Psychological Medicine (2009), **39**, 1065–1076. © 2008 Cambridge University Press
doi:10.1017/S0033291708004716 Printed in the United Kingdom

REVIEW ARTICLE

Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review

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Background. Spontaneous movement disorders (SMDs), such as spontaneous dyskinesia and parkinsonism, have been described in patients with schizophrenia who have never been treated with antipsychotic medication. Their presence has been documented extensively in chronic schizophrenia but not at the time of illness onset.

Method. We performed a systematic review of studies investigating spontaneous abnormal movements elicited on clinical examination in antipsychotic-naive patients with first-episode psychosis.

Results. We identified a total of 13 studies. Findings suggest a spontaneous dyskinesia median rate of 9% and a spontaneous parkinsonism median rate of 17%. Information on akathisia and dystonia was limited. The presence of SMDs may be associated with negative symptoms and cognitive dysfunction.

Conclusions. These findings support the notion that spontaneous abnormal movements are part of a neurodysfunction intrinsic to the pathogenesis of schizophrenia. Future studies should further investigate the role of basal ganglia and extrapyramidal pathways in the pathophysiology of psychosis, with particular attention to treatment implications.

Received 13 June 2007; Revised 11 September 2008; Accepted 26 September 2008; First published online 12 November 2008

Key words: Antipsychotic-naive, first-episode psychosis, spontaneous dyskinesia, spontaneous movement disorders.

Introduction

Motor abnormalities are often described in patients on treatment with antipsychotic medication. However, a wide range of neurological motor disturbances has been reported in patients with schizophrenia who have never been treated with antipsychotic drugs. Spontaneous movement disorders (SMDs) such as dyskinesia and parkinsonism occur spontaneously in antipsychotic-naive individuals with schizophrenia. Dyskinesia is characterized by involuntary choreoathetoid movements, most commonly of the tongue, mouth or limbs. Classic parkinsonian symptoms include rigidity, bradykinesia and tremor.

Throughout the pre-neuroleptic era numerous reports appeared in the literature of involuntary abnormal movements resembling current descriptions of both dyskinesias and parkinsonian motor signs observed in medicated patients (Kraepelin, 1919; Turner, 1989; Fenton *et al*. 1994). In the post-neuroleptic era, information about SMDs in schizophrenia has been obtained from studies of chronically ill patients, mainly in developing countries, who were never exposed to antipsychotic medications (Owens *et al*. 1982; McCreadie & Ohaeri, 1994; Hoffman *et al*. 1996; McCreadie *et al*. 1996; Srinivasan *et al*. 2001) and, to a lesser extent, from evaluations of first-episode drug-naive patients (Table 1). The majority of these studies confirmed that a proportion of abnormal movements, such as spontaneous dyskinesia and parkinsonism, are already evident in patients with schizophrenia before exposure to antipsychotic treatment. Therefore, many investigators proposed that idiopathic extrapyramidal disturbances may be intrinsic to the pathophysiology of schizophrenia and that antipsychotic medication might be acting by modifying the expression of disease-based motor dysfunctions (Yarden & DiScipio, 1971; Crow *et al*. 1982; Rogers, 1985). Thus, spontaneous abnormal movements may reflect specific alterations in subcortical dopamine neuronal activity, possibly due to basal ganglia dysregulation (Caligiuri *et al*. 1993).

Over the past few years the observation that movement disorders might be a part of the clinical manifestation of schizophrenia has been more widely

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Table 1. *Studies included in this review, listed in reverse chronological order*

