

Historical Perspective on Movement Disorders

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Before atypical antipsychotics were developed, neuroleptics given to patients for the treatment of psychosis often caused movement disorders. Although the role of neuroleptics in the development of tardive dyskinesia was never certain, this adverse effect was of great concern to physicians because its effects could be irreversible and devastating to the patient. It is important to understand whether involuntary movement disorders are an intrinsic part of schizophrenia, because if so, then a certain percentage of patients will develop the dyskinetic syndromes whether they are treated or not. To uncover the role of antipsychotic medications in tardive dyskinesia, it is necessary to examine the descriptions of abnormal movements made by those who were first researching schizophrenia, as well as modern descriptions of neuroleptic-naïve individuals with schizophrenia. The physicians who initially described the syndrome of tardive dyskinesia had observed preneuroleptic schizophrenia firsthand and saw a difference in the movements of treated and untreated patients. Nevertheless, the idea of a chronic movement disorder caused by treatment with neuroleptics would become controversial for many years. With the development of the atypical antipsychotics, the incidence and prevalence of tardive dyskinesia have dropped remarkably, suggesting that psychosis, its treatment, and dyskinesias are not inextricably linked.

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Until the development of the atypical antipsychotics, neuroleptics commonly given to patients for the treatment of psychosis often caused movement disorders. Psychosis can be very frustrating for the patient to live with and for the physician to treat, and the extra burden of drug-induced movement disorders can further discourage those involved. Even though they were aware of the risk for serious side effects, physicians had no choice but to prescribe neuroleptics for patients with psychosis because it could not go untreated and there were no other available medications.

The only course of action open to the physician was to prescribe a neuroleptic and “keep an eye on” the patient for any possible movement disorders. Monitoring was, and is still, done by performing regular Abnormal Involuntary Movement Scale (AIMS)¹ assessments of patients. A great concern to physicians was the development of tardive dyskinesia. Tardive dyskinesia could be irreversible and devastating to the quality of life of the patient. However, the steps to be taken if the AIMS assessment revealed signs of tardive dyskinesia were never clear. Physicians

could switch from a higher to a lower potency neuroleptic or discontinue neuroleptic treatment altogether, but many patients could not function without treatment, and it was never certain that medication discontinuation would reverse the tardive dyskinesia. The few data that were available on interrupted treatment of psychosis discouraged it as a measure for counteracting tardive dyskinesia.

Fortunately, this treatment situation has changed over the past 15 years. In the new era of psychosis treatment, there are acceptable treatment options available when tardive dyskinesia is discovered in a patient. With a medication change, there is a likelihood that the tardive dyskinesia will decrease in severity and possibly resolve completely.

DO ANTIPSYCHOTIC MEDICATIONS INCREASE THE RISK OF TARDIVE DYSKINESIA?

When tardive dyskinesia was first described in the middle of the last century, it was considered to be a new syndrome and quite rare. These early reports raised the question of whether an old observation—spontaneous movements associated with schizophrenia—was being recognized anew and confused with tardive dyskinesia. Several psychiatrists inquired as to whether these movements were ascribable to neuroleptics, and if they were, whether the drugs were merely unmasking movements that were often present in schizophrenia.

Although there are unanswered questions concerning the role of antipsychotic drugs in tardive dyskinesia, there is no debate about the role the neuroleptics played in

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Table 1. Verbatim Descriptions of Spontaneous Dyskinesia in Patients From the Preneuroleptic Era^a

“Peculiar facial grimacing, especially of the mouth . . . twisting her mouth when talking . . . sometimes makes pouting motion with lips.”

“There was much facial grimacing, frowning, jutting the lower jaw forward and forming his mouth in the shape of a snout.”

“There were a fair number of mannerisms and facial movements, the most noticeable one being flipping of his lower lip.”

“She was twitching her body about, making aimless jerking motions with her arms and hands. She was sucking her lips in and out making a hissing sound.”

