Motor Disorders Induced by Neuroleptics

A Proposed New Classification

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A comprehensive classification of motor disorders attributed to neuroleptic drugs is proposed. Some manifestations resemble those occurring in known diseases of the central nervous system; other abnormalities are typical effects of drugs with neuroleptic action. A factor analysis on the most frequently occurring motor disorders generated the following symptom clusters: (1) tremor, bradykinesia, rigidity, and attendant symptoms; (2) buccolingual-masticatory dyskinesia, astasia, dyskinesia of the lower extremities and posture in extension; and (3) dyskinesia of the upper extremities and postural disorder. The classification and the factors were used to study the effects of drug withdrawal on a sample of patients over a six-month period. Symptoms of cluster 1 decreased while those of cluster 2 increased in severity. In a control group receiving standard drugs during a comparable period, no significant changes were noted.

MANY investigators have developed systems for the classification of motor disorders induced by neuroleptic drugs, but there still is considerable uncertainty with regard to their nomenclature and clinical meaning. These effects often are referred to as extrapyramidal, a term which may be applied to such symptoms as bradykinesia, dystonia, and possibly tremor. It would be incorrect, however, to include pharyngeal spasms, trismus, or opisthotonus in the class of extrapyramidal disorders because the dysfunction underlying such manifestations is located in the brain stem or in the spinal cord. Similarly, the buccolingual syndrome resulting from prolonged treatment with neuroleptics is most likely caused by dysfunctions in areas of the mesencephalon, ordinarily not included in the extrapyramidal system.[1] It is possible that certain dyskinesias are release phenomena due to disinhibition from higher striatal centers, but this has not yet been proven.

Recently, Duvoisin[2] has subdivided motor abnormalities due to neuroleptics into four categories: pseudoparkinsonism, akathisia, acute dystonic reactions, and tardive dyskinesias. The term parkinsonism, which has been used extensively in the psychopharmacological literature, is unsatisfactory because the constellation of symptoms and the sequence in which they develop in the course of treatment may not be the same as those observed in Parkinson's disease. This, plus the fact that the drug-induced disorder is rapid in onset and, in most instances, easily reversible, has prompted investigators, including Duvoisin, to adopt the term pseudoparkinsonism or Parkinson-like syndrome. Akathisia "refers not to any type or pattern of movement, but rather to a subjective need or desire to move."[2] Yet, many clinicians have used the term akathisia or takisenisia to describe all types of involuntary movements. The group of the so-called acute dystonias is heterogenous and also includes manifestations which resemble tetanus rather than dystonia. The problem of defining motor disorders has become even more complicated since the so-called tardive dyskinesias have been brought to the attention of the medical community.[3] The term tardive dyskinesia is used to define a variety of clinical manifestations having in common a relatively late onset in the course of treatment and persistence after discontinuation of drug therapy. Investigators have described them as choreic or choreiform but, as one becomes better acquainted with this syndrome, the resemblance between the most common manifes-

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tations of tardive dyskinesia and chorea appear to be superficial in the majority of cases. "Chorea consists of quick, jerky, irregular, purposeless, involuntary movements . . . they are variable in depth and location, producing an irregular pattern of constantly changing movements of different parts of the body."[4] A syndrome simulating chorea is rare in drug-treated patients (see section on frequency). On the other hand, the disorder which will be referred to as complex dyskinesia is frequent and consists of slow, repetitive movements involving specific functional areas of the body. The complex dyskinesias are also likely to mimic purposeful activities such as lip-smacking, clenching of the fist, or changes of posture.

Thus, neuroleptic drugs may affect a great number of anatomical structures of the central nervous system. The types and patterns of motor disorders are accordingly numerous and varied. Certain symptoms mimic those of naturally occurring neurological diseases; others have characteristics of their own.

The frequency of neurologic side effects and the matter of chronic dyskinesia have been controversial issues in psychopharmacology for a number of years. In their recent reviews, Duvoisin[2] and Kurland[5] experienced some difficulty in explaining the discrepancies found in the incidence of neurologic effects reported in the literature. Even less understandable is the fact that chronic dyskinesias have been described only in an occasional case, or have not been reported at all in recent drug studies, when systematic investigations of these types of dyskinesias have revealed that a sizable proportion of patients on long-term treatment with neuroleptic agents are so afflicted. In two separate investigations, one of us (G. E. C.) found that the incidence of tardive dyskinesia was 25%[6] and 28%[7] in samples of adult schizophrenic patients. As the focus was on tardive dyskinesia, Parkinson-like symptoms were not reported but they were present in 8% of the cases.

