

# Neurological Syndromes Associated With Antipsychotic Drug Use

## A Special Report

**A**cute dystonias, akathisia, and parkinsonism have long been recognized as extrapyramidal side effects which occur in susceptible individuals who are taking neuroleptic (antipsychotic) drugs. These side effects often occur early in treatment and they usually respond to dosage reduction and/or the addition of corrective medication.

More recently a quite different syndrome, tardive dyskinesia has been found to be associated with antipsychotic drug use. Many aspects of the characteristics, etiology, prevention, and treatment of this variegated set of symptom complexes are very unclear at this time. However, patients who clearly show this syndrome are not uncommon and the condition sometimes persists with little improvement for periods of one to two years or indefinitely. The condition does not respond to antiparkinsonian medication. The Neuropharmacology Division of the Bureau of Drugs, the Food and Drug Administration (FDA), and the American College of Neuropsychopharmacology have recognized the seriousness of these complications and established a joint task force to (a) revise the package insert for these agents and (b) distribute other material for education of all physicians in the use of these drugs. This paper is one component of that effort. A brief article has appeared in the *FDA Drug Bulletin* and, as an interim measure, the FDA has added the following statement under the "Adverse Reactions" section of the package insert of antipsychotic drugs:

### **Tardive Dyskinesia**

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to

reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and if the medication is stopped at that time the syndrome may not develop.

The purpose of this editorial is to review our current knowledge about tardive dyskinesia and to contrast it with other neurological conditions associated with antipsychotic drug use. Hopefully, this paper will aid the practicing physician in diagnosing these conditions and in deciding what clinical practices are indicated.

In our opinion, the antipsychotic drugs are uniquely necessary to the effective treatment of schizophrenic illnesses. The limited information available on tardive dyskinesia, in particular, must be utilized with this fact in mind. To clearly differentiate other drug-related extrapyramidal disorders from tardive dyskinesia, the other conditions will be discussed first.

### **Acute Dystonic Reaction**

Acute dystonic reactions are of sudden onset and consist of bizarre muscular spasms which have been misdiagnosed as tetany or hysteria. The muscles of the head and neck are predominately affected, and the most commonly noted feature is an involuntary spasm of tongue and mouth muscles leading to difficulties in speaking and swallowing. The masseter muscles may be tightly contracted, in which case the mouth cannot be opened. Facial grimacing may also be prominent. The neck muscles are also frequently affected; thus opisthotonos, torticollis, etc, can occur and may be associated with oculogyric crisis, ie, spasm of the external ocular muscles with painful upward gaze persisting for minutes or hours. The back, arm, and leg muscles are less frequently affected but, when they are, they can produce bizarre gaits and difficulty in walking. The acute dystonic reactions usually take place within 24 to 48 hours from start of medication and occasionally may occur or recur when there is an increase in dosage. Acute dystonic reactions occur more often in young people than in old, and more frequently in males than in females. The occurrence of this phenomenon appears to be a matter of individual sensitivity as well as of the dose and type of antipsychotic drug administered. These reactions are easily treated by parenteral adminis-

tration of a wide variety of agents, eg, antihistaminics, barbiturates, and antiparkinson agents. Response is dramatic and continued medication is usually not required.

### **Akathisia**

Akathisia refers to a subjective desire to be in constant motion rather than any specific motor pattern. Affected individuals complain of an inability to sit or stand still and of a drive to pace up and down. The subjective feeling of muscle discomfort often precedes the onset of observable motor restlessness. Further subdivisions of this phenomena, such as *tasikinesia* or restless legs are included in this category.

Akathisia may occur early in treatment and is sometimes mistaken for psychotic agitation; this clinical error can lead to an unnecessary further increase of the antipsychotic medication. The use of parenteral antiparkinson agents at this stage may produce an immediate response to the condition; however, it is not unusual for this type of extrapyramidal side effect to show an inadequate response to antiparkinson medication, and it is frequently necessary to reduce the dosage of the antipsychotic medication or add a sedative agent such as diazepam or diphenhydramine hydrochloride. Treatment may then be continued with combined antiparkinson medication and after a few weeks or months, the gradual withdrawal of this latter agent may be undertaken.

### **Parkinsonism**

This condition may be clinically indistinguishable from postencephalitic-parkinsonism or idiopathic parkinsonism. It occurs at varying time intervals after initiation of antipsychotic drug therapy at conventional dosage levels. Like the dystonias, it can be patient-related or dose-related. Thus, very high doses of medication can (but do not always) rapidly produce a parkinsonian picture. The signs are similar to those of the classical illness: ie, the first signs are usually a reduction in facial movements followed by a reduction in arm movements. Fully developed cases have a generalized slowing of volitional movement, tremor at rest especially involving distal upper extremities, and rigidity. Treatment is by reduction of dosage and/or addition of conventional antiparkinson agents.

