

Akathisia: Prevalence and Associated Dysphoria in an In-patient Population with Chronic Schizophrenia

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In a sample of 120 long-stay in-patients who fulfilled DSM-III-R criteria for schizophrenia, chronic akathisia and pseudoakathisia were relatively common, with prevalence figures of 24% and 18%, respectively. Compared with patients without evidence of chronic akathisia, those patients with the condition were significantly younger, were receiving significantly higher doses of antipsychotic medication, and were more likely to be receiving a depot antipsychotic. Patients who experienced the characteristic inner restlessness and compulsion to move of akathisia also reported marked symptoms of dysphoria, namely tension, panic, irritability and impatience. The findings support the suggestion that dysphoric mood is an important feature of akathisia. Male patients appeared to be at an increased risk of pseudoakathisia. No significant relation was found between chronic akathisia and tardive dyskinesia, although there was a trend for trunk and limb dyskinesia to be commonest in patients with chronic akathisia while orofacial dyskinesia was most frequently observed in those with pseudoakathisia. Akathisia may mask the movements of tardive dyskinesia in the lower limb. There was no evidence that akathisia was associated with positive or negative symptoms of schizophrenia nor with depression.

Akathisia is a relatively common side-effect of antipsychotic medication. During acute treatment, around 20–25% of patients will develop the condition, and in out-patients receiving maintenance drug treatment, a similar prevalence has been reported (Braude *et al*, 1983; Barnes & Braude, 1985; Gibb & Lees, 1986). Drug-induced akathisia is characterised by a sense of inner restlessness and unease, usually accompanied by a desire or compulsion to move. In addition, patients exhibit typical patterns of restless movement, such as shuffling or tramping their feet when sitting and rocking from foot to foot or pacing when standing (Braude *et al*, 1983; Barnes, 1990).

Akathisia can be particularly distressing and difficult to tolerate. This may lead to poor compliance with medication (Van Putten, 1974) and contribute to an exacerbation of the original psychotic illness for which treatment was prescribed (Van Putten *et al*, 1974). The condition has also been associated with violent, aggressive behaviour (Kekich, 1978; Kumar, 1979; Schulte, 1985) or impulsive suicidal behaviour (Shear *et al*, 1983; Weiden, 1985; Schulte, 1985; Drake & Ehrlich, 1985; Shaw *et al*, 1986).

The differential diagnosis includes agitation or psychotic excitement and the 'restless legs' syndrome (Ekbohm, 1960). A further diagnostic problem is that akathisia may not be a unitary disorder, but rather a collection of clinical syndromes which stand in uncertain relation to one another. To date, several

variants have been described: acute akathisia, which may prove to be persistent in some cases; chronic akathisia, with emergence or exacerbation in patients on long-term treatment; and pseudoakathisia, a condition in which the objective limb movements of akathisia are present but the typical subjective report is not obtained (Munetz & Cornes, 1982; Barnes & Braude, 1985). Whether these akathisia subtypes represent separate clinical entities requires validation in prospective studies.

Associations between akathisia and other drug-related movement disorders have been reported. Barnes & Braude (1985) found that orofacial dyskinesia and choreoathetoid limb dyskinesia were both more common in patients with chronic akathisia and pseudoakathisia than in those without akathisia and those with acute akathisia. Their findings, however, suggested that orofacial dyskinesia may be associated with pseudoakathisia and trunk and limb dyskinesia with chronic akathisia. The coexistence of acute akathisia and severe Parkinsonism has also been reported (Braude *et al*, 1983).

The present study was designed to assess the prevalence of akathisia and its subtypes in a long-stay in-patient population suffering from schizophrenia. The population was also surveyed for other movement disorders, psychopathological variables, drug treatment and demographic details, to explore the clinical correlates of the different forms of akathisia.

Method

The study population comprised all 137 patients between the ages of 18 and 65 years who had been resident on the long-term wards at Horton Hospital for more than one year, and who fulfilled DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenia.

Basic demographic information was collected for all patients as well as details of current medication. For each patient, the antipsychotic drug dose was converted to chlorpromazine equivalents in milligrams (mg) a day (Davis, 1976; Baldessarini, 1978; Rey *et al*, 1989).

