug and dystonia are evident in the timing: the typical patient who develops acute dystonia from oral medication does so on the second day, and almost never after the fourth day, of continued treatment (62). Dystonic reactions can evolve following an increase in a previously stable chronic regimen of a dopamine-blocking medication. Like acute akathisia, acute dystonic reactions are idiosyncratic reactions that are not necessarily linked to the mechanisms of antipsychotic effect. In fact, oculogyric crises or sudden dystonic posturing can provoke a great deal of anxiety in an individual immobilized by this condition.

Acute reactions are generally stereotyped axial and cranial dystonias. Torsion of the trunk (especially backward) is more common in younger individuals, especially males (62,63). Older individuals tend to have more cranial manifestations, such as jaw-opening or -closing, a clenching sensation of the throat, and dystonic arm postures. Oculogyric deviation with altered head position is commonly seen with acute dystonic reactions. The sustained state of eye deviation (oculogyric "crisis") can resemble similar clinical manifestations observed in the era of von Economo's encephalitis. Conjugate deviation of gaze is upward, sometimes to one side, toward which the head is also deviated. With head-posturing there can be involuntary twisting of the head to the side or backward, which can cause considerable pain in the involved muscles. A patient may be unable to sit because of an associated kinetic component of the dystonia, or possibly an akathisia. Although the rigid state of parkinsonism can be induced simultaneously, the asymmetrical and upper-body site of predilection is usually clearly distinguishable from the other manifestations of dopamine blockade. The stereotyped clinical manifestations sometimes recur in identical fashion for a

patient who has previously experienced them. In some instances, the rigid state and agitation of the patient may raise appropriate concerns that he or she is experiencing the earliest stages of neuroleptic malignant syndrome (64).

When acute dystonia of the neck is the only manifestation, the problem can resemble nothing more than a sudden neck strain. In other settings, the features can have a peculiar and distressing quality. A sense of choking or tightening in the throat can be manifested in the voice or in swallowing. In very rare instances, the prominence of laryngeal or pharyngeal contraction may be severe enough to compromise respiration (64,65).

Certain factors increase the risk for experiencing an acute dystonic reaction. Drugs of increased potency (or large doses of low-potency agents such as thioridazine) are more commonly associated with these responses. Antipsychotic regimens of greater than 1400 mg/day of chlorpromazine equivalents, however, have a lower incidence of dystonic reactions (66). The vulnerability for this idiosyncratic reaction best correlates to age and gender. As in tardive dystonia, the risk for males is at least double that for females. The incidence of acute dystonic reaction declines linearly with age, with occurrence rates approximately halved from the second to the fourth decade (67). Among the variety of "extrapyramidal reactions," such as parkinsonism or akathisia, that can occur with neuroleptic drugs, one study showed that almost one-third are acute dystonic reactions (68). When patients who have experienced acute dystonia are followed for more than a year, there is a strong likelihood of a second episode of acute dystonia if medications are not taken to prevent this reaction. There may be some increase of risk contributed by conditions such as recent cocaine use, hypocalcemia, hypoparathyroidism, hyperthyroidism, or familial history of dystonia (69).

The evidence for dopaminergic blockade as an etiological mechanism is even stronger for the acute as compared to tardive dystonia. Anticholinergic drugs can effectively reverse acute dystonia. Even relatively low-potency anticholinergics, such as diphenhydramine, are adequate for most situations. The dose does not seem to be critical for achieving optimal effects. However, the short pharmacokinetic profile of these drugs, when given parenterally, may permit a reemergence of dystonia as the effect of the anticholinergic declines. Drugs with a longer plasma half-life, such as the sustained-release form of trihexyphenidyl, may be a good therapeutic choice when given at the same time as an injection of this or another anticholinergic drug. There may be synergism in effect by also treating patients with a benzodiazepine. This strategy may be especially helpful in the setting of anxiety and discomfort produced by the dystonic reaction. The possible role for other pharmacological approaches has been suggested (69). Experimental approaches to the treatment and prevention of acute dystonia implicate a combination of events pertaining to dopaminergic neurotransmission, and possibly other systems, such as the sigma opiate receptor (70). The complexity of neuroleptic-induced dystonia is emphasized by the report of an acute

reaction of retrocollis and orolingual dystonia in a patient receiving 400 mg/day of clozapine. This drug is known to exert only a weak blockade of dopamine D-2 receptors (71). There have been no other reports of acute dystonia with clozapine, and this reaction occurred following the cessation of diazepam, confirming other observations that the benzodiazepine class of drugs may also provide prophylaxis against acute dystonia (72).

Many clinicians routinely use continuing anticholinergic therapy as a means of averting dystonic reactions. There is no evidence that tardive dyskinesia or dystonia can be avoided, nor is there evidence that sustained use is necessary. Since the risk profile for acute dystonia follows the start or rise of dopamine-blocking medication, a short course of therapy is probably most appropriate. If discontinuation of anticholinergic treatment is associated with the emergence of features of parkinsonism, this therapy can be continued for a good reason. Sometimes amantadine is better tolerated for relief of parkinsonian signs and symptoms, and this drug too appears to provide prophylaxis against acute dystonic reactions. The first experience of a dystonic or other "extrapyramidal" type of reaction is associated with an increased risk for recurrence, although the ability to predict the likelihood of a second episode is quite limited (68).

IV. OTHER EXAMPLES OF DRUG-INDUCED DYSTONIA

Other drugs have been associated with various forms of dystonia, as rare side effects of an idiosyncratic nature. Dystonic reactions can occur after excessive dosing with phenytoin, and similar movements might conceivably be in the spectrum of involuntary movements associated with toxicity of other anticonvulsants as well (73). Two drugs related to quinine—amodiaquine (74) and chloroquine (75)—can also produce dystonia. Buspirone, a nonsedative anxiolytic, has been described to induce dystonia on rare occasions, and an exacerbation of a pre-existing dystonia has been reported (76). Buspirone's actions may be through its minor actions on dopamine receptors or dopamine turnover. Another means of abruptly decreasing catecholaminergic neurotransmission—administration of alpha-methyl-para-tyrosine—can result in dystonia (77).

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