### **Tardive Dyskinesia**

Tardive dyskinesia which has also been called "terminal extrapyramidal insufficiency," "complex dyskinesia," and "persistent dyskinesia," is a reasonably well-defined clinical entity which can conceivably occur after several weeks or months of neuroleptic treatment but is usually observed only after several years of treatment. In an unknown percentage of cases, the syndrome is apparently irreversible and can be called "permanent dyskinesia." Paradoxically, it may appear for the first time shortly after antipsychotic drug treatment has been discontinued; antipsychotic agents can suppress the dyskinesia by inducing a mild parkinsonism. The incidence of the condition is almost impossible to state with any assurance since no clear criteria exist on which to base a diagnosis of minimal tardive dyskinesia and most reported prevalence surveys do not adequately define the population studied. It is

rarely seen in acute psychiatric units, even in patients with recurring schizophrenia; and prevalences on the order of 20% have been reported in very chronic, older institutionalized patient groups. Perhaps 3% to 6% of patients in a mixed psychiatric population receiving neuroleptics would exhibit some aspects of this syndrome at one time or another. Patients with symptoms overt enough to be recognized by a casual observer are not uncommon. Patients with severe and incapacitating symptoms are quite rare, fortunately.

The syndrome is more likely to be present in elderly patients and may well be more common in females and in patients with a prior history of brain damage.

A syndrome resembling tardive dyskinesia has been reported to occur in children receiving antipsychotic medication. In contrast to the adult syndrome, the mouth and face were affected rarely while repetitive choreiform movements of the extremities were most common. In one published study, these movements disappeared over a one-year period in all ten children studied. In an unpublished report, half the 18 affected children had complete disappearance of the syndrome within a month. In both studies the syndrome was detected only *after* antipsychotic medication was stopped. There are informal reports of similar phenomena occurring in adult psychiatric patients after only a few months of treatment. Again the syndrome disappeared after a few weeks or months. It is unclear whether or not the above more transient conditions should be called tardive dyskinesia.

**Description.**—Tardive dyskinesia as usually seen in older, more chronic patients is characterized by stereotyped, repetitive, involuntary movements of the mouth, lips, and tongue and sometimes accompanied by choreiform movements of the limbs or trunk.

The most widely described symptoms make up the "bucco-linguo masticatory" (BLM) triad; this consists of sucking and smacking movements of the lips, lateral jaw movements, and the tongue will thrust, roll, or have fly-catching movements. This movement may be carried on with the mouth closed, in which case the tongue will hit the inside of the cheek and a chewing-the-cud type of movement will be seen. While the BLM syndrome is the most frequently described and seen, it is by no means the only mode of onset. Sometimes tic-like movements involving the lips and eyes may antedate these symptoms and other parts of syndrome to be described later may also appear first. The oral movements usually worsen under emotional tension; they disappear during sleep.

The extremities may show choreiform movements which are variable, purposeless, involuntary quick movements. They sometimes intensify on attention but are irregular in occurrence. Frequently associated with these symptoms are athetoid movements which are continuous arrhythmic worm-like slow movements in the distal parts of the limbs. The choreo-athetoid movements particularly affecting the arms and fingers are to be differentiated from schizophrenic stereotyped movements.

Another feature of the syndrome may be axial hyperkinesia; ie, a to-and-fro clonic movement of the spine in the interoposterior direction, a rare symptom, but one that has been seen as the only manifestation of the syn-

drome. Ballistic movements can also occur, as can rhythmical swaying movement of the body from one side to the other which can take on a rocking quality if the patient sits down. All of these features are seldom present at the same time, but the BLM signs, plus choreo-athetoid movements of the limbs with an inability to stand or sit still, are frequent grouping of signs in severe cases. All involuntary movements disappear during sleep.

Parkinsonian symptoms can coexist with tardive dyskinesia.

**Characteristic Features.**—Tardive dyskinesia should not be confused with the acute dystonic phenomenon described above. The tardive syndrome is characterized by:

1. A late onset. The patient has usually received neuroleptic drugs for many years, often while chronically hospitalized.

2. The manifestations may be masked by the neuroleptic drugs which the patient is taking and thus will only be seen if the drug is discontinued or the dosage markedly reduced.

3. In many cases the tardive dyskinesia symptoms will lessen or disappear, at least for a time, if large amounts of potent neuroleptic drugs are given to the patient, but this mode of therapy is not recommended lest a vicious circle occur.

4. *Persistence* of the symptoms after the discontinuation of the medication is its most single characteristic manifestation. Involuntary movements may persist for weeks or years and, in some patients, they may persist indefinitely.

5. Full-blown cases of tardive dyskinesia may gradually subside if the neuroleptic drugs are discontinued, but other approved methods of successful therapy are so far lacking.