Each patient was observed while completing a self-rating for anxiety, modified from the Leeds Anxiety Scale (mLAS; Snaith *et al*, 1976) by selecting only the subjective items and adding a new item for rating impatience. Patients were then assessed using the Extrapiramidal Rating Scale (EPRS; Simpson & Angus, 1970), and a version of a scale for rating tardive dyskinesia (Barnes & Trauer, 1982). The latter scale had been modified to allow separate ratings of choreiform and dystonic movements, tics and stereotypies, and mannerisms.

Akathisia was assessed using the Barnes Akathisia Rating Scale (BARS; Barnes, 1989). The first 42 patients were assessed on the BARS by two raters (SMH and TREB) to establish adequate inter-rater reliability. All the subsequent ratings were carried out by SMH.

For the diagnosis of akathisia, the global item of the BARS scale was used. This rates the severity of akathisia on a six-point (0–5) scale ranging from absence of the condition to severe akathisia. Akathisia was diagnosed if the score on this item was 2 or more. Pseudoakathisia was diagnosed if a patient scored 1 or more on the objective item of the scale, which rates akathisia movements, but scored 0 on the subjective item, which rates awareness of restlessness. Patients with pseudoakathisia scored 0 on the global akathisia item of the BARS.

Mental state was assessed using the Manchester Scale (MS; Krawiecka *et al*, 1977) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989) by a rater (JCS) blind to the assessments of movement disorder.

Results

One hundred and twenty patients consented to take part in the study. Ratings for movement disorders and self-reported anxiety were obtained for the total sample, while the MS and SANS were completed in all but one case.

The prevalence of akathisia and pseudoakathisia in a subsample of 105 members of this study population has already been reported (Barnes *et al*, 1992). All akathisia identified was diagnosed as chronic in that the onset of symptoms had not occurred recently or consequent upon starting, or receiving an increased dose of, antipsychotic drugs (Barnes & Braude, 1985).

Chronic akathisia was present in 29 (24%) patients in this sample. The severity was rated as mild in 16, moderate in 10, marked in 2 and severe in only 1 case. Pseudoakathisia was diagnosed in 22 (18%) patients (Table 1).

The relation between sex and akathisia subtypes is presented as a relative risk in Table 2. This was calculated

Table 1
Point prevalence of akathisia in chronic schizophrenia

	Barnes & Braude's (1985) out-patient sample	Present study - in-patient sample
Number of patients	82	120
Mean (s.d.) age: years	44.3 (12.6)	52.9 (9.43)
Number (%) with:		
acute akathisia	6 (7)	0 (0)
chronic akathisia	23 (28)	29 (24)
pseudoakathisia	10 (12)	22 (18)
no akathisia	43 (52)	69 (58)

using the following formula: male prevalence of akathisia subtype divided by the female prevalence of akathisia subtype multiplied by 3.1, where 3.1 is the male to female ratio in the whole sample (91:29).

The data in Table 2 reveal that pseudoakathisia was strikingly more common in males (relative risk 6.8), whereas women were marginally more likely than men to have either chronic akathisia or no akathisia. However, this difference was only statistically significant at a trend level ($\chi^2=8$, $P=0.055$).

Age in this patient sample (Fig. 1) was not a normally distributed variable, using the Kolmogorov-Smirnov goodness of fit test (K-S) ($P=0.01$), but heavily skewed towards the older age range. It was therefore considered more appropriate to use non-parametric statistics when analysing the data referring to age.

Table 2
Akathisia subtypes by sex

	No akathisia	Chronic akathisia	Pseudoakathisia	Total sample
Male	50	20	21	91
Female	19	9	1	29
Relative risk	0.84	0.71	6.8*	1

* $P=0.055$ (χ^2).

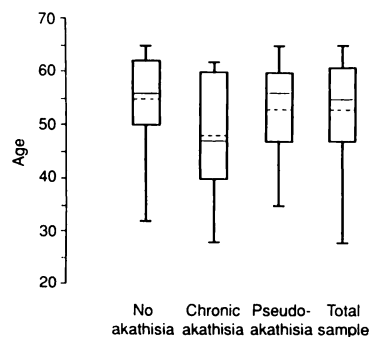


Fig. 1 'Box and whisker' plot of age by akathisia subtypes. Bars indicate range, boxes show upper and lower quartile; — median, - - - mean.

