Behavioral Toxicity of Antipsychotic Drugs

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Extrapyramidal symptoms cause much misery, often go undiagnosed, and can interfere with treatment and rehabilitation. Akinesia is a behavioral state of diminished motoric and psychic spontaneity that is difficult to distinguish from the negative symptoms of schizophrenia. The most useful clinical correlates of akinesia are a subjective sense of sedation and excessive sleeping. Akinesia interferes with social adjustment and may manifest as "postpsychotic depression." The subjective restlessness of akathisia is usually accompanied by telltale foot movements: rocking from foot to foot while standing or walking on the spot. Akathisia is strongly associated with depression and dysphoric responses to neuroleptics and has even been linked to suicidal and homicidal behavior in extreme cases.
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Over the past decade our work has indicated that extrapyramidal symptoms cause much misery, often go undiagnosed, and can interfere with treatment and rehabilitation. However, they remain a controversial and ill-studied area in which there are many assertions and dramatic case reports. Part of the problem is that the measurement of extrapyramidal symptoms is in a primitive state.

Tardive dyskinesia is characterized by observable involuntary movements and usually can be measured adequately—both in clinical practice and in research—with rating scales such as the Abnormal Involuntary Movement Scale (AIMS).[1] Dystonic reactions are similarly observable, but more subjective and intermittent dystonic reactions such as intermittent leg cramps, a tightening of the jaw, cramps of the abdominal wall muscles, or intermittent neck discomfort are often not regarded as dystonic. When dystonic reactions are intermittent they may be regarded as "hysterical." The diagnosis of akinesia and akathisia, however, is in a primitive state.

AKATHISIA

Akathisia is often difficult to diagnose. In severely thought disordered, agitated patients, the distinction between akathisia and psychotic excitement may be impossible. At the other extreme, it may be very difficult to distingush vague anxiety or emotional unease from akathisia. The lack of precise diagnostic criteria may be related to the dual nature of akathisia: a subjective or psychological experience of restlessness and observable motor restlessness. Investigators disagree about the relative importance of these two aspects.

Our group, as is the custom in the United States, has diagnosed akathisia primarily by the patient's responses to structured questions about inner restlessness and by response to antiparkinson drugs. Thus, we ask questions to which nearly all patients can respond intelligibly, such as "Do you feel restless or jittery inside?" and "Is it difficult to sit still?" Amelioration of the reported restless state with the usual antiparkinson medications then confirms the diagnosis.

The British,[2] however, have rightly stated that akathisia cannot be reliably diagnosed by the patient's subjective report. We agree with Barnes and Braude[2] that "general complaints of emotional unease" or "inner restlessness" are too nonspecific for a diagnosis of akathisia. Barnes and Braude have added the more observable criterion of restless leg movements. They claim to distinguish "between patterns of normal restless movement and abnormal (dyskinetic) movements." We, however, are unable to distinguish in a great number of cases between those "purposeless" and "fidgety" movements of the upper and lower extremities that are normal, restless, or diskinetic, and we doubt that others can.

We[3] proposed that the restless movements of akathisia be confined to those foot movements that all clinicians are familiar with: rocking from foot to foot while standing or walking on the spot. These foot movements are easily recognized and, in our experience, are present in all patients with moderate or severe akathisia. Barnes and Braude[4] agreed.

Barnes and Braude[4] also agreed that mild akathisia may not be manifested in observable movements (particularly if the patient has coexisting akinesia). This subjective state can, nevertheless, be tormenting[5,6,7] and may affect the course of treatment.[7,8] A reasonable criterion for "subjective akathisia" is an experience of restlessness relieved to some degree by antiparkinson medication.

We realize that "subjective akathisia" cannot always be reliably differentiated from subtler psychotic excitement or a host of pathologic emotions. Nevertheless, the state, as any clinician will attest, does exist.