Study	Sample, *n* (M/F)	Age, yr mean (S.D.)	Diagnosis	DUP mean (months)	Scale and threshold	Parkinsonism *n* (%)[a]	Dyskinesia *n* (%)[a]	Akathisia *n* (%)[a]
Kopala *et al*. (2006)	13 (11/2)	22·3 (4·5)	Scz; Sczphr; Sczaff	–	ESRS ⩾2	1 (8)	1 (8)	1 (8)
Chong *et al*. (2005)	174 (90/84)	28·1 (6·7)	Scz; Sczphr; Sczaff	17	SAS ⩾3	4 (2·3)	–	–
Cortese *et al*. (2005)	39 (32/4)	23·6 (6·1)	Scz	–	SAS ⩾3 ESRS-D ⩾1	7 (18)	5 (13)	–
Honer *et al*. (2005)	167 (128/39)	22·3	Scz; Sczphr; Sczaff	6·5	ESRS ⩾2	45 (26·9)	7 (4·2)	10 (6)
Peralta *et al*. (2000)	47 (33/14)	26·9 (9·1)	Scz; Sczphr; Sczaff	12·8	SAS ⩾3	9 (19)	–	–
Jager (2000)	18 (12/6)	27·9	Scz; other psychosis	19	SAS ⩾3 AIMS S&K BARS ⩾2	1 (5·6)	2 (11)	1 (5·6)
Puri *et al*. (1999)	27 (18/9)	27·2 (8·4)	Scz; Sczphr	22	SAS ⩾3 AIMS S&K BARS ⩾2	1 (4)	3 (11)	0 (0)
Gervin *et al*. (1998)	49	27·7 (9·7)	Scz; Sczphr	–	AIMS S&K	–	5 (10)	–
Kopala *et al*. (1997)	22 (17/5)	25 (5·9)	Scz; Sczphr	60	ESRS ⩾2	3 (14)	0 (0)	0 (0)
Fenn *et al*. (1996)	22 (19/3)	28 (5·3)	Scz	50·4	Sct Hans >10 AIMS S&K	4 (18)	3 (14)	–
Chatterjee *et al*. (1995)	89 (47/42)	26·2 (6·5)	Scz; Sczaff	64·8	SAS ⩾1 TDS S&K	15 (17)	1/89 (1)	5 (5·5)
Caligiuri *et al*. (1993)	24 (20/4)	42·2 (14)	Scz	–	SAS ⩾1	5 (20·8)	–	–
Chorfi *et al*. (1985)	50 (44/6)	24	Scz	12	AIMS S&K	–	0 (0)	–
Prevalence, median (25th; 75th percentiles)	–	–	–	–	–	17 (5·6; 19)	9 (0·75; 11·5)	–[b]

M, Male; F, female; DUP, duration of untreated psychosis; Scz, schizophrenia; Sczphr, schizophreniform disorder; Sczaff: schizo-affective disorder; ESRS, Extrapyramidal Symptom Rating Scale (Chouinard *et al*. 1980); SAS, Simpson–Angus Scale (SAS) for extrapyramidal side-effects (Simpson & Angus, 1970); Sct Hans, Sct Hans Rating Scale for Extrapyramidal Symptoms (Gerlach, 1993); BARS, Barnes Akathisia Rating Scale (Barnes, 1989); TDS, Tardive Dyskinesia Scale (Simpson *et al*. 1979); AIMS, Abnormal Involuntary Movement Scale (Schooler & Kane, 1982); S&K, Schooler & Kane severity criteria for definite tardive dyskinesia: a score of 2 on at least two items or a score of ⩾3 on one item of the AIMS.

[a] Number and percentage of patients positive for the specific movement disorder in each study, according to the threshold used in that study.

[b] Median prevalence rates not reported because of the small number of studies available.

accepted. The discovery that, in the new era of antipsychotic drugs, psychosis treatment and movement disorders are not integrally related and the broadening awareness and recognition that basal ganglia structures, viewed as part of a larger system, may play an important role in the pathogenesis of psychotic symptoms have both contributed to this concept (Whitehorn & Kopala, 2002; Friedman, 2004). Moreover, recent evidence indicates that a possibly dopamine-induced dysbalance of basal ganglia neurocircuits may be an important pathophysiological component linking movement disorders to psychosis (Bocti *et al*. 2003; Mehler-Wex *et al*. 2006). In schizophrenia and movement disorders such as Parkinson's disease, cortical and subcortical motor organization is influenced by primary disease conditions. Basal ganglia and thalamic connections seem to have a key role in cortical and subcortical interaction. Thus, crucial changes in cortico-striato-thalamo-cortical networks are associated with dysfunctions in perception, attention, affective regulation, information processing and motor disturbances. The latter may, therefore, represent a clinical sign of the disconcerted cortical–subcortical connectivity that putatively underlies psychotic disorders. Consequently, neuromotor dysfunction and psychotic symptoms may be better understood as manifestations of related rather than distinct pathophysiological processes in schizophrenia.

A fundamental issue is whether these abnormal movements are already present at the time of first presentation of the illness or whether they develop over time, in relation to illness progression and/or ageing. Thus, an investigation of drug-naive patients in the early stages of the illness has the following potential advantages in comparison to studying already treated or drug-naive chronic patients: it can clarify whether SMDs are part of a neurodysfunction that underlies schizophrenia rather the consequence of a degenerative process; it can elucidate whether an SMD is simply an antipsychotic-induced epiphenomenon; and it can disentangle the 'true' estimates of medication-related extrapyramidal signs and symptoms (EPSS). To date, the literature documenting the presence of SMDs in antipsychotic-naive patients with first-episode psychosis has not been reviewed.