6. Younger patients, and those whose symptom complex is less well developed, may clear in relatively short periods of time after the discontinuation of neuroleptic agents.

**Differential Diagnosis.**—Abnormal movement disorders occur in some patients who have never received neuroleptic drugs. Depending upon the type of onset, a differential diagnosis might include Sydenham's chorea, Huntington's chorea, congenital torsion dystonias, hysteria, and the stereotyped behavior or mannerisms of schizophrenia.

**Early Detection.**—The full-blown picture of tardive dyskinesia is easy to diagnose but early cases are frequently missed. Possible early signs are the presence of tics in the facial region, ill-defined abnormal mouth or eye movements, mild mouthing or chewing movements, the presence of rocking or swaying movements, or the occurrence of restless limb movements in the absence of the subject's discomfort associated with akathisia.

The temporary withdrawal of antipsychotic medication can be used as a way of detecting underlying early tardive dyskinesia.

**Possible Etiology.**—Tardive dyskinesia resembles the abnormal movements seen with parkinsonian patients on levodopa treatment and is suppressed by antipsychotic drugs including the phenothiazines and haloperidol which may block dopaminergic synapses and by tetrabenazine and reserpine which deplete the brain of dopamine. It is therefore possible that tardive dyskinesia in some way is

related to excessive dopaminergic activity in the brain.

**Treatment.**—Antiparkinsonian agents do not relieve tardive dyskinesia and may aggravate it. Since tardive dyskinesia is presumably a result of treatment with antipsychotic drugs, it seems reasonable to withdraw such drugs entirely once the condition is diagnosed. On the other hand, in our current state of ignorance it is impossible to tell whether or not continued antipsychotic medication will aggravate the condition. In the rare very severe cases with mouth lesions or respiratory symptoms, an antipsychotic drug may have to be used to relieve the patient's distress.

In chronic patients whose clinical state remains stable without antipsychotic drugs, complete withdrawal is indicated. In patients whose psychosis worsens when these drugs are removed, a clinical choice between two evils must be made. The use of the lowest possible dose of antipsychotic drug adequate to control psychopathology would appear to be the best thing to do. In the absence of any real data indicating that any particular antipsychotic drug is more likely to be associated with tardive dyskinesia than any other, a patient with tardive dyskinesia needing such a drug might well be given the drug least like the one on which dyskinesia emerged. The use of sedative or antianxiety drugs may occasionally enable the clinician to avoid resorting to an antipsychotic agent.

Although some patients show little or no improvement in the dyskinesia even after months or years of drug withdrawal or minimal antipsychotic use, the condition does not usually progress in severity and some patients gradually improve or recover completely.

**Prevention.**—Because of the lack of adequate substitutes for the neuroleptic drugs in the treatment of psychosis, tardive dyskinesia has been accepted as an undesirable but occasionally unavoidable price to be paid for the benefits of prolonged neuroleptic therapy. However, the physician may be able to reduce the risk of this syndrome by:

1. Minimizing the unnecessary use of neuroleptic medication (especially at high doses) in long-term patients. Many chronic patients can be satisfactorily maintained for long periods without antipsychotic drugs. Drug holidays in patients receiving long-term medication are advised for the following reasons: first, and most importantly, they allow the doctor to ascertain whether or not the patient has evidence of tardive dyskinesia. If the patient presents these symptoms, every effort should be made to treat him without the use of neuroleptic drugs. Second, the occasional discontinuation of the drug may afford a small amount of protection from the long-term hazards of these otherwise very useful agents.

2. If possible, neuroleptics should be discontinued at the first sign of abnormal oral movements or other manifestations of tardive dyskinesia. Some neurologists suggest that fibrillation of the tongue is a significant warning sign.

3. These precautions should be carefully observed in the elderly (women especially) and probably in all over age 50.

It should be recognized that the above recommendations have evolved in the absence of any clear evidence that tardive dyskinesia is specifically related to any particular drug, dosage level, or dosage duration.

## Conclusion

Tardive dyskinesia is sufficiently persistent and prevalent to warrant advising the medical profession of its occurrence. Since the antipsychotic drugs appear to combine with some unknown patient characteristics to produce the condition and since these drugs are currently indispensable in the treatment of schizophrenia, an educational campaign directed particularly toward psychiatrists and primary care physicians is strongly indicated, and is necessary in addition to special warnings in the package insert.

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## Editorial Comment

This special review by the American College of Neuropsychopharmacology reminds us that pharmacotherapy should never be trivialized into a mindless routine—either by physicians or the public. The communication is addressed to the professionally competent whose search for improvement and whose serious mode of proceeding has, however, been obscured by publicity-seeking pseudopsychiatrists' and the media's myth-makers in mental health. The professional ideal is that no medical regimen is undertaken without assessment of the ratio of risk to gain, without diagnosis of the nature and intensity of the dysfunction in question, the person who is the patient, and the resources he can realistically utilize. Physicians then oblige themselves to weigh old and new data in the decisions of giving or withholding medication, selecting the drug of choice, arriving at optimal dosage, and—in continuing collaboration with the patient throughout this—the decisions to change, sustain, or terminate, the regimen.