The Subjective Experience of Akathisia

Patients with akathisia may describe vague feelings of inner tension, emotional unease, or anxiety, using such phrases as "all wound up like a spring," "nervous-like," "unable to relax," "a hurry-up feeling," "unable to feel comfortable in any position," "tense," "feeling like I have

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to do something," "rowdy-like," "an impatient feeling," "irritable," "keyed up or wired," or "like jumping out of my skin." Kalinowsky[9] stated that akathisia can be "more difficult to endure than any of the symptoms for which . . . [the patient] was originally treated" and cautioned that it may be mistaken for "agitated depression."

It may be useful to describe how akathisia was experienced in some of our more extreme cases. A 24-year-old woman began to cry 3 hours after taking a 12-mg test dose of thiothixene hydrochloride. She felt that she was at her "wit's end," and when asked about restlessness, she answered that she was "miserable with a jittery feeling." She began hearing voices urging her to leave the hospital, and she developed such strange behaviors as climbing the bookcases and crawling. An antiparkinson drug markedly alleviated the akathisia, the associated dysphoria, and the strange behavior. A 31-year-old man, 3 hours after taking a 16-mg test dose of thiothixene hydrochloride, said he had "never felt worse." He stated: "The voices have changed; they now say I'm going to die because I've taken the medication." In his rambling the words "death" and "dying" became frequent. When asked about restlessness, he spoke of an "inner queasiness." An antiparkinson drug improved the akathisia and associated dysphoria. Other patients equated their akathisia with "that awful feeling" or "the worst misery." Even if we allow for a certain amount of histrionic exaggeration, these experiences and behaviors are very similar to what normal subjects experience when they are given a high-potency antipsychotic drug.[10-12]

At times, akathisia can be associated with dramatic exacerbations of psychosis,[13,14] an occurrence that probably depends on the meaning and significance that a psychotic mind attaches to the experience of akathisia. In extreme cases, akathisia is thought to have triggered (or caused) suicidal[15-17] and even homicidal behavior.[18-20] Shaw et al.[20] reported the case of a 43-year-old male paranoid schizophrenic patient who was switched under blind conditions from BW-234U (a neuroleptic without extrapyramidal symptoms), to haloperidol, and back to the experimental drug. Self-report, spouse report, and blind objective clinical ratings indicated rapid clinical decline during haloperidol treatment that included moderately severe akathisia, suicidal and homicidal ideation, increased paranoia, and intensified anxiety, tension, and agitation. Keckich[18] reported a 29-year-old man with a predisposition to violence who, while receiving haloperidol 4 mg h.s., experienced akathisia and "violent urges to assault anyone near him." These feelings culminated in an assault on his dog with an intent to kill. Schulte[19] reported a 23-year-old psychotic man with a predisposition to violence who, 1 to 2 hours after an injection of 10 mg of haloperidol in an emergency room, went on a rampage during which he murdered and maimed several people. This patient described severe extrapyramidal symptoms of an akathetic nature that were, in his words, the "determining factor." Schulte described four other patients in whom akathisia was thought to have triggered (or caused) suicide (by hanging or by severe self-inflicted stab wounds of the abdomen) and two patients who committed severe homicidal assaults. Shear et al.[16] reported two violent suicides (jumping off a building and jumping in front of a subway train) attributed to unrelieved akathisia after injections of depot fluphenazine. Drake and Ehrlich[15] reported two cases of impulsive suicide attempts associated with akathisia in which suicidal ideation appeared suddenly, concurrent with neuroleptic-induced akathisia, and disappeared when the akathisia was treated. Other reports of the presuicidal state of schizophrenic patients suggest that akathisia may have been a factor in precipitating suicidal behavior. Planansky and Johnston[21] reported that 79% of 52 schizophrenic subjects who had made suicide attempts showed "restlessness, pacing, irritability, tension, apprehension with delusional fears, and severe psychomotor upset" at the time of the attempts. Farberow et al.[22] described 30 schizophrenic subjects before they completed suicide as "extremely tense, restless, and impulsive. They made many requests or demands that something be done to relieve their tensions. . . . They appeared driven to find some kind of relief."

