# Tardive Dyskinesia in Patients Treated with Major Neuroleptics: A Review of the Literature

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*Since 1959 a growing number of reports have described a new type of neurological disorder in mental patients. This disorder, known as tardive dyskinesia, has been observed in approximately 500 cases but, judging from the accurate observations made by three separate groups of investigators, the syndrome is likely to be more frequent than one may suspect. Although manifestations of tardive dyskinesia occur in a number of diseases of the central nervous system, there is considerable evidence that the large-scale use of phenothiazines or similar drugs in recent years is responsible for the great number of patients in mental hospitals exhibiting myoclonia and choreo-athetoid symptoms.*

SINCE 1959, 21 papers including 23 reports by 18 authors have appeared in the scientific press describing an unusual neurological syndrome in patients treated with phenothiazines and other neuroleptics. This syndrome, which has been called tardive dyskinesia by Faurbye(12, 34), or terminal extrapyramidal insufficiency syndrome by Haddenbrock(14) is characterized by: 1) involuntary movements; 2) late occurrence in the course of treatment and often after discontinuation of drug administration; 3) persistence of disabling manifestations for months and years in a high percentage of cases; and 4) poor response to any type of therapy.

Sigwald and associates(30, 31) were the first to report such symptoms; the three authors who have contributed the largest number of clinical cases are Faurbye and associates(12, 34) of Roskilde, Denmark; Degkwitz(7, 8) of Frankfort, Germany; and Hunter(18, 19) of London, England.

The increasing number of cases of dyskinesias reported in the literature of the last two years, as well as reports of other types of complications attributed to neuroleptics, has been a source of considerable concern, particularly in regard to the risks involved in long-term therapy(17, 20).

## The Syndrome

The most conspicuous and frequent disorder is localized in the oral region and may be sufficiently severe to affect the functions of speech and deglutition. Sigwald(31) described the symptomatology of his first patient as follows:

> The tongue permanently projected forward and backward following a rapid rhythm; at times the projection is to the side, sometimes to the right, sometimes to the left; a torsion motion, or rotation on its axis complicates its incessant coming and going motion. The mouth is half open and lip movements accompany this continuous dyskinesia. The patient is slightly bothered by this, and her speech is slightly troubled, but remains comprehensible. Besides, the act of speaking or of swallowing temporarily suspends these motions which resume immediately afterwards. Asking the patient to execute a hand motion considerably accentuates the seriousness of the lingual-facial dyskinesia. . . . The lips participate in this dyskinesia in the form of stereotyped suction motions, pursing, rolling and incessant champing in synergy with rhythmic contractions of the jaw. Sometimes, on the other hand, there is a rhythmic opening of the mouth which facilitates protrusion of the tongue.

Other authors who observed this syndrome had little to add to this dramatic

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presentation by Sigwald. Disturbances of motility in other regions of the body were also described. Hunter(19) reported dyspnea and cyanosis in two patients, which he attributed to the lack of coordination of the respiratory muscles and spasms of the glottis. He also observed a peculiar gait with abduction of the arms. Faurbye(12), Haddenbrock(14), Druckman(10), and others called attention to continuous jerky movements of the upper and lower extremities, particularly of the fingers, ankles, and toes. Tonic contraction of the muscles of the neck and back were frequently encountered.

As to the characteristics of such disorders, Degkwitz(8) summarized his and other authors' observations as follows:

> Terminal extrapyramidal hyperkinesia has been described predominantly as a choreiform, and in some cases also as an athetoid and ballistic motor disorder. However, observations have shown that myoclonia (as it had been noted already during the great encephalitis epidemic) was involved in a large number of cases; we noted brief, more or less marked rhythmical twitches of individual, or frequently of symmetrical muscle groups having more or less marked motor effect of varying frequencies . . . in sporadic cases we have noted myoclonia of the ocular muscles. . . . When patients are observed while they are pursuing their activities, or while they are getting dressed or undressed, hyperkinesia is noted much more frequently than under the conditions customary to neuro-psychiatric examinations.