“Grimacing . . . there was considerable grimacing with sucking and protruding of her lips.”

“Ritualistic gestures with feet . . . holds lips in an exaggerated pout.”

^aReprinted with permission from Fenton.⁴

inducing certain other movement disorders. Acute dystonic reactions had not been seen outside the context of encephalitis lethargica and post-encephalitic parkinsonism before antipsychotic medications were developed, and akathisia was a rare phenomenon outside of its association with Parkinson’s disease. Acute akathisia and tardive akathisia are also clearly associated with neuroleptics, as is reversible parkinsonism. Now, acute dystonic reactions are not associated with certain new antipsychotics.

The importance of understanding whether involuntary movement disorders are due to the schizophrenic disorder or its treatment is that the information will help neurologists localize the parts of the brain involved and thereby aid in focusing research. It will also help in assessing the potential long-term adverse effects of the newer generation of antipsychotic drugs. If dyskinesias of various types are inherent to schizophrenia, then a certain percentage of patients will develop the syndromes whether they are treated or not.

MOVEMENT DISORDERS IN PATIENTS WITH SCHIZOPHRENIA NOT TREATED WITH ANTIPSYCHOTICS

To uncover the role of antipsychotic medications in tardive dyskinesia, it is necessary to go back to the early literature on schizophrenia and examine the descriptions of abnormal movements written by those who were first researching this disorder. The early patients were never treated with neuroleptic drugs, and therefore any signs of dyskinesia they showed might indicate abnormal movements inherent in psychosis.

Movement disorders were described in patients with schizophrenia prior to the development of neuroleptics, although reports are conflicting in separating out symptoms of psychosis from movement disorders. Bleuler,² writing in 1908, believed that all the movement abnormalities he and others observed in schizophrenic patients were “dependent upon psychic factors for their origin as well as their disappearance. The motor symptoms which

we have been able to analyze could often be explained entirely on a psychic basis.”^{3(p445)}

In 1919, Kraepelin³ described movements that he called “spasmodic phenomena”:

Some of them resemble movements of expression, wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongue and lips, twisting of the eyes, opening them wide, and shutting them tight, in short, those movements which we bring together under the name of making faces or *grimacing*; they remind one of the corresponding disorders of choreic patients. . . . Connected with these are further, smacking and clicking with the tongue, sudden sighing, sniffing, laughing, and clearing the throat. But besides, we observe especially in the lip muscles, fine lightning-like or rhythmical twitchings, which in no way bear the stamp of voluntary movements. The same is the case in the tremor of the muscles of the mouth, which appears sometimes in speaking and which may completely resemble that of paralytics. . . . Several patients continually carried out peculiar sprawling, irregular, choreiform, outspreading movements, which I think I can best characterize by the expression ‘athetoid ataxia.’^{3(p83)}

These terms are accurate descriptions for the phenomenology of tardive dyskinesia and have often been cited as evidence supporting the existence of tardive dyskinesia-like movements in medically untreated schizophrenic patients.⁴⁻⁶ However, to put Kraepelin’s quote in context, near the section on athetoid ataxia he also described a variety of physiologic abnormalities that he considered typical, although not diagnostic, of dementia praecox: pupillary abnormalities, episodic aphasia, subnormal body temperatures, hypotension, “blood crises,” and others. None of these have stood the test of time. The same movements Kraepelin described as “athetoid chorea” were classified by Kraepelin himself in another chapter as “stereotypies and mannerisms” of schizophrenia.

In a review, Fenton⁴ described research using exquisitely detailed charts on patients who were residents at a small private hospital in the United States between 1950 and 1975. Those patients discussed here are the ones who were not treated with neuroleptics. He quoted descriptions of the movements of several patients, as shown in Table 1. Fenton and colleagues⁷ analyzed these reported movements with respect to diagnosis and found significantly higher rates of abnormal movements among patients with schizophrenia (23.4%) than without (7.3%) ($p = .0003$). In addition, he found abnormal orofacial movements described in enough detail to be considered definite spontaneous dyskinesias. These were present in a much higher proportion of the schizophrenic patients (14.9%) than of patients without schizophrenia (1.7%). An unstated number of patients had received electroconvulsive therapy or insulin coma treatment, although no significant association was found between these treatments and the move-

ments for either the schizophrenic patients or the non-schizophrenic patients.