The aforementioned case literature reads convincingly: it is reasonable to conclude that akathisia, in the extreme case, can drive people to suicide or to homicide.

Incidence of akathisia

Little is known about the incidence of akathisia because, to our knowledge, no one has systematically attempted to measure it. We[23] reported a precise tally of akathisia in two groups of schizophrenic patients: one group was treated with haloperidol and the other was treated with thiothixene hydrochloride. The patients were newly admitted (or readmitted), drug-free (for at least 2 weeks, but usually several months) schizophrenic patients who were given an oral test dose of either haloperidol 5 mg or thiothixene hydrochloride 0.22 mg/kg. Following administration of the test dose, the patients were observed for 24 hours; thereafter, a fixed-dose regimen of haloperidol 10 mg at bedtime or thiothixene 0.44 mg/kg at bedtime (mean dose ± SD = 28.5 g ± 8.6 mg) was continued.

In the haloperidol group, 17 (40%) of 44 patients experienced akathisia within the first 6 hours after the 5-mg test dose. Further, this akathisia was not mild or inconsequential. Of those patients who experienced akathisia during the first six hours after taking a 5-mg tablet of haloperidol, five (25%) experienced moderate, three (17%) experienced severe, and four (22%) experienced very severe akathisia. During the initial week of treatment with haloperidol (10 mg at bedtime), progressively more patients experienced akathisia; by the seventh day of treatment, 31 (76%) of the patients had experienced akathisia.

The incidence of akathisia with thiothixene was somewhat lower than that with haloperidol: 20% of 67 patients experienced akathisia 12 hours after taking a 0.22 mg/kg (0.1 mg/lb) test dose of thiothixene. However, 7 patients who had a dystonic reaction and were given an antiparkinson drug were excluded from the analysis on the assumption that the antiparkinson drug would prevent akathisia. (The inclusion of these 7 patients would have raised the cumulative percentage of patients with akathisia or dystonia to 28% within 24 hours of the administration of the

first tablet of thiothixene.) During the next 4 weeks of treatment with a fixed dose of thiothixene (0.44 mg/kg or less), the cumulative percentage of patients with akathisia rose to 63%.

The high percentage of patients experiencing akathisia after taking even one dose of haloperidol or thiothixene raises the question of whether it was the physician or the patient who was so sensitive to akathisia. The answer is neither: the reported incidence of side effects depended on how the side effect data were elicited. Reports of side effects were elicited with increasing frequency depending on whether one relies on spontaneous complaints, general questions ("How do you feel?"), or specific questions. For akathisia, we asked: "Do you feel restless or jittery inside? Is it difficult to sit still?" In addition, the physician was probably more sensitive to side effects. For example, if a patient mentioned feeling "strange," "frightened," or "weird," the physician would first rule out akathisia by asking specific questions. In doubtful cases, amelioration by an antiparkinson drug would then support a diagnosis of akathisia.

We suspect that this high incidence of akathisia may also (at least in part) be a function of our sample of rather calm and cooperative schizophrenics. It is commonly known that activited, excited patients (particularly those with schizoaffective disorder) can tolerate huge doses of neuroleptics.[24] Thus, the literature on rapid neuroleptization with haloperidol[24-28] does not mention akathisia. There is, however, the unpleasant possibility that these studies may have overlooked akathisia because they relied on spontaneous complaints of akathisia and that excited schizophrenics with thought disorders are not readily capable of communicating their distress.