Wertheimer(35) reviewed part of the literature and found simple bucco-lingual-masticatory dyskinesia in 14 cases, the same syndrome associated with tremor in two cases, bucco-lingual-masticatory syndrome in association with involuntary movements of the limbs in three cases, dyskinesia of the neck and limbs in one case, parkinsonism in one case, and akathisia and tasikinesia in two cases. Although this classification of symptoms is not entirely clear, it is quite obvious that oral dyskinesia is by far the most frequent manifestation.

Movements of the lips and tongue are grotesque, often socially objectionable, and thus are a source of considerable embarrassment to the patient and his family. As a rule, however, patients do not complain of these symptoms, particularly if they are demented. The neurological syndrome may cause a number of complications, such as hypertrophy of the tongue and ulcerations of the mouth(10). The speech may become dysarthric to the point of being incomprehensible(19). In extreme cases, swallowing may become difficult and this may cause a considerable loss of weight(29). Severe dystonia involving muscles controlling the balance of the body and of the head may be painful and thus greatly reduce the patient's activity. Standard neurological examinations reveal essentially negative findings other than gross motor disorder(35).

## Prevalence

Degkwitz(8) in a review of the literature reported 232 cases of what he terms "*terminale extrapyramidale Hyperkinese.*" To these should be added 272 patients included in his article and 17 additional patients reported in papers not mentioned by Degkwitz. Even if allowances are made for duplications and inclusion of some cases of questionable symptomatology, the number of patients published thus far is over 500. This number is far from being impressive considering the many millions of hospitalized and ambulatory patients who were treated or are being treated with neuroleptics.

However, there are two disconcerting facts about this little-known syndrome. In the first place, more than 90 percent of the cases of dyskinesia have been reported since 1964; in the second place, the frequency of this syndrome in samples of chronic patients appears to be considerable, according to three groups of investigators. Hunter (19), who focused only on severe irreversible symptoms found that 13 of 250 women were afflicted by this disorder. Faurbye(12) diagnosed drug-induced dyskinesia in 103 out of 417 chronic patients, and, finally, Degkwitz(8) reported 137 cases in a population of 817 in one hospital and approximately 100 cases in a population of 443 in another institution.

## Characteristics of Patients

*Age.* Detailed information as to age was available for 279 patients, and the age

distribution was as follows: 20-29 years of age, seven; 30-39, 18; 40-49, 29; 50-59, 90; 60-69, 92; and over 70, 44. The youngest patient was 27 and the oldest 82 years old. It seems that the highest incidence of dyskinesia occurs between the ages of 50 and 70, although no conclusion can be drawn from the data at hand since the age distributions of the patient populations are not known. However, the age distribution of Faurbye's sample (12) is typical of a chronic hospitalized population.

*Sex.* The ratio of women to men was approximately three to one, excluding the two large series of patients reported by Faurbye, who obtained his data from female services only. Hunter(19) found that the percentage of patients exhibiting dyskinesia was five percent for women and zero percent for men. On the other hand, in the first series of Degkwitz(8), 21 percent were women and ten percent were men; in his second series, the percentage of women was 27 and that of men, 19. Thus, it seems that women are more frequently affected than men, although the marked disparity between Hunter's and some of Degkwitz' data is difficult to explain.

*Principal and secondary diagnoses.* The majority of patients had diagnoses of chronic deteriorating schizophrenia, which is not surprising since the bulk of patients were studied in chronic hospital wards. A number of patients were diagnosed as having organic brain disorder (senile cerebral arterial sclerosis, general paresis, etc.) and an even larger number of patients, such as those of Hunter(18), had a history of having received various types of physical therapy, including leukotomy. This has led to the opinion that brain damage may predispose to dyskinesia(4, 26, 28).