There are, in fact, considerable data and guidelines to help determine sound judgments at these various junctures. Further, there is a cadre of experienced clinicians who can offer the skills of scientifically tutored judgment on behalf of the patient and the continuing education of professional colleagues.

We are familiar with the commonly encountered side effects in the use of phenothiazines, the orthostatic hypotension and rashes, weight gain, and so forth. Most common are the neurological syndromes: akathisia,<sup>2,3</sup> parkinsonian syndromes and dystonias.<sup>4,5</sup> The atropine-like side effects of any anti-Parkinson medication (including delirium with higher dosages) can be readily prevented and treated. It is now suggested that, among the neurological side effects intrinsic to the phenothiazine and antipsychotic drugs, one should seriously monitor for symptoms of what has been described as tardive dyskinesia and adjust dosages and treatment regimens accordingly.<sup>6,9</sup> Among the simple, practical, precautionary steps from a public health view, is a close review and reduction of dosage, or elimination of drug regimen in those chronic populations in whom the syndrome is most likely and evident, and for some of whom drug therapy is questionable.<sup>10</sup>

Should these drugs still be used with confidence? The overwhelming clinical and objective evidence<sup>11,12</sup> indicates that the physician today should ask why he would *not* offer pharmacotherapy to a majority of his schizophrenic patients. Research underway may define subpopulations for whom pharmacotherapy may specifically *not* be indicated, and we await definitive delineation of such subgroups. Nevertheless, of the variables contributing to favorable outcome in schizophrenia, none contributes as weightily as does pharmacotherapy.<sup>11,12</sup> The recent follow-up study of the NIMH group is characteristic.<sup>13</sup> It indicates the role both of pharmacotherapy and of special casework in follow-up. Seventy-three percent of patients who had neither casework nor active medication relapsed during a year's time; in contrast, 63% with casework and placebo relapsed, while of those with casework who actually took maintenance phenothiazine, only 14% relapsed. Accordingly, the data reviewed by ACNP provides *no*

mandate for disregarding the risks to the patient of withholding medication; nor is there an excuse for not assessing and monitoring side effects.

The fact that secondary (sedating) effects of phenothiazines can be exploited by caretakers, families, and communities, always requires alertness in judging these motivations for treatment. But physicians who are oriented to the person who is the patient, to his needs and capacities, cannot view the patient's disability in organizing perceptions and actions as a simple act of will or an artifact of scapegoating and "labeling." The therapist's aim is to aid the patient to maximize *his* capacity for selectivity and self-regulation in various social settings by utilizing appropriate psychological, social, and pharmacotherapies.

The communication from ACNP is intended to sharpen perception and practices, even though it is not as yet possible to understand exactly who is vulnerable to the persisting effects, nor why. For over 12 years, the evidence has been growing of the probability of imbalances at critical aminergic receptors which may be involved in clinical disorder and which these drugs clearly affect.<sup>14-16</sup> While this concept comprises a truly promising lead, extensive basic and applied research are required if understanding and development of more molecularly specific medications is to advance.

Communications such as these may be viewed by uninformed alarmists as an opportunity to trivialize the suffering of the mentally ill, while offering their personal agendas or brand of salvation to replace soundly conceived treatments. But the attempt by ACNP to alert physicians

(a continuing professional practice) demonstrates a fact systematically overlooked by extremists among the consumer advocates, Federal "planners," and those Jovian gamblers with medical education, seeking minimal clinical and scientific preparation of new physicians. That fact is that there indeed *are* resources in American psychiatry exercising medical accountability and equipped to exert scientific scrutiny over issues which affect the welfare of the mentally ill. At a maximum, Federal and private investment in clearly psychiatric and therapeutic research has been no more than \$25 million; less than \$4 million is annually devoted to developing and sustaining researchers in medical centers. These sums are far less than 1% of our national expenditures on mental illness. These sums are being cut back or abolished. Accordingly, those who seek for improvement in our capacity to aid the mentally disabled should be sharply queried about the authenticity of their investment.

It is boring to reiterate the chaos impending for our capacity to train knowledgeable specialists, or sustain the research to control and understand medications and the mechanisms of disease, and the momentum to design more specific and safer therapies. Yet, if this communication is to be read seriously, if certain Congressional headline-hunters are also eager for authentic answers, they must ask whether the New Federalism can be permitted to abdicate responsibility for sustaining a national resource: the quality of professional practice and the emerging new manpower and knowledge to aid it.

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