Subjects with chronic akathisia were significantly younger than those without akathisia (Mann-Whitney U test (M-W U), $P=0.007$). These data are presented in Fig. 1, which uses box and whisker plots to prescribe the range and distribution of age in the subgroups. Patients with pseudoakathisia were not significantly different in age from either those with chronic akathisia or those with no evidence of akathisia.

Chlorpromazine equivalents in mg a day was not a normally distributed variable in this sample of patients (K-S, $P=0.001$) (Fig. 2). The same statistical considerations apply as in the preceding section. Patients with chronic akathisia were receiving significantly higher doses of antipsychotic drug than those without akathisia (M-W U , $P=0.015$) (Fig. 2). There was no statistically significant correlation between the rating of global severity of akathisia and antipsychotic drug dosage. No patient with moderate or severe akathisia was receiving doses of antipsychotic medication over 3500 mg chlorpromazine equivalents per day. The range for the whole sample was 0–11371 mg per day.

It was found that 86% of subjects with chronic akathisia were receiving a depot antipsychotic, compared with 68% of those with pseudoakathisia and 66% of those with akathisia. This difference, however, did not reach statistical significance (χ^2 test, $P=0.13$). The four subjects who were receiving no antipsychotic medication were in the non-akathisia group. There were no significant differences between the three akathisia subtypes (chronic akathisia, pseudoakathisia, no akathisia) in the frequency of anticholinergic prescription. Those subjects whose drug regime included a depot neuroleptic received an average of 1600 mg of chlorpromazine equivalents per day. This was 2.5 times greater than the average daily dose of 600 mg of chlorpromazine equivalents in those taking only oral antipsychotics. This difference was highly significant (M-W U , $P<0.001$).

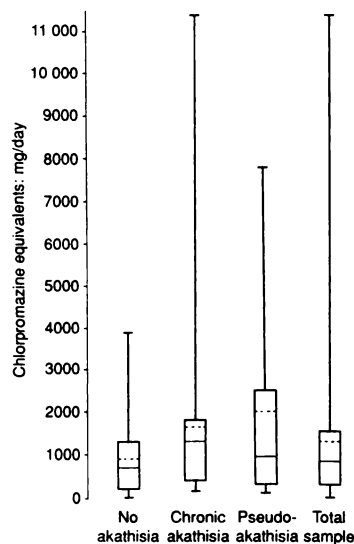


Fig. 2 'Box and whisker' plot of chlorpromazine equivalents by akathisia subtype.

The mean (s.d.) age of the 91 males in the sample was 52.6 (9.4) years and they were receiving a mean daily drug dose of 1269 (1801) mg chlorpromazine equivalents. The respective figures for the 29 females were 54.0 (9.6) years and 1381 (1139) mg chlorpromazine equivalents. There were no significant differences in age or chlorpromazine equivalents between the sexes.

In the total sample, antipsychotic drug dose fell significantly with increasing age ($r = -0.37$, $P=0.001$). The nature of the interaction between age, drug dosage and the three akathisia subgroups was further investigated by performing an analysis of variance (ANOVA) of chlorpromazine equivalents by akathisia subtypes with age as a covariate. When age was taken into account by this method, the significant interaction between akathisia subgroups and chlorpromazine equivalents remained ($F=3.24$, $P=0.043$).

Parkinsonism was not a severe clinical problem and was rated as moderate to severe in only seven cases. The condition was detectable in 22% of those without akathisia, 17% of the chronic akathisia group and 27% of the pseudoakathisia group. Seventy-five patients (63%) were taking anticholinergic medication.

Tardive dyskinesia

In this in-patient sample, 76% had a diagnosis of tardive dyskinesia. They exhibited orofacial dyskinesia (70%) or trunk and limb dyskinesia (37%); 31% had both orofacial and trunk and limb dyskinesia but only 6% had trunk and limb dyskinesia alone.

The point prevalence of orofacial dyskinesia in patients with chronic akathisia was 52%, compared with corresponding figures of just over 75% in the non-akathisia and pseudoakathisia groups. This difference was significant at the $P<0.05$ level ($\chi^2=6.11$). This finding could have been a reflection of the age difference between the akathisia subgroups, as the prevalence of tardive dyskinesia increases with advancing age. An ANOVA of akathisia subgroup and orofacial dyskinesia was carried out, taking age into account as the covariate. While this revealed a significant association between age and orofacial dyskinesia ($F=26.8$, $P<0.0001$), there was no statistically significant relation between akathisia subgroup and orofacial dyskinesia. In the 84 patients with orofacial dyskinesia, presenting either alone (47 cases) or coexisting with trunk and limb dyskinesia (37 cases), only 15 (18%) also had chronic akathisia.