While these descriptions are certainly compatible with tardive dyskINETIC movements, they are also compatible with stereotypies, Huntington's disease, and tics. The problem with historical reports that lack film records is that language is often too inexact to convey a movement disorder well enough to be diagnosed without being seen. If possible, authors should publish a videotaped record of patients' abnormal movements to allow members of the medical community to judge for themselves how closely the movements resemble the phenomenology of tardive dyskinesia.

Literature is still published on the prevalence of movement disorders in untreated schizophrenics, and while the fulminant symptoms of catatonia are markedly less frequently seen and less fulminant than they were a century ago, the occurrence of dyskINETIC movements and parkinsonism in untreated schizophrenics persists.

McCreadie et al.⁸ recently reported observations of a cohort of Indian patients with schizophrenia who refused treatment with antipsychotic medications. Of 108 patients identified as schizophrenic at baseline, 37 were available for follow-up 18 months later. The other patients had either received antipsychotic treatment (N = 36), had died (N = 8), or were untraceable (N = 27). The mean age of the patients followed was 52 years, and their mean duration of illness was 17 years. Using the Schooler and Kane⁹ criteria for dyskinesias, 17 (46%) of the 37 patients had dyskinesias at baseline, and 13 (35%) had dyskinesias at 18 months. Only 9 patients had dyskinesias at both baseline and follow-up. Eight had dyskinesias at baseline but not follow-up, and 4 had dyskinesias at follow-up but not at baseline. Surprisingly, the only group difference between the sustained dyskinesia group and the others was a higher level of parkinsonism at the second assessment. The variable presence of the movements is typical of psychogenic movement disorders but could also be seen with episodic disorders or, possibly, movements that wax and wane in parallel with psychiatric exacerbations.

McCreadie et al.¹⁰ also evaluated 70 chronically ill, never-treated patients with schizophrenia and 181 of their first-degree relatives. Using Schooler and Kane criteria,⁹ they found that 23 of the 70 patients had probable dyskinesia. An additional 6 had mild movements, defined as a score of 2 on the AIMS in at least one body part. In addition, 19 had parkinsonism. Siblings of schizophrenic patients with dyskinesias had a higher rate of dyskinesias, although none had ever been treated with neuroleptics. The higher rate of dyskinesias in siblings suggests a familial component to dyskINETIC movements. However, the rate of parkinsonism was no different in siblings of patients with dyskinesias than in siblings of patients without dyskinesias.

Therefore, movement disorders have been described in patients with schizophrenia without antipsychotic treatment, although whether they were caused by the psychosis or by a secondary disorder is not necessarily clear.

POSSIBLE CAUSES OF MOVEMENT DISORDERS OTHER THAN ANTIPSYCHOTIC MEDICATIONS

In 1959, Mettler and Crandell¹¹ reviewed neurologic diagnoses made during 1955 and 1956 in a large psychiatric hospital that had a close working relationship with the Neurological Institute of New York. Because of this relationship, the hospital had a larger-than-average percentage of patients with neurologic diagnoses. Of 5704 patients, the researchers found only 35 with major choreic syndromes. They noted, however, that patients with minor signs would be overlooked in a population this large. The movement disorders were never thought to be due to the psychosis alone and always had a separate "organic" cause.

