Prevalence of Spontaneous Dyskinesia in Schizophrenia

Wayne S. Fenton, M.D.

Spontaneous abnormal involuntary movements phenomenologically identical to neuroleptic-induced tardive dyskinesia have been described in schizophrenia for over a century. Because at present nearly all patients with schizophrenia are exposed to neuroleptic medications, information about the prevalence of spontaneous dyskinesia is obtained from accounts from the preneuroleptic era, evaluations of first-episode patients before neuroleptic treatment, and the identification and assessment of drug-naive patients in developing countries. In this report, data from 14 studies of neuroleptic-naive patients with schizophrenia are used to generate age-adjusted estimates of the prevalence of spontaneous dyskinesia. While the precision of this estimate is limited by the difficulty of obtaining large, untreated samples, available data suggest a spontaneous dyskinesia rate of approximately 4% in first-episode schizophrenic patients, 12% for patients ill several years but below age 30 years, 25% for those aged between 30 and 50 years, and 40% for those aged 60 years or older. Relative to the incidence and accrued prevalence of spontaneous dyskinesia expected during the natural history of untreated schizophrenia, the cumulative impact of treatment with new neuroleptic agents has yet to be determined.
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Spontaneous dyskinesias are abnormal involuntary movements found in individuals never exposed to neuroleptic medications and present in a variety of neurologic disorders and in a small proportion of the normal elderly.[1–3] Spontaneous dyskinesias, particularly tongue protrusions, chewing movements of the mouth, and choreoathetoid movements of the extremities, were described as specifically characteristic of patients with schizophrenia at least 100 years before the introduction of phenothiazines.[4,5]

Kraepelin provided the first systematic description of these movements in 1919. He described "the spasmodic phenomenon in the musculature of the face . . . distortions of the corners of the mouth, irregular movements of the tongue and lips . . . connected with these are further smacking and clicking of the tongue . . . several patients continually carried out peculiar sprawling, irregular choreiform outspreading movements . . . best characterized by the expression athetoid ataxia."[6,7] In the 1930s, Leonhard defined a subtype of schizophrenia, parakinetic catatonia, in which "voluntary actions are carried out in an unnatural awkward way and involuntary movements are jerky and reminiscent of choreiform movements. The involuntary movements that occur seem to be distorted reactive and pseudo-expressive movements. Facial movements are especially affected."[8] Early in the century, 5% to 10% of all schizophrenic patients were diagnosed with the parakinetic schizophrenia subtype.[5]

Bleuler attributed abnormal facial movements in schizophrenia to psychological factors such as the covert expression of contempt.[9] Today, the spontaneous emergence of movement disorders in the course of untreated schizophrenia is thought to represent a motor manifestation of the underlying cerebral pathology associated with severe schizophrenic illness.[10–14]

Spontaneous dyskinesia among never-medicated patients complicates efforts to define the risk of neuroleptic-induced tardive dyskinesia. To evaluate whether or not a neuroleptic agent is associated with a risk of tardive dyskinesia, the proportion of patients exposed to the medication who develop tardive dyskinesia must be compared to the expected rate of emergence of spontaneous dyskinesia in patients with the same diagnosis.[15,16]

While it is well established that abnormal movements occur during the course of schizophrenia, few data allow an estimate of the incidence of spontaneous dyskinesia in this disorder. Generating an accurate estimate of the rate of spontaneous dyskinesia in schizophrenia requires prospective longitudinal evaluation of patients not exposed to medication. Because withholding treatment is ethically unacceptable, such a study will never be conducted. As a consequence, available information about the prevalence of spontaneous dyskinesia is obtained from accounts from the preneuroleptic era, evaluations of first-episode patients before neuroleptic treatment, and the identification and assessment of drug-naive patients in developing countries.

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Reprint requests to: Wayne S. Fenton, M.D., Chestnut Lodge Hospital, 500 W. Montgomery Ave., Rockville, MD 20850 (e-mail: WSFMD@AOL.COM).

In this article, I review available data on the prevalence and clinical correlates of spontaneous dyskinesia in neuroleptic-naive patients with schizophrenia. The rate, clinical correlates, and diagnostic specificity of abnormal involuntary movements in young adult patients treated at Chestnut Lodge Hospital prior to the use of neuroleptics is compared to rates obtained from examination of other rare nonneuroleptic-exposed populations of differing ages. These data are used to estimate the age-adjusted risk of movement disorder in schizophrenia absent neuroleptic exposure.