The prevalence of choreiform trunk and limb dyskinesia did not differ across the akathisia groups to an extent that was statistically significant. Nevertheless, the prevalence was highest in those with chronic akathisia at 45% and lowest in those with pseudoakathisia at 31%, with the non-akathisia cases intermediate at 35%. A further ANOVA was carried out examining the association between choreiform trunk and limb dyskinesia and the akathisia groups, with age as the covariate. The association was significant at a trend level ($F=2.75$, $P=0.07$). This result reflects the finding that, of the 44 patients with trunk and limb dyskinesia occurring either alone (7 cases) or in combination with orofacial dyskinesia (37 cases), 13 (29%) had a diagnosis of chronic akathisia.

Self-reported anxiety

The mLAS contains five items, namely irritability, palpitations, impatience, tension and panic, on which the subject is invited to report his or her condition on a four-point ordinal scale. This is translated into a rating between 0 and 3. The total mLAS score was calculated by adding together the five subscales. This score was not normally distributed but analyses using parametric (*t*-test) and non-parametric (Mann-Whitney *U* test) tests agreed closely.

The mean (s.d.) total mLAS score was significantly higher in the chronic akathisia group (6.6 (4.5)) compared with either the non-akathisia group (3.6 (3.7)) ($t = -3.45$, $P = 0.001$; and M-W *U*, $z = -3.05$, $P = 0.002$) or the pseudoakathisia group (3.4 (3.8)) ($t = 2.68$, $P = 0.01$; and M-W *U*, $z = -2.68$, $P = 0.01$). There was no significant difference between mean total mLAS scores in the non-akathisia and pseudoakathisia groups. The global severity of akathisia was highly correlated with the total mLAS score ($r = 0.35$, $P = 0.001$). There was not a steady gradient in mLAS score with increasing global severity of akathisia, but rather an abrupt increase from those with a score of zero on the global severity of akathisia to those with a score of 1 or more (Fig. 3).

In the total sample, multiple correlation analysis of the 5 mLAS subscales against the subjective, objective and distress subscales of the BARS was carried out. This analysis revealed significant associations between the scores for subjective experience of akathisia and distress on the BARS and the ratings of tension, panic, irritability and impatience on the mLAS. However, the rating of the objective movements of akathisia showed no significant correlation with any item on the mLAS. Further, none of the BARS subscale scores showed any significant correlation with the mLAS item for palpitations (Table 3).

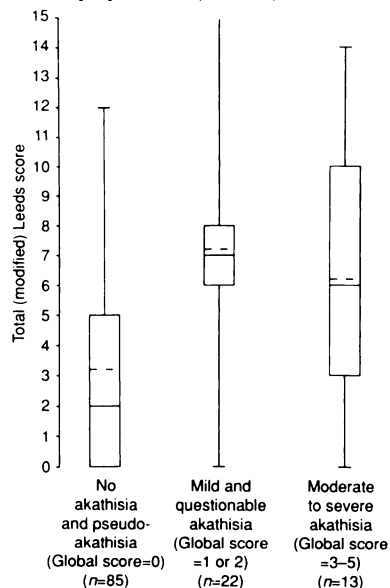


Fig. 3 'Box and whisker' plot of total Leeds score by global severity of akathisia (Pearson's $r = 0.35$, $P = 0.001$).

Table 3
Correlation between BARS and mLAS subscales

BARS	mLAS				
	Tension	Panic	Irritability	Palpitations	Impatience
Objective	0.16	0.09	0.16	0.01	0.11
Subjective	0.34**	0.25*	0.38**	0.21	0.35**
Distress	0.28*	0.22*	0.24*	0.15	0.20

* $P = 0.01$, ** $P = 0.001$ (Pearson's r , one-tailed significance).