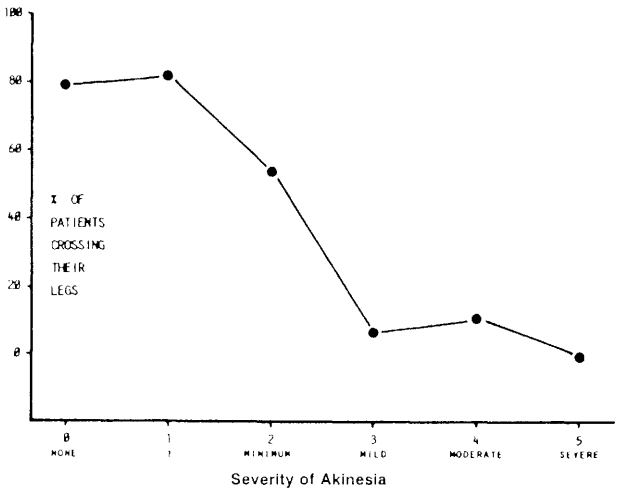
AKINESIA

Akinesia may be the most toxic behavioral side effect of antipsychotic drugs. It is defined by Rifkin et al.[29] as a "behavioral state of diminished spontaneity characterized by few gestures, unspontaneous speech and, particularly, apathy and difficulty with initiating usual activities." As defined, this side effect often goes unrecognized.

It is notoriously difficult to differentiate schizophrenic apathy and blunting from akinesia. A measure that can distinguish between akinesia and the negative symptoms of schizophrenia or the psychomotor retardation of depression is needed. Constriction of handwriting (micrographia) is *not* a reliable correlate of akinesia[30]; neither is antipsychotic drug or prolactin plasma level.[31] One useful correlate of akinesia, however, is a subjective sense of sedation. When rated at 9:00 a.m. (12 hours after h.s. dose), 88% of the akinetic patients rated themselves as slightly drowsy, as opposed to 18% of the nonakinetic patients.[5]

Leg crossing may be another useful correlate of akinesia. Most persons (except the very obese or tense) will cross their legs when seated in a comfortable chair; persons with Parkinson's disease do not.[32] Figure 1 shows the relationship between severity of akinesia and leg crossing in 130 schizophrenic patients (as rated during an interview

Figure 1. Relationship Between Severity of Akinesia and Leg Crossing in 130 Schizophrenic Patients



ranging from 5 to 20 minutes). About 80% of nonakinetic schizophrenic patients crossed their legs when seated in a comfortable chair, but only 10% of patients with mild akinesia crossed theirs.[33] Thus, if a schizophrenic patient does not cross his legs during a brief interview, there is a good chance that he is experiencing a drug-induced akinesia.

The Experience of Akinesia

Sacks[34] described encephalitic patients who were "awakened" from incapacitating parkinsonian akinesia with L-dopa when it was first introduced. These patients experienced akinesia as a peculiar thoughtless, emotionless, and will-less state. One patient had this to say about her years of akinetic immobility: "I ceased to have any moods. I ceased to care about anything. Nothing moved me—not even the death of my parents. I forgot what it felt like to be happy or unhappy. Was it good or bad? It was neither. It was nothing."

In the treatment of schizophrenic illness with neuroleptics, akinesia, in our experience, produces a type of improvement. The patient talks less of psychotic material, but he talks less of everything; he is less bothered by his hallucinations, but he is less bothered by everything else as well; he is less invested in his delusions, but he is less invested in all else as well. Many patients with akinesia experience a peculiar absence of emotions, appear emotionally dead, and often state that everything is all right. This type of improvement, which occurs particularly with higher doses, is one that we should not be proud of.

Akinesia has been associated with improvement of psychosis and a deterioration in blunted affect, emotional withdrawal, and motor retardation. In a prospective study[35] of 76 newly admitted schizophrenic patients treated with haloperidol, the correlation between akinesia and the Brief Psychiatric Rating Scale (BPRS) factor was +.43 ($p = .0001$) and the correlation between akinesia and the BPRS schizophrenia factor was −.39 ($p = .004$; pooled within-subject correlations).

Some psychotic patients whose positive symptoms are

only partially sensitive to neuroleptics can improve only if they have akinesia. When intractable positive symptoms are distressing (subjectively or to others), an akinetic dampening of the entire mental life is often desirable. In those whose positive symptoms are neuroleptic-sensitive, however, everything should be done to minimize akinesia because it is socially disabling.