Kraepelin³ stated that his patients looked like "paralytics," a term he used to refer to people with syphilis. In their book *Neurosyphilis*, Merritt et al.¹² noted that neurosyphilis may indeed produce mental changes compatible with the diagnosis of dementia praecox, although manic depressive symptoms are more common. Stroke is common in neurosyphilis, so that posterior cerebral artery syphilitic vasculitis may produce "chorea, athetosis, ataxia or choreoathetoid movements."^{12(p112)} Merritt et al. further explained that "paranoid formulations and oddities of conduct and thought of a schizophrenic nature occur in a moderate number of cases of paresis in the early periods" and that "tremors of the facial muscles, of the extended tongue and of the outstretched fingers occur very early."^{12(p222)}

Spontaneous dyskinesias have been recognized in the nonpsychiatric population as well as in patients with psychiatric disorders. Stereotypies, for example, are common, especially among the edentulous.¹³ Individuals who are edentulous generally grind their gums together, appearing to be chewing when the mouth is actually empty. Excluding the edentulous and those with poorly fitting dentures and loose teeth, there is still a noteworthy prevalence of dyskinesias in the general population.

Older patients are also susceptible to dyskinesias. Bourgeois et al.¹⁴ found that of 270 residents of a nursing home, 18% of those who were never treated with neuroleptics had dyskinesias. Forty-two percent of the residents who had previously been treated with neuroleptics had dyskinesias. Another similar study by Blowers et al.¹⁵ examined dyskinesias in 500 residents of several nursing homes and found spontaneous dyskinesias in 31.7% of residents never treated with neuroleptics, a significantly ($p = .001$) smaller percentage than among the residents who had taken neuroleptics. Klawans and Barr¹⁶ found

much lower rates of dyskinesias than Bourgeois et al.¹⁴ and Blowers et al.¹⁵ in elderly people never treated with neuroleptics, possibly because the population was also limited to those without any history of central nervous system disease. Klawans and Barr¹⁶ found the prevalence of lingual-facial-buccal dyskinesias in individuals in their sixth decade to be 0.8%, in their seventh decade to be 6%, and in their eighth decade to be 7.8%. Kane et al.¹⁷ found a rate of mild dyskinesias of 4% in 151 subjects attending senior citizen activity programs, excluding those with psychiatric histories or confounding neurologic or medical problems.

Thus it is clear that there is a small rate of spontaneous dyskinesias among the non-neuroleptic-treated elderly, and there are abnormal movements among never-treated schizophrenics, which include both hyperkinetic movements similar to classic oral-buccal-lingual tardive dyskinesia and parkinsonism.¹⁸ It is unclear if the schizophrenic movements are so similar as to be mistaken for tardive dyskinesia.

MOVEMENT DISORDERS IN PATIENTS TREATED WITH ANTIPSYCHOTIC MEDICATIONS

While the notion that neuroleptics do not cause tardive dyskinesia has been raised, there is good evidence to believe that neuroleptics do induce tardive movement disorders. Non-tardive dyskinesia choreoathetoid disorders, excepting spontaneous facial dyskinesias in the elderly, are quite rare, and non-drug-induced dyskinesias in the elderly represent only a fraction of tardive dyskinesia cases. Also, the clinicians who first started using neuroleptics in the 1950s and were familiar with untreated psychotic patients clearly noticed a new syndrome after using neuroleptics. Furthermore, the prevalence of tardive dyskinesia has dropped markedly with a switch from neuroleptics to atypical antipsychotics.

Conventional Antipsychotic Medications

Reserpine was first used to treat mania in 1949, and chlorpromazine was developed in France in 1952 and released in the United States in 1954. The first published report on tardive dyskinesia is generally credited to Schönecker¹⁹ in 1957,²⁰ although his report was overlooked by some early authorities.²¹ Two of the patients described by Schönecker had lip-smacking movements lasting up to 11 weeks after stopping chlorpromazine. A third had movements that persisted for 3 months during treatment. Interestingly, one of the patients developed abnormal movements within 2 weeks of starting chlorpromazine. Schönecker's report was noteworthy because the dyskinesias he described lasted well into treatment and persisted after treatment was discontinued, while the dyskinesias that clinicians were familiar with at the time were transient.²⁰