SPONTANEOUS DYSKINESIA IN NEUROLEPTIC-NAIVE YOUNG ADULTS WITH SERIOUS MENTAL ILLNESS

From the 1940s through the 1960s, Chestnut Lodge, a small private hospital in Rockville, Md., specialized in treating young adult patients with serious mental illness with intensive (4 times/week) individual psychotherapy. Small caseloads, extensive documentation, and the verbatim transcription of clinical case conferences yielded a rich and unique narrative archive of clinical treatment of patients treated largely before the introduction of neuroleptics. These records, typically 100 or more pages per patient, were sufficiently detailed to allow estimation of the rate of abnormal involuntary movements in schizophrenia and other psychiatric disorders.

In a long-term follow-up study of patients with serious mental illness, the records of all patients treated at Chestnut Lodge between 1950 and 1975 (N = 532) were reviewed, patients were rediagnosed according to modern diagnostic criteria, and blindly followed up an average of 23 years after index admission to determine long-term outcome.[17,18] To study the natural history of schizophrenia subtypes, including movement disorders, original medical records were reviewed blind to both baseline and outcome data collected earlier. Ratings were based on all clinical information obtained up to and including the first 3 months of hospitalization. The reliability of all sign and symptom ratings, subtype diagnoses, longitudinal illness course variables, and medication exposure has been reported.[19,20]

All descriptions of movement abnormalities were copied verbatim from records and transcribed onto forms that allowed rating at a later date blind to all clinical information, including treatment history. Two raters (W.S.F. and R.J. Wyatt, M.D.) independently rated these transcriptions for the presence or absence of abnormal movements in 7 body areas; adequate reliability was achieved, and disagreements were resolved by consensus judgment.[21] Spontaneous dyskinesias were considered definite if abnormal oral or facial movements were noted along with an explicit clinical description (Table 1).

In the follow-up cohort, 94 of 187 patients diagnosed with DSM-III schizophrenia, 44 of 87 with schizoaffective disorder, 10 of 15 with schizophreniform disorder, 21 of 33 with schizotypal personality disorder, 33 of 58 with borderline personality disorder, 32 of 59 with unipolar affective disorder, and 14 of 23 with bipolar disorder had no lifetime exposure to neuroleptic medications up to and including index admission (mean year = 1959).[22] The mean ± SD age of schizophrenia patients at admission was 28.5 ± 7.8 years, 51% were female, and patients had been ill a mean ± SD duration of 8.3 ± 6.6 years. Neither age, gender, nor duration of illness differed significantly across diagnostic groups. Although a greater proportion of schizophrenic patients had a history of electroconvulsive therapy or insulin coma treatment or both, exposure to these treatments was not significantly associated with abnormal movements for any diagnostic group.

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

"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."

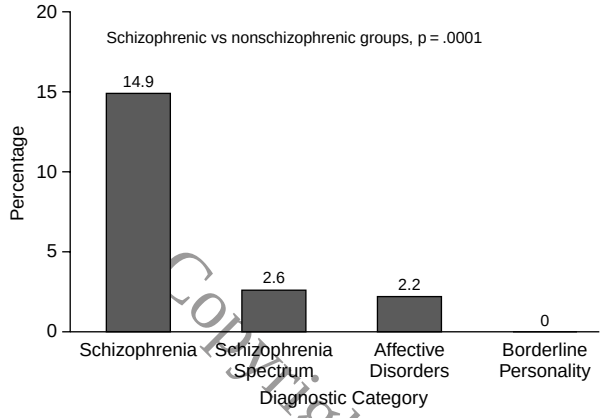
Specificity to Schizophrenia

Abnormal movements in one or more of 7 body areas—face, mouth, eyes and periorbital area, neck, arms, legs, and trunk as well as gait—were documented in the record of 22 (23.4%) of 94 of patients with schizophrenia. Significantly lower rates were found in 13 (7.3%) of 179 patients with nonschizophrenia diagnoses ($\chi^2 = 12.96$, $p = .0003$). Most abnormal movements among nonschizophrenic patients were found in the records of 5 (11.4%) of 44 patients with schizoaffective disorder and 3 (14.3%) of 21 patients with schizotypal personality. Abnormal orofacial movements described in sufficient detail to be considered definite spontaneous dyskinesias (Figure 1) were found almost exclusively among 14 (14.9%) of 94 schizophrenic patients; 3 (1.7%) of 179 nonschizophrenic patients had such movements ($\chi^2 = 16.25$, $p = .0001$).