Akinesia and Social Disability

Even mild akinesia is severely disabling. Akinetic apathy and lack of spontaneity are mistaken for the negative symptoms of schizophrenia and add to the notorious social and emotional disability of schizophrenic patients on maintenance therapy. The onus of detection is on the physician, for the patient seldom complains. Indeed, even when asked if he feels "slowed up" or "sluggish," the patient often denies any difficulty and is seemingly locked in a peaceful, apathetic remoteness.

These are bold assertions, born more from clinical experience than controlled investigation. But there is some scientifically based evidence that akinesia has far-reaching consequences. Rifkin and Kane[36] studied 126 stable schizophrenic outpatients maintained on fluphenazine decanoate 12.5–50 mg every 2 weeks. Half of these patients were then randomly assigned to a 10% dilution (namely, 1.25–5 mg every 2 weeks). Stable low-dose patients reported better social adjustment than stable standard-dose patients, particularly in areas of role function. Family reports also indicated more satisfaction with stable low-dose patients than with stable standard-dose patients.

Poor social adjustment may well be one of the side effects of neuroleptics. Rifkin and Kane[36] speculate that the mechanism is akinesia: ". . . akinesia should not be thought of as limited to a few neurological signs, such as diminished arm swing while walking, slow arm dropping, and slow gait, but should include complex behavior as well, such as social behavior." Since antiparkinson drugs were prescribed in their study, it is clear that antiparkinson drugs cannot be counted on to completely correct akinesia.

Incidence of Akinesia

If akinesia is defined as a "behavioral state of diminished spontaneity characterized by few gestures, unspontaneous speech and, particularly, apathy and difficulty with initiating usual activities"[29] (which we regard as the most useful definition), then the incidence is rather high. Rifkin and associates[37,38] had to withdraw fluphenazine decanoate maintenance therapy from 35% of patients because of disabling akinesia, despite the use of a low dose (0.5 ml or 12.5 mg biweekly) and prophylactic procyclidine. In another study, Rifkin and associates[39] withdrew antiparkinson drugs from long-term aftercare patients stabilized on antipsychotic drugs. After 3 weeks, 27% of patients receiving procyclidine placebo developed akinesia. The magnitude of these figures derived from raters sensitive to akinesia indicates that akinesia often goes undiagnosed.

We performed a study[35] in which 76 newly admitted schizophrenic patients were randomly assigned to receive either 5, 10, or 20 mg of haloperidol for 4 weeks. The 5-mg and 10-mg dose groups experienced only minimal akinesia as long as they received antiparkinson drugs. Patients assigned to the 20-mg daily dose, however, experienced mild to moderate akinesia by the third and fourth weeks of treatment in spite of antiparkinson drug treatment.

Akinesia and Postpsychotic Depression

Schizophrenic patients with postpsychotic depression have been described as "wooden" in appearance,[40] motorically "inactive or retarded," lacking initiative to perform routine tasks,[41] experiencing overwhelming fatigue and neurasthenic symptoms,[42,43] "hypersomnic," and "emotionally withdrawn."[44] Nearly all reports comment on the patient's disinclination to speak.[45] All of these symptoms, however, can be manifestations of akinesia induced by antipsychotic drug treatment.[2] Indeed, persons with Parkinson's disease regularly experience "a blunting of interest and drive, amounting to apathy, a limitation in intellectual activity, and an apparent slowing of thought process and memory."[46] There is a high incidence of depression associated even with the early stages of parkinsonism,[47] and the depression of Parkinson's disease seems out of proportion to the physical handicap.[48]

In one investigation,[49] 28 of 94 schizophrenic inpatients developed mild akinesia and 32 were free of extrapyramidal symptoms. Those who developed akinesia became less psychotic, but they also experienced a significant, although modest, increase in depression ratings. Vigorous treatment of akinesia with trihexyphenidyl resulted in significant improvements in depression, somatic concern, anxiety, emotional withdrawal, blunted affect, and motor retardation as measured by both physicians' and nurses' ratings. A strong association between akinesia and both objectively rated and subjectively experienced sedative effect indicates that an "akinetic depression" is not likely if the patient does not look or feel drowsy. The 32 nonakinetic patients also became less psychotic, but not more depressed. Rifkin and associates,[37] in a maintenance study of remitted schizophrenics, also found that akinetic patients became significantly (although modestly) more depressed and withdrawn compared with their own baseline and with those who did not develop akinesia.