Sigwald et al.,²² only 2 years later, described "facial-bucco-linguo masticatory dyskinesia" in 4 women under age 69 years who had taken chlorpromazine for 3 to 18 months. In these patients, the movements persisted for over 2 years after they had stopped taking the anti-psychotic. The authors noted that neuroleptic-induced dyskinesias may develop acutely, subacutely, or chronically, and that the first 2 types are transient while the latter is not. The chronic form was thought to be rare. The idea of a chronic movement disorder caused by treatment with neuroleptics would become controversial for many years.²³

As a result of either more widespread use of antipsychotic medication or greater recognition of the syndrome, or both, reports describing the disorder increased. The first American reports appeared in 1960²⁴ and 1962.²⁵ Kruse²⁴ described 3 patients with limb dyskinesias, 1 of whom also had parkinsonism. It was probably the first report of tardive akathisia²⁶: "We have now seen three cases (among more than 2,000 patients that have been treated with various phenothiazines over long periods) where these symptoms persisted for 3–18 months after the drug was stopped. The question arises whether phenothiazines are always as innocuous as we had believed them to be."^{24(p153)}

Druckman et al.²⁵ were probably the first to describe tardive dystonia.²⁰ The researchers described a 46-year-old man who "developed a dystonic type of involuntary movement with head extension."^{25(p72)}

The first British reports of tardive dyskinesia were by Hunter et al. in 1964.^{27,28} The researchers noted the clinical similarities of respiratory dyskinesias and fly-catcher tongue to the movement disorders seen with Von Economo's encephalitis.

In 1964, Faurbye et al.²⁹ introduced the term "tardive dyskinesia." Their experience was that tardive dyskinesia rarely developed with less than 6 months of exposure to antipsychotic medications, and it was most commonly seen after several years of treatment. Older age and organic brain disorders were considered risk factors.

Tardive dyskinesia, although recognized, was still considered rare by some circles³⁰ until around 1964, after about a decade's worth of experience with neuroleptic medications. In his classic 1961 study of drug-induced movement disorders, Ayd³¹ had not even reported on tardive dyskinesia. But in 1964, Faurbye et al.²⁹ reported a 26% prevalence rate of tardive dyskinesia among patients with schizophrenia treated with neuroleptics, and in 1967, Degkwitz and Wenzel³² reported an 11% prevalence rate. By 1973, prevalence rates of up to 40% were reported.³³

Some authorities argued that most patients who were described as having tardive dyskinesia were still taking the medications that caused it and many would remit if the medications were discontinued.^{34–36} In addition, tardive dyskinesia "was initially regarded as a complication of antipsychotic drug therapy largely restricted to elderly,

chronically institutionalized, frequently brain-damaged patients receiving prolonged drug treatment."³⁷ The term *tardive dyskinesia* was not universally employed, although the syndrome was increasingly recognized. Delay and Deniker,²¹ known for their recognition of the neuroleptic malignant syndrome, did not use the term *tardive dyskinesia*; instead, they described "lasting syndromes" persisting after discontinuation of the neuroleptics and classified them into 3 categories: buccolingual hyperkinesia and dyskinesia; truncal dyskinesias, as reported by Uhrbrand and Faurbye³⁸; and choreic movements of the limbs, categorized under the title "terminal extrapyramidal syndrome," as reported by Degkwitz et al.³⁹