Predictors of Risk

To identify risk factors associated with spontaneous dyskinesia in schizophrenia, clinical and illness natural history indicators were compared between schizophrenia patients with (N = 14) and without (N = 80) orofacial spontaneous dyskinesia. Compared to patients without orofacial movements, schizophrenic patients with orofacial spontaneous dyskinesia demonstrated significantly lower premorbid IQ, more severe negative symptoms—as measured by the Posi-

Figure 1. Spontaneous Orofacial Dyskinesia in Schizophrenia, Schizophrenia Spectrum Disorders, Affective Disorders, and Borderline Personality Disorders[a]



[a]Data from Fenton et al.[22]

tive and Negative Syndrome Scale—and remained symptomatic for a significantly greater proportion of the follow-up period.[21] The deficit syndrome[23] was often associated with spontaneous dyskinesia: one third—9 (32%) of 28 deficit syndrome patients—compared with 5 (8%) of 66 nondeficit syndrome drug-naive schizophrenic patients demonstrated definite orofacial spontaneous dyskinesia ($\chi^2 = 7.52$, $p = .005$). Thus, within schizophrenia, spontaneous dyskinesia appeared to be associated with cognitive dysfunction, deficit psychopathology, and poor long-term outcome.[24]

COMPARISON WITH OTHER NEUROLEPTIC-NAIVE COHORTS

To date, the prevalence of spontaneous dyskinesia has been reported for 1 additional preneuroleptic era sample based on case record review,[25] 4 first-episode patient cohorts,[26–29] 5 untreated patient samples from developing countries,[30–34] 2 elderly neuroleptic-naive schizophrenia patient groups,[35,36] and a small group of neuroleptic-naive veterans with paranoid schizophrenia.[37] These studies, ordered by mean age of the patient sample, are summarized in Table 2. As noted, most studies that conducted direct examination of neuroleptic-naive cohorts defined spontaneous dyskinesia based on Abnormal Involuntary Movement Scale scores. When clinical correlates or predictors of spontaneous dyskinesia were evaluated, older age, longer duration of illness, greater severity of negative symptoms, and poor prognosis were most consistently associated with the phenomenon.

Seven studies of spontaneous dyskinesia including conventional neuroleptic-treated comparison groups[26,29,30,33,36,38] report a numerically higher prevalence of dyskinesia in the drug-exposed group, although this difference was statistically significant in only 3 studies.[26,30,34] Small sample sizes, an older mean age in drug-exposed groups, and/or the masking of dyskinesia in drug-treated patients may account for the relatively narrow differences in prevalence reported for neuroleptic-exposed patients compared with naive patients.

Consistent with the finding that spontaneous dyskinesia is relatively specific to schizophrenia,[22] in the only other study to evaluate several diagnostic groups, Turner[25] found spontaneous dyskinesia described in the records of 28.6% of patients with schizophrenia, 0.5% of those diagnosed as manic-depressive; 3.6% of those diagnosed as organic, and none of those classified as neurotic. A relatively greater prevalence of spontaneous dyskinesia has also been reported in patients with schizophrenia spectrum diagnoses.[22,39]

ESTIMATED AGE-ADJUSTED RISK OF SPONTANEOUS DYSKINESIA IN SCHIZOPHRENIA

When the rate of spontaneous dyskinesia in each sample of schizophrenic patients studied is correlated with the mean age of the sample, the reported prevalence of spontaneous dyskinesia is significantly associated with the sample's mean age ($r = 0.71$, $p < .005$). Figure 2 illustrates these data and the resulting regression line.

The weighted mean prevalence of spontaneous dyskinesia in 4 studies[26–29] of first-episode patients is 4%. Weighted prevalence of spontaneous dyskinesia from studies[21,31,32] of non–first-episode patients with a mean patient age of 30 years or younger is 12%. Three studies[25,30,37] of patients with a mean age of 31 to 50 yield a pooled weighted spontaneous dyskinesia prevalence of 25%. Finally, 4 studies[33,34,36,38] with a mean sample age over 60 years yield a pooled weighted spontaneous dyskinesia prevalence of 42%.

CONCLUSIONS

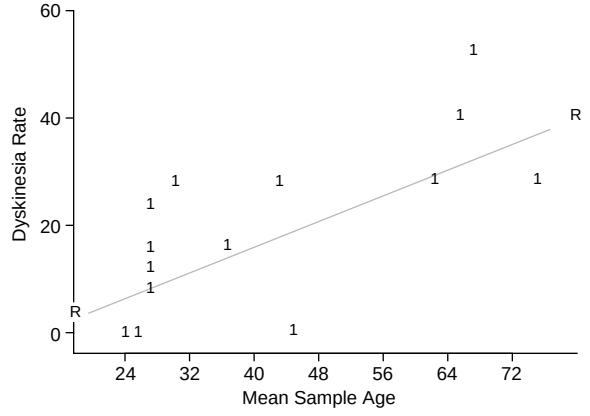
The scarcity of schizophrenic patient populations that have never been exposed to neuroleptic medications limits the precision with which we can estimate the prevalence of spontaneous dyskinesia in this disorder. Nonetheless, available data suggest a rate of approximately 4% in first-episode schizophrenic patients, 12% for patients ill several years but below age 30 years; 25% in those aged 30 to 50 years, and 40% for those aged 60 years or older. In addition to age, risk appears to be influenced by illness-related factors such as cognitive impairment, negative symptoms, and a poorer prognosis. Untreated schizophrenia, particularly in its most severe form, appears to have a motor component in a significant number of cases. While the pathophysiology of spontaneous dyskinetic movements in schizophrenia is poorly understood, phenomenologically these abnormal movements appear to be identical to neuroleptic-induced tardive dyskinesia.