Some of the akinetic patients who did *not* become more depressed did experience dysphoria, stating that they felt "blah," "listless," or "tired" or that they had no "interest," "life," or "ambition." However, they did not complain much and specifically denied sadness or depression; some of them seemed quite accepting of the dysphoric feelings. It appears that both the patient and the doctor can get used to a mild akinesia.

If an extrapyramidal symptom, particularly akinesia, is associated with depression (or if patients experience it as depression), then populations of schizophrenics stabilized with antiparkinson drugs should experience depression on withdrawal of the antiparkinson drug. This is so. In two different samples (one in Boston,[50] the other in Greece[51,52]) of chronic schizophrenic patients stabilized on antiparkinson drugs, sudden or gradual double-blind with-

Table 1. Correlations in 105 Schizophrenic Patients Between Subjective Response to Medication and Outcome, Both Measured at the Same Time*

Group	Pearson Product-Moment Correlation (r)				
	Doctor		Nurse		
Subjective Response	Total BPRS	CGI	Total MACC	Total NOSIE	CGI
Haloperidol (N=40)					
7 days	.441[a]	.444[b]	.294	.153	.400[b]
28 days	.534[c]	.609[d]	.377[e]	.377[e]	.469[e]
Thiothixene (N=65)					
48 hours	.562[c]	—	.200	—	—
28 days	.381[b]	.387[e,f]	.361[b]	.283	.403[e]

* Adapted from reference 53. Abbreviations: BPRS=Brief Psychiatric Rating Scale, CGI=Clinical Global Impressions scale, MACC=Mack Behavior Adjustment Scale, NOSIE=Nurses' Observation Scale for Inpatient Evaluation.
[a] $p < .025$.
[b] $p < .05$.
[c] $p < .005$.
[d] $p < .001$.
[e] $p < .01$.
[f] One extreme outlier omitted (including outlier, $r = .290$, $p < .05$).

drawal of antiparkinson drugs resulted in increased anxiety, depression, and general dysphoria and suffering.

DYSPHORIC RESPONSES TO NEUROLEPTICS

Dysphoric responses to medication erode the quality of life. Lack of vigor, ever-present fatigue, lack of interest or motivation, muscular cramps and aches, inner restlessness or impatience, and vague complaints of "just not feeling right" are feeling states that schizophrenics often correctly attribute to their medications. Hogarty (Hogarty GE; personal communication, 1977) speaks of a "neuroleptic-induced anguish" which, in his opinion, is poorly captured by conventional rating scales.

Even with moderate dosages and without gross side effects, a substantial minority of schizophrenic patients have a dysphoric response. These patients complain that the medication "keeps me closed in," "makes me feel spacey," "takes me away from my normal frame of mind," "slows my thinking," "makes my whole body feel like it is in a physical prison," or "makes me confused." The majority of these dysphoric responders do not regard the medication as helpful.

To what degree are the patient's and the professional's perceptions of drug effect in agreement? The correlations between subjective response in two inpatient samples—one treated with haloperidol 10 mg/day, the other with thiothixene 0.44 mg/kg/day—and the doctors' and nurses' ratings of improvement are shown in Table 1.[53] These correlations indicate a respectable agreement, both at the beginning and at the end of treatment, between subjective response and staff's ratings of improvement—with two different drugs in two different samples. Stated another way, if the patient finds the medication helpful (a syntonic response), the staff's ratings bear him out; conversely, patients with a dysphoric response are seen by the staff as doing less well.