Motor Disorders and Their Main Characteristics

In Table 1 we attempt to provide a comprehensive list of abnormal movements and postures exhibited by patients exposed to neuroleptic agents. The symptoms are arranged in the approximate order in which they make their appearance in the course of treatment. As one progresses from the top to the bottom of the list, symptoms tend to become more chronic. Many items included in this table have been described extensively in textbooks of neurology and have been the object of numerous reports in the psychiatric literature of the last 15 years; hence, they require only a few remarks. On the other hand, neurologic manifestations that have been identified only recently in drug-treated patients deserve a more detailed description, as they are seldom mentioned in the psychiatric literature.

Acute Dyskinesias, Acute Dystonias, Oculogyrus.—These syndromes are often lumped together in the class of the acute dystonias, but we prefer to separate the dystonias, which are characterized by tonic contractions of groups of muscles, from the acute dyskinesias which manifest themselves as intermittent spasms or tetanic contractions of certain muscles. Drug-induced trismus, risus sardonicus, and opisthotonus which are sometimes mistaken for symptoms of bacterial tetanus[8] are included in the class of acute dyskinesias.

Akathisia.—Constant changes in activity and posture observed in patients who are affected by akathisia cannot be defined as abnormal or purposeless. The patient's activity is not stereotyped and affords a measure of relief from inner restlessness and agitation. On the other hand, Fouks et al[9] have pointed out that tic-like movements often are superimposed on the picture of pure akathisia. It is also worth mentioning that single doses of chlorpromazine (75 mg/day) may produce feelings of inner restlessness as well as abnormal postures in normal volunteers. Balter and associates at the Psychopharmacology Research Branch of the National Institute of Mental Health, who carried out these experiments (unpublished data), noted that their subjects were experiencing difficulty in maintaining their heads and trunks in a normal relation to the rest of the body and felt compelled to assume unusual compensatory postures. Thus, acute dystonia and akathisia may be two aspects of the same syndrome.

Lingual Myokymia.—Movements are vermicular and involve the intrinsic muscles of the tongue without displacing the organ. Therefore, no abnormality is observed when the mouth is closed. At times, forceful pulsating clonic movements can be observed in the distal portion of the tongue.[10] There are no long-term studies of this disorder; hence, it is not known whether it is reversible. These movements may evolve into different types of dyskinesias.

Tremor.—It may be coarse or fine depending on whether the frequency of the cycles is below or above 5/sec. Tremor of the toxic type is very rapid. Movements affect the whole body and appear to be synchronized. The tongue exhibits particularly violent excursions. All types of tremors are usually reversible upon discontinuation of treatment. Residual intermittent, coarse tremors may be observed, however, in older subjects and in other individuals after the prolonged use of neuroleptics.

Hypokinesia.—All symptoms listed here show some similarity to the manifestations of idiopathic Parkinson's disease or of the sequelae of epidemic encephalitis. When moderate or severe bradykinesia and attendant symptoms are associated with tremor and autonomic dysfunction, the patient's appearance is in-

Table 1.—Abnormal Motor Disorders and Postures in Patients Treated With Neuroleptics

1. Acute dyskinesias
2. Acute dystonias
3. Oculogyrus
4. Akathisia
5. Lingual myokymia
6. Tremor
   a. Fine type
   b. Coarse type
   c. Rapid (toxic) type
7. Hypokinesia
   a. Bradykinesia
   b. Amimia
   c. Rigidity
   d. Shuffling gait
   e. Anteroretropulsion, festination
   f. Symptoms related to bradykinesia or rigidity (dysphagia, drooling, aphonia, micrographia, etc)
   g. Posture in flexion
8. Complex dyskinesias
   a. Oculofacial type
   b. Buccolingual-mandibular type
   c. Of the upper extremities
   d. Of the lower extremities
   e. Of the respiratory type
9. Astasia
10. Chorea
11. Athetosis
12. Dystonia
13. Ballismus
14. Postural disorders
   a. In extension
   b. In torsion
   c. In lateral flexion
15. Retrocollis
16. Other