This is probably correct, but there is also considerable evidence that young patients without a history of brain damage may be affected by this disorder. In Degkwitz' series(8), 85 out of 137 patients had vascular disease, diabetes, brain injury, and/or a history of having received EST and insulin. It is not clear whether some of the patients had more than one of these potentially traumatic factors, but at least 52 patients did not have a history of brain injury. In Uhrbrand and Faurbye's paper 15 of 29 had some evidence of brain damage, but in Faurbye's second report there were only 18 of 103 patients who appeared to have gross neurological disorders.

An analysis of 12 separate studies reporting adequate histories(10, 11, 14, 15, 21, 22, 25, 27, 29, 31, 33, 35) revealed that 15 of 43 patients had evidence of brain damage due to senility, alcoholism, or some degenerative disease. The remainder of these patients did not seem to have neurological disorders nor did their past histories reveal the administration of an excessive number of ESTs. Dementia, which conceivably may be associated with some organic change, was absent in a large number of cases. For instance, in Sigwald's(30) series, there were two patients who had no apparent mental disease, but were receiving neuroleptics for the relief of neuralgic pain.

The role of EST is also of particular interest since this type of treatment alone may cause dyskinesia (reported in four patients) according to Faurbye(12). The same author also found that 44 percent of the patients who had previously received EST showed dyskinetic symptoms, as opposed to 22 percent who had not received any type of convulsive therapy. In the same report the author stated that leukotomized patients were not more prone to dyskinesia than subjects who had not had neurosurgery.

## Types of Drugs

Faurbye(12) observed dyskinetic manifestations in patients treated with the following drugs: chlorpromazine, perphenazine, thioridazine, prochlorperazine, and haloperidol. In an earlier paper(34) the same author reported that of 29 patients exhibiting dyskinesia, 15 had been treated with perphenazine, ten with chlorpromazine, and one with reserpine, and the rest with various combinations of drugs. Faurbye suspects that perphenazine may be more toxic than chlorpromazine inasmuch as the latter drug had been used more extensively than the former in the Sanct Hans Hospital of Roskilde.

Haddenbrock(14) is of the opinion that high doses of perphenazine and of butyprophenones, the use of phenothiazine followed by EST, and the combination of phenothiazines and barbiturates over long

periods of time are particularly conducive to tardive dyskinesia. All three patients described by Evans(11) had received trifluoperazine in doses varying from 3-4 mg. a day. Some patients seemed to be particularly sensitive to certain types of drugs: a patient reported by Rodová(27) developed a marked oral syndrome five days after her medication was changed from conventional neuroleptics to thioproperazine; one of Wertheimer's patients(35) had a similar response to a brief course of haloperidol.

The general impression is that dyskinesias develop only in patients treated with large doses of phenothiazines, yet many patients, particularly the elderly, received doses which most investigators would consider moderate. Furthermore, one of Sigwald's patients(30) who had received daily doses of 75 mg. of chlorpromazine for three months developed a typical bucco-lingual syndrome which persisted for at least ten months after all neuroleptic drugs had been discontinued. Another patient described by Evans(11) had a similar reaction after four months of treatment with 3-4 mg. of trifluoperazine a day. This patient, however, may have had previous courses of treatment with psychotropic drugs.

## Onset and Evolution of Symptoms

Another widely held opinion is that tardive dyskinesia occurs only after many years of continuous medication. According to Wertheimer(35), one of his patients had been treated for eight years and another for nine years before the syndrome became manifest. Hunter's cases had been on medication from 18 months to five years. On the other hand, one patient reported by Sigwald(31) and another by Evans(11) developed long-lasting extrapyramidal symptoms after three or four months of treatment. Faurbye(12) found that only 34 of 75 schizophrenic patients first manifested dyskinesias after three or more years of treatment, three patients having exhibited symptoms in less than one-half year, six between one-half and one year, and 32 between one and three years. In any event, the neurological manifestations discussed in this paper become apparent in the course of treatment later than those of classical parkinsonism or akathisia (maximum 73 days according to Ayd[1]) and considerably later than those of acute dystonia (less than one week).