Table 2. Prevalence of Spontaneous Dyskinesia in Neuroleptic-Naive Schizophrenic Patients[a]

Prevalence, %	Age, y, mean ± SD	Population	Spontaneous Dyskinesia Criteria	N	Predictors	Authors
0	24	DSM-III, first episode	AIMS, not blind	50		Chorfi and Moussaoui, 1989[26]
1	25.8 (16–40)[b]	RDC, first episode	AIMS, Schooler and Kane	89	Spontaneous EPS (16.9%) associated with negative symptoms, poor treatment response	Chatterjee et al, 1995[27]
7	27 ± 8	DSM-IV, first episode	AIMS, Schooler and Kane	27		Puri et al, 1999[29]
10	27.7 ± 9.7	DSM-III-R, Ireland, first episode	AIMS, Schooler and Kane	49	Spontaneous dyskinesia associated with lower educational attainment	Gervin et al, 1998[28]
14	28 ± 5.3	DSM-III-R, Morocco	AIMS, Schooler and Kane	22	Total AIMS increased with age and duration of illness	Fenn et al, 1996[31]
23	28 (16–55)[b]	DSM-III or Feighner, preneuroleptic inpatients	Medical record review	94	Spontaneous dyskinesia associated with lower IQ, more negative symptoms, poorer outcome	Fenton et al, 1994[21]
27	29.6 ± 6.5	DSM-IV, Morocco, never treated	AIMS, Schooler and Kane	75		Hoffman et al, 1996[32]
14	37 ± 12	DSM-III-R, male, paranoid inpatients	AIMS ≥ 1 in ≥ 2 body areas	21	Muscle force instability associated with positive symptoms	Caligiuri and Lohr, 1994[37]
29	41–45[b]	RDC, preneuroleptic inpatients	Case record review	142	Spontaneous dyskinesia associated with long LOS and poor prognosis	Turner, 1989[25]
0	45 ± 14	DSM-III, Nigeria, never treated	AIMS, Schooler and Kane	12		McCreadie and Ohaeri, 1994[30]
26	62	DSM-IV, rural India	AIMS, Schooler and Kane	19		McCreadie et al, 1997[34]
38	65 ± 8	DSM-IV, rural India	AIMS, Schooler and Kane	21	Spontaneous dyskinesia associated with negative symptoms (trend)	McCreadie et al, 1996[33]
53	66.7 ± 11.7	Chronic inpatients	AIMS ≥ 2 on 1 item	47	Spontaneous dyskinesia associated with older age	Owens et al, 1982[38]
29	75	UK, catchment area	AIMS ≥ 2 global	7		McCreadie et al, 1982[36]

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, EPS = Extrapyramidal symptoms, LOS = length of stay, RDC = research diagnostic criteria, Schooler and Kane = Schooler and Kane Center for Tardive Dyskinesia, UK = United Kingdom.
[b]Age range.

Figure 2. Prevalence of Spontaneous Dyskinesia in 14 Studies of Neuroleptic-Naive Schizophrenia Patients



First-generation antipsychotic agents are associated with approximately a 5% risk of tardive dyskinesia per year of medication exposure for patients under age 40 years,[40,41] and a 3 to 5 times greater risk for older patients.[42] Reviews and meta-analyses of studies that use comparable assessments to evaluate the rate of dyskinesia in patients who have and have never been exposed to conventional neuroleptics (often elderly or institutionalized individuals or both) generally indicate a greater rate of dyskinesia among exposed compared to unexposed subjects.[43] Morgenstern et al.[44] estimated that, on average, the rate of dyskinesia was 2.9 times greater in exposed persons than would be expected absent conventional neuroleptic exposure: 65% of cases in exposed individuals were attributed to neuroleptic-induced tardive dyskinesia.

The risk of tardive dyskinesia associated with new neuroleptic agents appears to be substantially less than that associated with first-generation agents.[45–47] Relative to the incidence and accrued prevalence of spontaneous dyskinesia expected during the natural history of untreated schizophrenia, the cumulative impact of treatment with new neuroleptic agents is not yet clear. Longitudinal assessment of emergent movement disorders in patients treated at first episode with new agents and followed prospectively is required to determine whether long-term exposure to new neuroleptics is associated with a reduction, no change, or increase in the risk of developing a movement disorder over the course of schizophrenia.

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.

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