Table 2.—Factor Loadings of 14 Items From Table 1

Item*	1	2	3
Tremor (6)	0.494†	0.249	−0.015
Bradykinesia (7a)	0.879†	0.233	0.018
Amimia (7b)	0.789†	0.141	−0.051
Rigidity (7c)	0.478†	0.046	−0.038
Slow gait (7d)	0.874†	0.096	0.088
Anteroretropulsion (7e)	0.535†	−0.087	0.097
Flexion (7g)	0.554†	0.009	0.097
Dyskinesia, BLM (8b)	−0.197	−0.402†	−0.060
Dyskinesia, upper extremities (8c)	−0.205	−0.388	−0.420†
Dyskinesia, lower extremities (8d)	−0.050	−0.749†	−0.210
Astasia (9)	0.041	−0.797†	0.059
Postural extension (14a)	−0.046	−0.660†	0.204
Postural, other (14 b, c)	−0.016	−0.072	−0.767†
Rocking, swaying (16)	0.023	−0.219	−0.279

* Numbers in parentheses refer to the position of the item in Table 1.
† Acceptable loading of items for inclusion in factors.

Table 3.—Distribution of Symptoms in 97 Patients

Symptom	No. Patients
Tremor	28
Bradykinesia	20
Amimia	23
Rigidity	5
Shuffling gait	9
Anteroretropulsion and festination	2
Posture in flexion	4
Dyskinesia of the oral region	56
Dyskinesia of the upper extremities	71
Dyskinesia of the lower extremities	31
Astasia	19
Posture in extension	16
Other postures	10
Chorea	1
Athetosis	1
Dystonia	1
Facial tic	1
Ballismus	1

Table 4.—t-Tests Comparing 3 Factors

Scores at Weeks 0 and 40		Group 1	Group 2
Scores	Factor 1	−3.65*	0.0
	Factor 2	+1.68	−1.51
	Factor 3	+0.16	−0.25
Amounts of Change in Groups 1 and 2			
Scores	Factor 1	2.50*	
	Factor 2	2.23†	
	Factor 3	0.27	

* Significant at 0.01 level.
† Significant at 0.05 level.

distinguishable from that of an individual with advanced Parkinson's disease. On the other hand, when symptoms are mild, restricted to a limited area of the body, or are associated with other types of dyskinesias, the syndrome is mixed. In such cases, a description of individual symptoms is more desirable than the use of the term of parkinsonism. In the majority of patients, symptoms are reversible, but there are some exceptions.

Complex Dyskinesias.—They are the most common disorders observed in long-term patients and are often referred to as tardive dyskinesias. The movements have the following characteristics: (1) each cycle lasts from one-half to two seconds; (2) the pattern is usually repetitive but is easily modified by external factors such as attention, emotion, posture, and particularly by activity; (3) frequency and amplitude are reduced or abolished by voluntary activity of the muscles in affected areas but are predictably increased by movements in distant parts of the body; and (4) sleep and drowsiness abolish all types of motor abnormalities. The oculofacial type, which could also be designated as a facial tic, is manifested by a vertical rotation of the eyes (less sustained than in the typical oculogiric episodes), blinking, and bizarre movements of the facial muscles. The buccolingual-masticatory syndrome is the most conspicuous dyskinesia and the most extensively reported. The cheeks, lips, tongue, and jaw are affected in various combinations, giving rise to characteristic syndromes such as fly-catcher's tongue, puffing, and lip-smacking. The fingers may exhibit movements in extension with fanning or sequential flexing (guitar playing). Abnormal motility of the fingers or toes becomes rhythmical and resembles tremor when the hand or foot rests on a firm surface. The feet and ankles rotate in all directions and assume an equinovarus position for brief periods of time. Alternating adduction and abduction of the thighs often accompany movements in the distal portions of the lower extremities. Respiratory dyskinesia is related to abnormal diaphragmatic motility. Peculiar vocalizations and characteristic grunts should be included in this category too.

Astasia.—The term astasia is used here to describe an inability to maintain a stable standing posture. Abrupt oscillations of the pelvis, shifting of weight from foot to foot and, less frequently, irregular movements of the shoulders are expressions of this postural difficulty. Unlike akathisia, astasia is not accompanied by subjective distress.