Crane was key in bringing the importance of tardive dyskinesia to the fore²⁰ in 2 influential articles, published in 1968⁴⁰ and 1973,⁴¹ and in a symposium held in 1968.⁴² In 1968, Crane⁴⁰ reported having found over 500 cases of tardive dyskinesia published in 21 papers. He thought tardive dyskinesia was a drug-induced syndrome, but noted "the causal relationship between treatment with neuroleptics and oral dyskinesias is presumptive, but is likelier than the other possibilities."^{40(p46)} Yet a 1973 paper opined that "the role of phenothiazines in the genesis of this syndrome is especially unclear,"^{36(p406)} due to the common confounding histories of lobotomies and ECT. The author concluded that "the evidence is not sufficient to establish tardive dyskinesia as a side effect of neuroleptics."^{36(p410)} This was in part due to the still puzzling temporal variability of tardive dyskinesia: sometimes developing while the patient was taking medication, sometimes not; worsening while the patient was taking medication, worsening while the patient was off medication; developing after weeks or after years of taking medication; resolving entirely or not resolving at all either on or off the offending medication. By 1979, the American Psychiatric Association had convened a special task force and issued a report devoted entirely to tardive dyskinesia.³⁷

The wide discrepancies in prevalence rates persist to the current time and reflect many different factors, including patient populations, treatment patterns, physician and staff training, criteria used for diagnosis, and reasons for assessing prevalence (i.e., a population with a tardive dyskinesia prevalence that seems larger than expected may trigger a prevalence study that produces a high rate, whereas a population with a low prevalence of tardive dyskinesia either may not have such a study or one may be conducted to demonstrate the low prevalence). The development of definitions and rating scales for tardive dyskinesia was very important for putting the various reports of dyskinesic syndromes into an understandable context. The generally accepted criteria for the diagnosis of tardive dyskinesia were defined by Schooler and Kane in 1982.⁹ For the criteria to be met for a diagnosis of tardive dyskinesia, a patient must have mild dyskinesic movements in 2 or more parts of the body, or moderate movements in a

single body part. The movements themselves are generally choreic or athetoid and must persist for 4 weeks or more during drug treatment, occur within 4 weeks of oral drug therapy, or appear after 8 weeks of depot injection. The duration of exposure to antipsychotic medications required to meet the criteria for tardive dyskinesia has been reduced over the years to the current 3 months for those under age 60 years and 1 month for those over. However, these are research criteria, and occasionally patients may have tardive dyskinesia after briefer exposure.

Newer Antipsychotic Medications

An interesting question related to whether abnormal movements in patients with schizophrenia are spontaneous dyskinesias intrinsic to schizophrenia, iatrogenic tardive dyskinesia, or intrinsic dyskinesias unmasked by neuroleptic drugs, is what has happened to patients with schizophrenia who are treated with the newer antipsychotics, known as atypical antipsychotics. Atypical antipsychotics have been a dramatic therapeutic advance in terms of side effect movement disorders such as tardive dyskinesia. Although it is uncertain whether these medications have dramatically improved the treatment of psychosis,⁴³ it is clear that they have dramatically reduced the problem of extrapyramidal side effects. As noted by Kane elsewhere in this supplement,⁴⁴ the incidence and prevalence of tardive dyskinesia have dropped remarkably as physicians have switched from treating patients with neuroleptics to treating them with atypical antipsychotics. To date, there are no cases of tardive dyskinesia induced by clozapine or quetiapine and very few by olanzapine. The rate associated with risperidone is also considerably lower than with the previous generation of drugs. The discovery that psychosis treatment and movement disorders were not integrally related has led to the continuing development of ever newer, safer treatments.

CONCLUSION

It is clear that there are abnormal movements among never-treated schizophrenics, which include hyperkinetic movements similar to classic oral-buccal-lingual tardive dyskinesia as well as parkinsonism. It is unclear if these schizophrenic movements are actually tardive dyskinesia. But, it appears that neuroleptics do induce tardive movement disorders. The clinicians who first started using chlorpromazine in the 1950s (and therefore were familiar with psychotic patients in the pre-neuroleptic era) clearly noticed a new syndrome during use of the drug, and the incidence and prevalence rates of tardive dyskinesia have dropped markedly with a switch from neuroleptics to atypical antipsychotics. This epidemiology alone suggests that tardive dyskinesia, in fact, exists in part due to antipsychotic treatment, although hopefully not for much longer.