Because many dysphoric responders (about 65% in both samples) stopped medication very early in their treatment course, we do not know whether they could have profited from antipsychotic medication. The dysphoric responders who completed 4 weeks of inpatient treatment tended to have a poorer outcome by both doctors' and nurses' criteria.[53]

The unreplicated work of Van Putten and associates[5,53] does not imply that antipsychotic drugs should be withheld from patients with a dysphoric response. Some patients with a dysphoric response eventually make peace with antipsychotic medication and experience good symptomatic improvement—often, in our experience, with very low doses, e.g., thioridazine 50 mg/day or fluphenazine decanoate 5 mg i.m. every 2 weeks. Others experience fair symptomatic improvement at the expense of ongoing dysphoria. If such persons are floridly psychotic and dangerous to others in an unmedicated state, then their dysphoria in a medicated state is clearly a worthwhile trade-off.

In our experience, dysphoric responses to antipsychotic medication tend to be associated with extrapyramidal symptoms—notably akathisia[5,53]; even with an antiparkinson drug, a persisting akathisia is not uncommon.

A PROSPECTIVE STUDY

In a recently completed prospective study[35] of 76 newly readmitted schizophrenic patients randomly assigned to receive haloperidol 5, 10, or 20 mg/day for 4 weeks, akathisia proved to be the most psychotoxic side effect. First, the patients with higher akathisia ratings dropped out of the study significantly more often. These dropouts talked only about leaving the hospital, and we believe this ideation to be a manifestation of akathisia. Second, the severity of akathisia was significantly related to the BPRS depression factor, both in individual patients ($r = .32$; $p = .0001$) and across patients ($r = .43$; $p = .0005$). There were also substantial correlations between the severity of akathisia and the Symptom Checklist-90 (SCL-90) ratings (a rating scale that measures subjective distress). Third, in a prior study[8] of outpatients by our laboratory we found significant relationships between akathisia and both depression and anxiety. We therefore regard akathisia as a substantial contributor to dysphoric feeling states in the usual, newly admitted patient treated with a conventional dose neuroleptic (haloperidol 10 or 20 mg/day) or the usual schizophrenic outpatient treated with fluphenazine decanoate in a dosage range of 5–25 mg biweekly. Since all patients with akathisia were treated with the usual antiparkinson drugs (usually benztropine up to 8 mg/day), it is really treatment-resistant akathisia that caused the dysphoria.

In the prospective study,[35] akinesia manifested itself behaviorally as blunted affect, emotional withdrawal, and motor retardation (akinesia vs. BPRS withdrawal-retardation factor, $r = +.48$ after 4 weeks of treatment). Kane et al.,[54] in a maintenance study that compared fluphenazine decanoate 1.25–5 mg with 12.5–50 mg every 2 weeks, also found statistically significant elevations in blunted affect, emotional withdrawal, tension, and motor retardation in the high-dose group. They too speculated that

subtle drug-induced neuroleptic side effects (akinesia) accounted for those dosage effects.

Do the results of this prospective study invalidate prior findings[49] of "akinetic depression" and of akathisia causing psychotic decompensation? The answer is no. The patients with akinetic depression in the earlier work had a much more severe form of akinesia, but in 1978 we were not nearly as sensitive to the diagnosis of akinesia as we are now. Likewise, patients in the earlier studies had more severe akathisia. (In 1974, our patients were on higher doses of neuroleptic, usually fluphenazine decanoate, and they experienced much more severe akathisia, which was hardly recognized at that time.) Several patients did become dramatically worse as a result of intractable akathisia. One man experienced "explosions in my body" and became suicidally preoccupied; another man, mildly retarded, experienced "worms crawling on my bones." Both men improved remarkably as the akathisia was controlled.

The chief problem with further research into akinesia and akathisia is our inability to measure these disorders exactly and uniformly from one center to the next. To overcome this deficiency, our laboratory is developing electronic hardware to measure extrapyramidal symptoms.

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