Age, medication and self-reported anxiety

The total mLAS score showed a significant, negative correlation with age ($r = -0.39$, $P < 0.001$) (Fig. 4) and a weaker, positive correlation ($r = 0.18$, $P = 0.05$) with the dosage of antipsychotic medication, expressed as the logarithm to base ten of the chlorpromazine equivalents in mg per day. Analysis of variance of total mLAS score by akathisia subtype revealed a significant relation between these two variables ($F = 3.76$, $P = 0.03$) after the effects of age ($F = 16.4$, $P < 0.001$) and medication ($F = 0.76$, $P = 0.39$) had been taken into account.

Akathisia with Manchester and SANS ratings

Six items of the MS (depression, anxiety, coherently expressed delusions, hallucinations, poverty of speech and flattening of affect) were analysed separately. The SANS subscales of affective flattening and alogia, representing the core negative symptoms, were also examined independently. When the MS items and SANS subscale scores were compared across the chronic akathisia, pseudoakathisia and non-akathisia groups, no significant differences were detected.

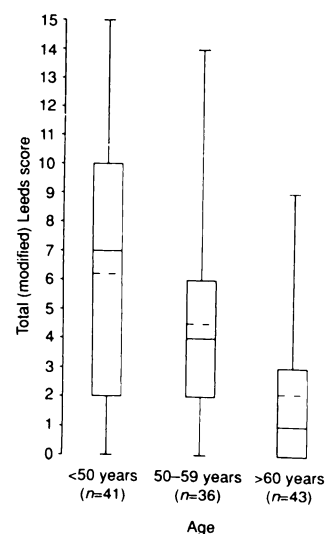


Fig. 4 'Box and whisker' plot of total Leeds score by age group (Pearson's $r = -0.39$, $P < 0.0001$).

Discussion

Almost a quarter (24%) of the sample of chronic schizophrenic in-patients were diagnosed as suffering from chronic akathisia because they presented both the characteristic, restless movements of akathisia and the typical subjective experience of the condition. They were significantly younger, were on significantly higher doses of medication and were more likely to be receiving a depot medication than other patients.

Those patients with chronic akathisia tended to be the most anxious. It was the subjective experience and distress items on the BARS which correlated with self-reported anxiety rather than the ratings on the objective movements or global items. In accord with this observation, the patients with pseudoakathisia had low anxiety levels. Further, the mLAS item for palpitations showed no correlation with any of the akathisia scale items, suggesting that the anxiety occurring with akathisia is not characterised by the physical symptoms of anxiety, but is experienced as psychic tension and dysphoria. This may partly explain why anxiety, objectively rated on the MS, showed no correlation with self-reported anxiety on the mLAS. These findings support the notion that the movements rated on the BARS were features of akathisia and not just non-specific restless movements denoting agitation.

Marder *et al* (1991) have reviewed three studies carried out by their group in which patients with schizophrenia were treated with different doses of an antipsychotic, either acutely (two studies) or during maintenance therapy (one study). They found that extrapyramidal side-effects, particularly akathisia and akinesia, may be experienced as anxiety, irritability or depression. They concluded that though higher doses of antipsychotic medication can provide greater suppression or remission of psychotic symptoms, the patient may also experience more side-effects. Patients on higher doses were also more likely to discharge themselves from hospital against medical advice or drop out of treatment.

The self-reported tension, panic, irritability and impatience which were associated with chronic akathisia in the present study support the concept that akathisia can present with dysphoric mood. The present study was unable to confirm the association between akathisia and depression reported by Marder *et al* (1991) but this might have been found if a self-report depression scale had been used in addition to the MS.

The patients with chronic akathisia were younger and were receiving more antipsychotic medication than other patients. However, the interpretation that younger age or high dosage of medication are risk

factors for the condition is confounded in this patient sample by the trend for dosage of antipsychotic medication to fall markedly with age. Nevertheless, a higher frequency of depot medication was recorded in the chronic akathisia group. Depot medication avoids the problem of drug non-compliance and reduces 'first pass' metabolism in the liver. Both of these effects may lead to increased bioavailability. It was also calculated that patients on depot were receiving very much higher doses of medication than those on oral medication, irrespective of pharmacokinetic considerations. There is, therefore, the possibility that exposure to high doses of antipsychotic drug is a potent risk factor for akathisia. Indeed, a link between high doses of antipsychotic medication and akathisia has been previously reported (Braude *et al*, 1983).