Hunter, Faurbye, and Degkwitz agree that in many cases dyskinesia makes its first appearance or becomes intensified following termination of drug administration or marked reduction of dosage. The last-named author(8) terminated drug administration in 35 women and, of these, 12 developed "extrapyramidal hyperkinesis" within one to 14 days. He postulated that terminal extrapyramidal insufficiency may be present but clinically not apparent during drug therapy; he proposed that drug-induced muscular rigidity may control symptoms of motor hyperactivity caused by irreversible changes in the central nervous system. Faurbye(12) feels that this may be true in some instances, but not in cases exhibiting normal muscular tone.

## Outcome and Treatment

A number of case histories suggest a rather rapid onset of the more distressing symptoms of dyskinesia and a gradual spreading to various areas of the body within a short time. However, most authors admit that they first noticed the syndrome when it was fully established and that they may have overlooked early and insidious manifestations. In most instances treatment was discontinued as soon as symptoms became apparent, or medication was manipulated in an effort to reduce hyperkinesia.

Of the 29 patients reported by Uhrbrand and Faurbye(34), 12 continued on drugs despite the presence of dyskinesia and of these two became symptom-free upon reduction of dosage. In the other ten cases, dyskinesia persisted. Of the 17 patients whose treatment was discontinued, 12 no longer exhibited abnormal symptomatology after periods extending from ten days to six months, and five continued to exhibit symptoms despite termination of treatment. Similarly, in Haddenbrock's series(14), four of ten patients became symptom-free.

According to three separate reports(21, 27, 35) symptoms disappeared upon withdrawal of the drug, to reappear when treatment was reinstituted. In a case described by Schmidt and Jarcho(29), dyskinesia was

reversible upon discontinuation of the drug during the first four years of treatment, but became permanent when the agent was readministered in 1962. The fact that symptoms may appear during treatment, after termination of treatment, or upon reinstitution of treatment is indicative of the complexity of the problem.

The number of patients who have exhibited irreversible dyskinesia is considerable. All 16 cases of Hunter's(18) exhibited dyskinetic symptoms for periods varying from three to 18 months after discontinuation of treatment. One of his patients has been afflicted by this disorder for at least six years. Schmidt(29) made similar observations in his five cases, with one patient exhibiting severe dyskinesia 44 months after drugs were discontinued. Rodová(27), Druckman(10), and Faurbye(12) reported patients whose symptoms persisted for over two years. Most authors, however, agree that the symptomatology decreases over a period of months after cessation of neuroleptic treatment.

There is little information about the evolution of symptoms in patients who continue to receive neuroleptics. In two cases of Sigwald's(30), treatment was continued after the appearance of dyskinesia because of the excellent therapeutic result achieved with the condition for which the drug had been prescribed, and the dyskinesia seemed unchanged after several months or years.

Treatment of severe forms of dyskinesia has been unsatisfactory. Hunter(18, 19) feels that discontinuation of drug therapy is essential even though one may expect only partial recovery from neurological complications. In more severe cases a paradoxical control of symptoms may be achieved by the treatment with large doses of the same drug(14). A change of medication (from haloperidol to perphenazine) seemed to help one patient(28). Sedatives and hypnotics may be of some help in that they induce sleep, and during sleep symptoms disappear.

Practically every author agrees that antiparkinsonian medication is either useless or harmful to the syndrome. Brandrup(6), in the mental hospital in Roskilde, successfully used tetrabenazine in four patients exhibiting classical dyskinesia. However, no further reports on the efficacy of this treatment modality were received from this institution, where research on dyskinesia has been very intensive during the last five years.

## Relation of Involuntary Movements to Drug Action

A cause-and-effect relationship between the action of neuroleptic agents and symptoms of parkinsonian tremor, dystonia, and akathisia was established early in the history of psychopharmacology, since such manifestations occurred shortly after treatment was instituted and subsided upon termination of drug administration. These conditions do not obtain in the case of tardive dyskinesias. To complicate matters, nontreated patients who may be used as a control group are virtually impossible to find.