The introduction of the atypical antipsychotics has almost certainly sounded the death knell for tardive dyskinesia, but we are not there yet. Patients previously treated with neuroleptics are certainly at risk for tardive dyskinesia, as are the 10% to 20% of patients still taking standard neuroleptics. Also, it is not certain that the lower rates of tardive dyskinesia currently encountered in patients treated with atypical antipsychotics will continue as the length of time that patients have been taking these medications increases, because it is possible that the atypical antipsychotics may require a longer exposure than the conventional neuroleptics to produce tardive dyskinesia. But the more time that passes without such an increase, the more secure we may feel that this iatrogenic problem will fade into the past and be primarily of historical and pharmacologic interest.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpalan and others), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Psychopharmacology Research Branch NIMH. Abnormal Involuntary Movement Scale (AIMS). In: Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare Publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
2. Bleuler E. Dementia Praecox or the Group of Schizophrenias. Zinkin J, trans. New York, NY: International Universities Press; 1950
3. Kraepelin EP. Dementia Praecox and Paraphrenia. Barclay RM, trans. Robertson GM, ed. Huntington, NY: Robert E. Krieger Publishing Co Inc; 1971
4. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *J Clin Psychiatry* 2000;61(suppl 4):10–14
5. Casey DE. Tardive dyskinesia: pathophysiology and animal models. *J Clin Psychiatry* 2000;61(suppl 4):5–9
6. Chatterjee A, Chakos M, Koren A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. *Am J Psychiatry* 1995;152:1724–1729
7. Fenton WS, Blyler CR, Wyatt RJ, et al. Prevalence of spontaneous dyskinesia in schizophrenic and in schizophrenic and non-schizophrenic psychiatric patients. *Br T Psychiatry* 1997;171:265–268
8. McCreedy RG, Padmavati R, Thara R, et al. Spontaneous dyskinesia and parkinsonism in never-medicated, chronically ill patients with schizophrenia: 18-month follow-up. *Br J Psychiatry* 2002;181:135–137
9. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia [letter]. *Arch Gen Psychiatry* 1982;39:486–487
10. McCreedy RG, Thara R, Srinivasan TN, et al. Spontaneous dyskinesia in first-degree relatives of chronically ill, never-treated people with schizophrenia. *Br J Psychiatry* 2003;183:45–49
11. Mettler FA, Crandell A. Neurologic disorders in psychiatric institutions. *J Nerv Ment Dis* 1959;128:148–159
12. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York, NY: Oxford University Press; 1946
13. Friedman JH. Stereotypy and catatonia. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and Movement Disorders. 3rd ed. Baltimore, Md: Williams and Wilkins; 1988:709–728
14. Bourgeois M, Bouilh P, Tignol J, et al. Spontaneous dyskinesias vs neuroleptic-induced dyskinesias in 270 elderly subjects. *J Nerv Ment Dis* 1980;168:177–178
15. Blowers AJ, Borison RL, Blowers CM, et al. Abnormal involuntary movements in the elderly. *Br J Psychiatry* 1981;139:363–364
16. Klawans HL, Barr A. Prevalence of spontaneous lingual-facial-buccal dyskinesias in the elderly. *Neurology* 1982;32:558–559
17. Kane JM, Weinhold P, Kinon B, et al. Prevalence of abnormal involuntary movements ("spontaneous dyskinesias") in the normal elderly. *Psychopharmacology (Berl)* 1982;77:105–108
18. Kopala LC. Spontaneous and drug-induced movement disorders in schizophrenia. *Acta Psychiatr Scand Suppl* 1996;389:12–17