An alternative explanation is that patients with akathisia appear more anxious and disturbed and are therefore given increasing doses of drug. This hypothesis is not supported by the data from the MS which gave no indication that those patients with akathisia were considered more anxious when rated objectively, and there were no significant differences in either affective or psychotic ratings across the akathisia groups. Further, the data relating to drug dosage suggest that clinicians had avoided very high doses of antipsychotic in patients with moderate to severe akathisia.

Analysis of the data from the SANS and the affective flattening and poverty of speech items of the MS failed to reveal any link between chronic akathisia and the negative symptoms of schizophrenia.

The prevalence of chronic akathisia in this in-patient sample (24%) is similar to that previously reported in a sample of 82 out-patients with chronic schizophrenia (28%) rated using the same diagnostic criteria (Barnes & Braude, 1985) (Table 1). However, the out-patient sample was significantly younger than the in-patient sample ($t = -5.55$, $P < 0.001$). The out-patients with chronic akathisia were younger (mean (s.d.) age 44.4 (12.9)) and on lower doses of medication (median 291 mg chlorpromazine equivalents a day, range 73–2288) than the in-patients with chronic akathisia (mean (s.d.) age 48.4 (10.5) years, median dose 1314 mg a day, range 149–11 371). The slightly higher prevalence of chronic akathisia in the out-patients despite lower doses of medication, may be explained by their lower age, if youth is taken as a predisposing factor for akathisia. Again, depot medication could also be proposed as a relevant factor, in that all of the out-patients were receiving depot medication.

Of the present study sample, 18% displayed the characteristic motor signs of akathisia in the absence

of a report of restlessness and were therefore diagnosed as cases of pseudoakathisia. Like the non-akathisia patients, those with pseudoakathisia were older than the akathisia patients and a smaller proportion was receiving depot medication. However, they resembled the akathisia patients in that they tended to be on higher doses of medication (Fig. 2). Out of 22 pseudoakathisia cases, only one was female and this was in marked contrast to the other groups, in which females were found in slightly higher numbers than expected.

Barnes & Braude (1985) had found that their out-patients with pseudoakathisia tended to be older than all other groups, to have been on treatment longer and to have higher negative symptoms scores. Males and females had an equal probability of having pseudoakathisia. These findings prompted the speculation that pseudoakathisia was a long-standing and attenuated form of akathisia, in which the subjective awareness had diminished. Though compatible with these previous findings, the results presented here do not show such a clear picture. The relation with age was not so consistent, nor were negative symptoms more frequently found in any group. The authors are unaware of any other reports of an association between pseudoakathisia and male sex and no firm conclusions can be drawn from the available data.

Furthermore, Barnes & Braude (1985) found that both orofacial and trunk and limb tardive dyskinesia occurred most frequently in patients with chronic akathisia and pseudoakathisia. While akathisia and tardive dyskinesia commonly coexisted in the present sample, no statistically significant associations remained between tardive dyskinesia and the akathisia groups when age was taken into account. This may partly reflect the high prevalence of tardive dyskinesia, with over three-quarters of the total sample exhibiting orofacial dyskinesia or choreiform trunk and limb dyskinesia. Nevertheless, orofacial dyskinesia was found to be most common in the pseudoakathisia group. Orofacial dyskinesia was least common in patients with chronic akathisia, although trunk and limb dyskinesia was most common in this group.

Barnes & Braude (1985) also found that choreiform movements of the upper and lower limbs were observed most frequently in patients with chronic akathisia. One possible explanation for this last finding is that the lower limb movements of akathisia were confused with those of choreiform limb dyskinesia. However, if this were the case, one would have expected an over-representation of trunk and limb dyskinesia in those patients with pseudoakathisia, especially as the subjective experience of

akathisia is not required to make the diagnosis, and this was not the case. Rather, the pseudoakathisia group, in the present study, had the lowest proportion of cases with trunk and limb dyskinesia, with only seven out of 22 (32%) showing such signs. When these seven cases were analysed, it was found that they all had the upper limb or trunk movements, characteristic of tardive dyskinesia, and five scored 2 on the objective movements subscale of the BARS which indicated that definite akathisia movements were observed for at least half the observation period. It is possible, therefore, that akathisia movements masked tardive dyskinesia in the lower limbs of these patients.

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