Chorea, Athetosis, Dystonia, and Ballismus.—These are well-defined syndromes of naturally occurring diseases. They have been observed in patients receiving neuroleptic drugs, but it is not easy to differentiate them from the classical manifestations of neurological diseases. Chorea, like dystonia, may be acute and reversible, or may occur in a chronic form resembling Huntington's chorea. Violent ballistic movements of the head and lower extremities have been observed in the treatment with levodopa and less frequently in patients on neuroleptics.

Postural Disorders.—One of the most typical disorders in drug-treated patients is a lordosis of the pelvis with a compensatory forward flexion of the neck. Abduction of the arms and extension of the fingers and of the big toe are often associated with abnormal motility in these areas. Torticollis, torsion, and lateral flexion of the spine may be noticeable when the patient is standing, but disappear in a supine position.

Retrocollis.—Overextension of the neck, with rigidity of the muscles of neck and shoulders, was described by Harenko[11] in patients over 74 who eventually died of respiratory complications. All disorders included in items 8 to 15 (Table 1) are long-lasting and, as a rule, rather stable when the patient is on medication. Even though more than 70 papers describing these syndromes have appeared in the literature of the last ten years there are still many unanswered questions regarding onset, evolution, and relationship to other neurologic disorders due to drugs.

Other Motor Disorders.—Here may be included nonspecific manifestations such as convulsions and ataxia, as well as disorders yet to be identified.

The classification of motor and postural disorders detailed in Table 1 was used for a study of the frequency of symptoms in a sample of approximately 100 hospitalized patients; a factor analysis of 14 symptoms frequently observed in patients on long-term drug therapy, and a comparative study of patients on and off drugs.

Methods and Procedure

Patients.—All patients included in this investigation had participated in two collaborative studies sponsored by the Psychopharmacology Branch of the National Institute of Mental Health.[12,13] They were schizophrenic, under 56 years of age, hospitalized for a minimum of two years, and free of physical disorders. Sexes were equally represented. On previous examinations, 102 subjects from four hospitals had manifested some neurological disorder attributable to drugs and were available for this investigation. Of these, 97 exhibited motor abnormalities at the time of the final survey. Seventy patients were receiving neuroleptic drugs and the rest were on no drug. Chlorpromazine, thioridazine, and trifluperazine accounted for two thirds of all drugs prescribed; antiparkinsonian drugs were administered to one third of the sample.

Assessment.—All patients were examined blindly by the same investigator (G. E. C.) on two occasions during a ten-month period. The symptoms were classified on the basis of the checklist in Table 1 and their severity was graded 0 to 4.

Factor Analysis.—This analysis was performed by one of us (E. R. N.) on 14 items in Table 1 (rare symptoms were excluded). The principal components method, with iteration to estimate communalities, was used. Three factors had latent roots larger than or

approximately equal to 1.00, accounting for 83% of the total ingoing variance. These factors were then rotated to the normal varimax criterion and the solution is shown in Table 2. The suggested cut-off level for loadings was 0.392. This was computed by the sum of the two highest loadings of each row divided by twice the number of items. One test (last item on Table 2) with communality less than one third of the mean communality was excluded during rotation.

Comparative Study.—A sample of 39 patients with well-defined motor disorders was divided into two subsamples: 22 patients were removed from all drugs during the last 24 weeks of a 40-week period of observation; 17 patients were maintained on the same treatment regimen throughout this period. Various *t*-tests were then conducted on all 14 variables to detect differences in type and severity of symptoms at weeks 0 and 40.

Results

Frequency and Types of Symptoms.—Table 3 shows the results of the final survey conducted on 97 patients exhibiting some motor disorder. (A previous examination provided similar findings.)

The total number of symptoms for the sample is 301 with an average of 3.1 per patient. Items consistent with tardive dyskinesia are quite common. Tremor and bradykinesia are also fairly frequent, but other manifestations reflecting a more advanced stage of neurological impairment, such as rigidity, a simian posture, or festination are observed less often. Chorea and similar disorders are rare, which raises the question of whether they are drug-induced or manifestations of a naturally occurring disease. Acute manifestations were not observed. These symptoms are temporary in nature, easily recognized, and responsive to drug manipulation; hence, they are not likely to be detected in surveys made at fixed points in time.