19. Schönecker M. Ein eigentümliches syndrom im oralen Bereich bei Megaphenapplikation. [Paroxysmal dyskinesia as the effect of megaphen.]. *Nervenarzt* 1957;28:550–553
20. Tarsy D. History and definition of tardive dyskinesia. *Clin Neuropharmacol* 1983;6:91–99
21. Delay J, Deniker P. Drug-induced extra-pyramidal syndromes. In: Vinken PJ, Bruyn GW, eds. Diseases of the Basal Ganglia. New York, NY: Elsevier North Holland; 1968:248–266
22. Sigwald J, Bouttier D, Raymondeaud C, et al. Quatre cas de dyskésie facio-bucco-linguo-masticatrice à l'évolution prolongée secondaire à un traitement par les neuroleptiques. *Rev Neurol (Paris)* 1959;100:751–755
23. Tanner CM. Drug induced movement disorders (tardive dyskinesia and dopa-induced dyskinesia). In: Vinken PJ, Bruyn GW, eds. Extrapyramidal Movement Disorders. New York, NY: Elsevier North Holland; 1986
24. Kruse W. Persistent muscular restlessness after phenothiazine treatment: report of 3 cases [letter]. *Am J Psychiatry* 1960;117:152–153
25. Druckman R, Seelinger D, Thulin B. Chronic involuntary movements induced by phenothiazines. *J Nerv Ment Dis* 1962;135:69–76
26. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. *Neurolog* 2003;9:16–27
27. Hunter R, Earl CJ, Janz D. A syndrome of abnormal movements and dementia in leucotomized patients treated with phenothiazines. *J Neurol Neurosurg Psychiatry* 1964;27:219–223
28. Hunter R, Earl CJ, Thormicroft S. An apparently irreversible syndrome of abnormal movements following phenothiazine medication. *Proc R Soc Med* 1964;57:758–762
29. Faurbye A, Rasch PJ, Petersen PB, et al. Neurological symptoms in pharmacotherapy of psychoses. *Acta Psychiatr Scand* 1964;40:10–27
30. A side effect of phenothiazines [The London Letter]. *CMAJ* 1964;91:1081
31. Ayd FJ. A survey of drug-induced extrapyramidal reactions. *JAMA* 1961;175:1054–1060
32. Degkwitz R, Wenzel W. Persistent extrapyramidal side effects after long-term application of neuroleptics. In: Brill H, Cole J, Deniker P, et al, eds. Neuropsychopharmacology: Proceedings of the 5th Collegium Internationale Neuropsychopharmacologicum. Amsterdam, the Netherlands: Excerpta Medica; 1967:608–615
33. Crane GE. Persistent dyskinesia. *Br J Psychiatry* 1973;122:395–405
34. Kline NS. On the rarity of "irreversible" oral dyskinesias following phenothiazines. *Am J Psychiatry* 1968;124(suppl 4):48–54
35. Turek IS. Drug induced dyskinesia: reality or myth? *Dis Nerv Syst* 1975;36:397–399
36. Curran JP. Tardive dyskinesia: side effect or not? *Am J Psychiatry* 1973;130:406–410
37. Baldessarini RJ, Cole JO, Davis JM, et al. Tardive Dyskinesia: Report of the American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs. Task Force Report 18 ed. Washington, DC: The American Psychiatric Association; 1979
38. Uhrbrand L, Faurbye A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. *Psychopharmacologia* 1960;1:408–418
39. Degkwitz R, Binsack KF, Herkert H, et al. Das terminale extrapyramidale Insuffizienz- bzw. Defektsyndrom infolge chronischer Anwendung von Neuroleptics. [On the problem of persistent extrapyramidal hyperkinesia following prolonged use of neuroleptics.]. *Nervenarzt* 1967;38:170–174
40. Crane GE. Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. *Am J Psychiatry* 1968;124(suppl 4):40–48
41. Crane GE. Clinical psychopharmacology in its 20th year: late, unanticipated effects of neuroleptics may limit their use in psychiatry. *Science* 1973;181:124–128
42. Crane GE, Gardner R Jr, eds. Psychotropic Drugs and Dysfunctions of the Basal Ganglia. Washington, DC: US Public Health Service; 1969. Publication 1938
43. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003;60:553–564
44. Kane JM. Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. *J Clin Psychiatry* 2004;65(suppl 9):16–20