Movement Disorders in Neurology and Neuropsychiatry

SECOND EDITION

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Drug-Induced Dyskinesias: An Overview

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INTRODUCTION

The term *dyskinesia* describes any abnormal involuntary movement, irrespective of etiology. It is commonly used in the context of drug-induced repetitive and stereotypic orofacial movement that persists even after the offending drug has been stopped; hence the term *tardive dyskinesia* (TD). While most drug-induced dyskinesias occur in a form of stereotypy, defined as a repetitive, coordinated, seemingly purposeful movement, other drug-induced dyskinesias are manifested by dystonia, chorea, tics, myoclonus, tremor, and miscellaneous involuntary movements (1). Orofacial stereotypy is the most typical presentation of TD, but repetitive orofacial movements can also occur spontaneously, as in edentulous elderly individuals (2–6). This review will focus on drug-induced dyskinesias.

Most drug-induced movement disorders are caused by dopamine receptor blocking drugs, also known as neuroleptics. The term *neuroleptic* which literally means "that which takes the neuron," was coined by Deniker (7) to denote a class of "major tranquilizers." The use of the word has broadened to include antipsychotic and antiemetic drugs that block dopamine receptors.

Involuntary buccolingual masticatory movements (e.g., chewing, puckering, smacking, "fly-catching" movements of the tongue) are the most recognized manifestations of TD. Choreic movements of the fingers, hands, arms and feet also occur in TD (8). In respiratory dyskinesias, the diaphragm and chest muscles are involved resulting in noisy and difficult breathing (9). Dyskinesia may also involve the abdominal and pelvic muscles producing truncal or pelvic rocking movements ("copulatory" dyskinesia). Other forms of TD include tardive dystonia (10–14), tardive tourettism (11,15,17–22), tardive myoclonus (23,24), tardive akathisia (25), and tardive tremor (26). Parkinsonism may also result from the same drugs that cause the hyperkinetic movement disorders, and the two types of movement disorders can coexist (27,28).

TD is the most recognized complication of neuroleptic therapy, but neuroleptic drugs can produce a variety of movement disorders. Acute dystonia, a sustained twisting movement, often occurs immediately after drug exposure (29). This acute dystonic reaction usually resolves spontaneously, but tardive dystonia can occur and persist as a permanent complication of neuroleptics (10–13). Akathisia, a feeling of restlessness, often presents within three months of neuroleptic use but may persist as tardive akathisia after the offending drug is stopped (30). Ninety percent of the patients with drug-induced parkinsonism (DIP) have the onset of symptoms within three months of initiation of neuroleptic treatment (31,32). Tardive dystonia and TD usually present after months to years of neuroleptic therapy (10,33).

Since the recognition of the predominant phenomenology of the movement disorder is critical to correct categorization, it will be discussed first. The pharmacology of specific drugs causing movement disorders and treatment of drug-induced movement disorders will be reviewed in the second half.

HISTORICAL BACKGROUND

With the introduction in 1952 of chlorpromazine (Thorazine; Smith, Kline and French Laboratories) came a dramatic improvement in the care of psychiatric patients. Effective outpatient care became possible, lessening the burden of inpatient admissions. In 1956, however, an emergence of abnormal movements as a complication of neuroleptic therapy was first documented (34). It is likely that movement disorders were seen earlier but were not

improving as compared with older patients (42). In a study of 13 psychiatric patients with TD, over half (53.8%) remitted during follow-up (mean follow-up: 1.6 years). The group's average age at onset was 62 years (range: 53–79) (11). Twenty-seven psychiatric patients were studied serially over a five-year period to determine if adjusting or eliminating the neuroleptic dose could substantially affect the long-term prognosis of TD (57). The majority of the patients improved by more than 50% with 29.6% (n = 8) experiencing total resolution of TD.

TD may be combined with other movement disorders, including parkinsonism. In a study of 132 psychiatric patients, 23 (17.4%) had coexistent TD and parkinsonism (25). In another study of 46 patients with TD, 15 (33%) had concurrent parkinsonism (28). In this series, patients with parkinsonism associated with TD had a later age of onset of TD (seventh or eighth decade) than those patients who experienced TD alone (mean age of onset: 54 years) (28). The coexistence of TD and parkinsonism seems to be an expression of opposite pharmacologic mechanisms, where parkinsonism is a consequence of dopamine depletion and TD reflects an excessive response to dopamine. It has been explained in terms of regional differences. For example, postsynaptic receptor supersensitivity in one region of the basal ganglia may be expressed as TD while parkinsonian symptoms may appear consequent to dopamine depletion in another area (28).