There is, however, considerable indirect evidence that the drugs are responsible for the neurological effects under consideration. Textbooks of psychiatry, such as Henderson and Gillespie(16), do not report symptoms of chorea, athetosis, myoclonias, etc., in schizophrenic patients, even in those who have reached a state of advanced deterioration. Yet the great majority of patients exhibiting tardive dyskinesia had diagnoses of schizophrenia. On the other hand, the symptoms with which this paper is concerned do occur in other pathological conditions of the central nervous system but, according to a survey made by Mettler and Crandell(24) in 1955 (just before drugs were introduced in the Greystone State Hospital of New Jersey), these conditions are extremely rare and may constitute a fraction of one percent of the total hospital population.

Recently a "chronic psychotic choreoathetosis" was observed by Dincmen(9) in a fair proportion of hospitalized patients. From the perceptive and careful descriptions of such neurological manifestations it seems that this "new morbid entity" is identical with the drug-induced tardive dyskinesia. Involuntary movements of the type described in this paper may be observed in senile, presenile, paretic, chronic alcoholic, and brain-injured individuals. This may lead to some diagnostic difficulty in the evaluation

of symptoms, particularly in elderly patients. According to Faurbye(12), "spontaneous dyskinesias may occur in 16 percent of a hospital population" (as opposed to 26 percent of patients treated with drugs) but such manifestations are "generally not as pronounced and distinct as those drug-induced, and they do not disappear with attention."

It has been mentioned earlier that dyskinesia develops with greater frequency shortly after withdrawal of medication or immediately after reinstitution of treatment. This time relationship between the events of pharmacotherapy and the development of symptoms provides additional indirect evidence that drugs are, at least in part, responsible for tardive involuntary movements.

## Pathogenetic Considerations

The dyskinesias reported in this review may be divided into three clinical categories: chorea (choreo-athetosis), myoclonias, and the bucco-linguo-masticatory triad of Faurbye(12).

Chorea and myoclonias were also described as early manifestations of von Economo's disease(3, 23); the significant postmortem findings of patients who died in this stage of the disease were in the midbrain and brain stem(35). In patients who survived the acute stages of encephalitis, choreiform movement and myoclonias disappeared to give way to parkinsonism of the chronic type. Pathologic changes were then found predominantly in the substantia nigra and basal ganglia.

Patients receiving neuroleptics exhibited both types of symptoms but their order of appearance seems to be reversed. Postmortem data from such patients will be published in the near future in Europe,[1] but at the time of this writing the literature does not provide any information based on autopsies.

As regards biochemical changes in choreo-athetosis, it is worth mentioning the work of two Canadian authors(32) who observed such abnormal movements in monkeys with discreet lesions of the midbrain. Pathological changes in the system of the substantia nigra seemed to cause coarse tremors but were not necessary for choreo-athetoid movements. On the other hand, two animals, exhibiting lesions of the dorsomedial fibers of the cerebral peduncle and the rubro-tegmento-spinal tract, showed choreiform movements in the contralateral limbs. Such lesions were associated with low levels of serotonin and normal levels of dopamine in the corresponding striatum. The injection of harmine or harmaline altered the character of these abnormal movements. These findings, if confirmed by more extensive experiments, could provide important clues as to the nature of drug-induced dyskinesias and also suggest therapeutic measures to correct such disorders.

The bucco-linguo-masticatory triad(12), which is frequently found in association with athetoid and myoclonic movements of the extremities does not have the characteristics of chorea but fits the description of bradykinesia,[2] "a term . . . applied to slow regular rhythmical movements of large amplitude." These include "tics, often consisting of complex, coordinated, rhythmical movements of the jaw, lips, tongue and palate" (5). This syndrome was also described as one of the sequelae of von Economo's disease and was called the fly-catcher's tongue by the neurologists of the period of the great epidemic of encephalitis. Thus, tardive dyskinesia appears to have many features in common with the neurological disorders of von Economo's disease.