Factor Analysis.—The first of the three factors includes a cluster of items featuring diffused slowing of movements and tremor. The three items of the second factor, dyskinesia of the lower extremities, shifting of position, and posture in extension, are consistent with a picture of hypermotility and a compensatory forward positioning of the pelvis. Oral dyskinesia (Table 1, item 8b) is also associated with the cluster of hyperactive symptoms. Excessive mouth movements, however, are limited to a small area of the body and may occur in a sizeable proportion of the sample not exhibiting signs of hypermotility. Thus, the loading of item 8b is barely acceptable for inclusion in factor 2. The third factor, whose main characteristic is "other" postural disorder, eg, torsion of the spine, also includes dyskinesia of the upper extremities (Table 1, item 8c). This item is widespread throughout the sample and has a loading which is only slightly above the cut-off level.

Comparative Study.—Group 1 consisted of the 22 patients who had been off medication, while control group 2 included the 17 patients who had continued to take neuroleptic drugs during a comparable period of time. We conducted *t*-tests comparing weeks 0 and 40 on all 14 variables of Table 2. The scores on items 8c and 8d (dyskinesia of upper and lower extremities) of group 1 were reliably higher at week 40 (scores of +3.30 and +2.93, $P < 0.01$). The scores on items 7a, 7b, and 7d (bradykinesia, amimia, and slow gait) were reliably lower at week 40 (scores of −3.80, −3.67, $P < 0.01$, and −2.16, $P < 0.05$). The scores of the remaining nine items for group 1 and the scores of all 14 items for group 2 failed to show a significant difference between weeks 0 and 40.

Then, *t*-tests were performed to compare the amount of change of the 14 item scores in group 1 vs group 2. The results of these tests revealed scores of 2.33 for dyskinesia of the upper extremities ($P < 0.05$), 2.34 ($P < 0.05$) for the lower extremities, 2.72 for bradykinesia, and 3.40 for amimia (for both items $P < 0.01$). Thus, symptoms of hypokinesia are reduced or reversed in the majority of patients after a six-month period without drugs, while the hyperkinesias of the extremities are increased at the end of this period. No significant change in symptomatology was observed in the group of patients whose treatment had remained the same over a period of ten months.

A similar investigation was done on the three factors described above. The subjects were scored on each factor and then *t*-tests were performed on the difference between weeks 0 and 40 and between the amounts of change between groups 1 and 2 (*t*-tests for correlated samples). The results are shown in Table 4. The cluster including reduced motility, rigidity, and tremor was significantly reduced after drug withdrawal. Furthermore, a comparison of the amount of change in the scores of the two groups also revealed a significant increase in the severity of hypermotility for the patients off drugs.

Comment

Neurologists have been of the opinion that there is an inverse relationship between the manifestations of Parkinson's disease and certain types of abnormal movements, such as those occurring in Huntington's disease. This was demonstrated most dramatically in parkinsonian patients treated with levodopa. Reports[2,14] have also indicated that this reciprocity exists for drug-induced motor disorders. One of us (G. E. C.)[15] among others, has shown that bradykinesia and tremor were low in patients with pronounced tardive dyskinesia and vice versa.

By means of a new classification of motor disorders in drug-treated patients and a factor analysis, it was possible to define the syndrome of reduced motility, often referred

to as pseudoparkinsonism, and the condition known as tardive dyskinesia. The analysis also generated a third syndrome which cannot be recognized as a neurological entity.

A number of investigators, particularly Degkwitz,[2] have indicated that the reduction or removal of neuroleptics may uncover or aggravate symptoms of tardive dyskinesia. Similarly, a study by Crane et al[16] revealed that dyskinesias of the extremities tended to increase in patients removed from drugs for three months, even though a total rating of all motor abnormalities was unchanged or diminished. A more recent investigation[7] has shown that the global ratings of tardive dyskinesia increased slightly when patients treated with high doses of trifluperazine were returned to therapy with moderate doses of neuroleptics. In another series of patients, similar responses were observed when routine drug treatment was replaced by a placebo. These findings were replicated and supported statistically by using the proposed classification and its factors.

In conclusion, the rating instrument and the analysis of data were sufficiently sensitive to make a distinction between patients on and off drugs and also to detect differential effects of drug withdrawal on two classes of motor abnormalities.

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Nonproprietary and Trade Names of Drugs

Levodopa—*Larodopa.*
Thioridazine—*Mellaril.*

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