Tardive Tremor

Tardive tremor is a relatively rare form of TD (26). This rhythmic movement is distinguishable from the more common stereotypy in that it consists of an oscillatory movement rather than coordinated, seemingly purposeful movement seen in tardive stereotypy. Tardive tremor differs from tremor observed in patients with Parkinson's disease in that it is predominantly postural and kinetic and it is not necessarily accompanied by other parkinsonian signs. Tardive tremor does not respond to therapy conventionally used for essential tremor or Parkinson's disease but rather improves within 30 to 60 minutes of tetrabenazine administration (26). In contrast, tetrabenazine would be expected to exacerbate parkinsonian tremor. In the absence of other etiologies for tremor, such as hyperthyroidism, the diagnosis of tardive tremor should be considered.

Tardive Dystonia

Tardive dystonia is a persistent dystonic movement disorder and therefore it differs from acute transient dystonic reaction (10–13). Criteria for its diagnosis include the presence of chronic dystonia, prior or concurrent neuroleptic use, exclusion of known causes of secondary dystonia, and a negative family history for dystonia (12). Characterized by sustained, patterned, slow or rapid twisting movements involving the face, neck, trunk, or limbs, tardive dystonia may occur after only three days of antipsychotic treatment, but usually it follows months of neuroleptic therapy (Figure 2.2) (13). The face and neck are the most frequently affected regions at onset and are also most frequently involved at the time of maximum severity of illness (13). Nearly half of the patients with neck involvement displayed retrocollis (Figure 2.3). The dystonic movements usually subside during sleep and are often relieved by tactile maneuvers, referred to as sensory tricks or geste antagonistique (13). The dystonic movements may be superimposed on stereotypic rapid jerking movements of TD. Coexistent TD was seen in 14 (21%) of 67 patients with tardive dystonia (13).

Because of resemblance to typical tardive dystonia, idiopathic dystonia with blepharospasm-oromandibular dystonia (Meige's syndrome) is frequently misdiagnosed as tardive dystonia, even though there is no history of neuroleptic exposure (58,59). Although there is no universal agreement, most authorities believe that if there is no history of neuroleptic use for at least six months prior to the onset of the movement disorder, then it could not be considered "drug-induced" (Table 2.2) (13). Tardive dystonia has been noted in 1.5% (5 of 331) of patients hospitalized in a psychiatric hospital (60). However, in another study, 21% of 125 patients in a Veterans Administration psychiatric facility had tardive dystonia (61). Mental retardation and electroconvulsive therapy were identified as risk factors for this movement disorder (60).

Tardive dystonia, frequently more disabling than classic TD, may be more persistent (12). In a study of nine psychiatric patients with tardive dystonia examined for an averaged follow-up period of 2.5 years (range: 4 months to 8 years), no spontaneous remissions were encountered (11). In other studies, five (12%) of 42 patients and five of 67 (7.5%) experienced spontaneous remission of tardive dystonia, respectively. This occurred within 2.4 years from onset

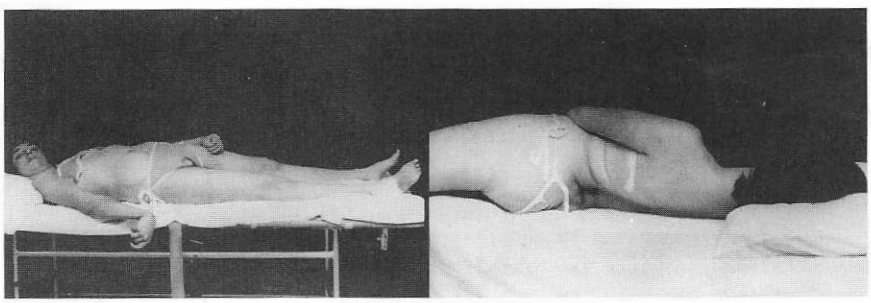

FIGURE 2.2 *A young schizoprenic woman with generalized tardive dystonia producing dystonic flexion of hand (left) and opisthotonic trunkal extension (right).*