## Comment

The cause-and-effect relationship between neuroleptics and tardive dyskinesias is difficult to establish with certainty and is based only on indirect evidence. From some of the more detailed clinical histories it is clear that dyskinesias were not present in patients prior to their treatment with neuro-

[1] In the June 1966 issue of the *International Drug Therapy Newsletter*(2) Ayd states: "Faurbye has performed postmortem studies of the CNS in 30 cases. In a provisional survey of the first 18 cases (15 drug-induced and three spontaneous) atrophic cells were found in the caudate nucleus in 13 cases."

[2] The choice of the term bradykinesia is somewhat unfortunate because, according to most authors, it means general slowing of movements.

leptics. The possibility of chorea and myoclonias being coincidental is very remote since such conditions are rare, at least in subjects past the period of adolescence(13, 14). The bucco-linguo-masticatory syndrome is easily recognized and is so typical that, based on four cases, Sigwald was able to state in 1959: "The symptomatology of such dyskinesias constitutes quite a typical clinical group and individual differences are only in details."

To my knowledge, this syndrome has not been described in any other condition except as a sequela of von Economo's encephalitis. Patients exhibiting this sequela must be exceedingly rare considering that the great epidemic ended 40 years ago. I would like to conclude this review by paraphrasing Evans(11): the causal relationship between treatment with neuroleptics and oral dyskinesia is presumptive, but is likelier than the other possibilities.

## Summary

This paper reviews data from 21 publications describing tardive dyskinesia in patients treated with phenothiazines and other neuroleptic agents. The literature reports approximately 500 patients exhibiting a syndrome characterized by: 1) choreiform myoclonic and peculiar rhythmical movements; 2) a high incidence of abnormal movements in the oral region; 3) late occurrence of the syndrome in the course of treatment, or even after discontinuation of drugs; 4) persistence of symptomatology for months or years in a large number of patients; and 5) a poor response to any type of therapy.

Older patients, women, and individuals with organic brain disorders seem to be particularly prone to this type of dyskinesia, although there are many exceptions. There is no definite proof that drugs are responsible for the so-called tardive dyskinesia but there is evidence that the syndrome is drug-induced on the basis of the following facts: 1) a time relationship between events of pharmacotherapy and the appearance of symptoms; 2) the extreme rarity of the syndrome before the use of psychotropic drugs; and 3) the similarity between tardive dyskinesia and certain manifestations observed during the great epidemic of von Economo's disease.

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## Addendum

Since this review was submitted for publication to this journal on July 11, 1966, five papers on dyskinesia published prior to that date came to my attention. One of the reports was by Schönecker, who described a bucco-lingual syndrome and attributed it to the use of phenothiazines in 1957, or approximately two years before Sigwald's report. Eighteen additional communications reporting new cases and/or discussing the syndrome of dyskinesia have appeared in the medical literature or have been read at scientific meetings from July 1966 to October 1967.

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# On the Rarity of "Irreversible" Oral Dyskinesias Following Phenothiazines

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*This author's inspection of the literature on oral dyskinesia following prolonged phenothiazine administration reveals that many of the cases reported do not meet the criteria necessary to establish the existence of a tardive, irreversible syndrome. He concludes that the incidence of this side effect has been misrepresented and that it should not be regarded as a significant danger in phenothiazine treatment.*

"EARLY" DYSKINESIAS which occur a few hours to days after patients are given reserpine, phenothiazines, or related preparations were reported as soon as the drugs were introduced. As early as 1954(28) at an AAAS meeting we reported such occurrences in young adolescents whose side effects could not be attributed to latent parkinsonism. In several series(1, 19, 30) of patients totaling almost 10,000 cases there was general agreement that such early neurological symptoms appeared about 40 percent of the time. These included akathisia in 20 to 25 percent, parkinson-like reactions in 15 to 20 percent, and dyskinesias or dystonias in one to four percent. The dyskinesias appeared about twice as frequently in females as in males, while the reverse was true in respect to the other neurologic symptoms.

Goldman(19) found that fluphenazine, carphenazine, and trifluoperazine produced dystonias in about three percent of cases, whereas other drugs (for each of which he had a minimum of 235 cases) were

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