Method

We reviewed studies that reported on the prevalence and demographic and clinical correlates of spontaneous dyskinesia or parkinsonism in antipsychotic-naive patients at the time of their first presentation to psychiatric services with a psychotic episode. In considering patients with first-onset psychosis, it is important to note that some studies have included not only patients with schizophrenia but also those with other forms of psychosis. As assessments are frequently performed at the very early stages of psychotic presentation, this over-inclusiveness is unavoidable. Therefore, for the purpose of this review, we include studies that have evaluated first-episode psychosis as a whole. Thus, studies were considered for inclusion if they (1) included patients who were experiencing their first episode of psychosis, (2) included patients with no history of treatment with antipsychotic medication, and (3) specifically reported on the presence of spontaneous dyskinesia or parkinsonism. We performed a systematic literature search of the databases Medline, PsychLit and EMBASE for articles published between 1966 and May 2007 using the following terms: first-episode and spontaneous dyskinesia*; first-episode and spontaneous parkinsonism*; antipsychotic-naive and extrapyramidal signs*; spontaneous movement disorders and early psychosis*; EPSS and never-treated psychosis*. We also examined cross-references from the articles identified and contacted the authors directly when appropriate.

We identified 13 first-episode studies on SMDs that are summarized in Table 1. A variety of instruments have been used to evaluate abnormal movements and different threshold criteria for the case definition applied, making direct comparison and interpretation of findings sometimes difficult.

Results

The prevalence of SMDs among never-treated first-episode psychosis patients

Parkinsonism

Parkinsonism in patients treated with antipsychotics is generally attributed to the striatal dopamine antagonism activity of these medications. We identified 11 studies that evaluated spontaneous parkinsonism in first-episode psychosis patients never treated with antipsychotics (Table 1).

The studies that evaluated drug-naive patients with first-episode psychosis reported a prevalence of parkinsonian motor signs ranging from 2·3% (Chong *et al*. 2005) to 27% (Honer *et al*. 2005). Rigidity, bradykinesia and tremor were most often evaluated with either the Simpson–Angus Scale (SAS) for extrapyramidal side-effects (Simpson & Angus, 1970) or the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard *et al*. 1980). In the papers reviewed, the authors used a total SAS score ranging from 1 to 3 and a total ESRS score between 1 and 2 as threshold criteria for case definition. Some investigators intentionally used more lenient criteria than those often used for studies of neuroleptic-induced parkinsonism. This allowed them

https://doi.org/10.1017/S0033291708004716 Published online by Cambridge University Press

to identify even mild and subtle cases of extrapyramidal signs, on the grounds that, as the patients were otherwise physically healthy and in the early course of their illness, any basal ganglia pathology would be subtly manifested (Chatterjee *et al*. 1995). Thus, variations in prevalence estimates reported across studies are likely to be the result of differences in patient population, definitions of parkinsonism and operational criteria. We should, of course, take into consideration that the prevalence rates of movement disorders might genuinely differ by ethnicity or genetic background. For example, some studies reported that African Americans had lower rates of parkinsonism and a higher risk of developing tardive dyskinesia than Caucasians, whereas Asians seem to have a lower or equal risk of developing tardive dyskinesia as compared with Caucasians (Eastham *et al*. 1996). However, the literature on SMDs to date is limited to either support or discard the above notion.

From the studies reviewed, the median prevalence rate of parkinsonism is 17%; thus, approximately one-sixth of antipsychotic-naive patients presenting with a psychotic disorder showed some parkinsonian motor signs. This proportion is similar to that reported for chronically ill drug-naive patients with schizophrenia, although few studies have addressed the subject, making reliable comparisons difficult. McCreadie *et al*. (2005), presenting data from a sample of 143 mixed first-episode and chronic patients, reported that parkinsonism was present in 15%. By contrast, Venkatasubramanian *et al*. (2003) failed to detect any parkinsonian signs in a sample of 25 never-treated chronic patients. The above rates seem to be at the lower end of the range of parkinsonism identified in patients treated with antipsychotics. In fact, prevalence figures for drug-related parkinsonism in patients on conventional antipsychotic medications range from 15% to 30%; thus, between one-fifth and one-third of patients exposed to typical antipsychotics have a clinically significant parkinsonian syndrome (Owens, 1999). In first-episode psychosis studies, drug-induced parkinsonism is present in approximately 35% of patients (Chakos *et al*. 1992; Caligiuri & Lohr, 1997). However, these rates seem to be lower in patients treated with atypical antipsychotic drugs (Stahl, 2000; Hunter *et al*. 2003).

Several studies have reported on the presence of specific EPSS in never-treated patients with first-episode psychosis. Muscle rigidity is reported as the most common parkinsonian sign in drug-naive patients. Rigidity and bradykinesia, often referred together as akinetic type, are reported much more frequently than non-akinetic type signs such as tremor, glabellar tap, and salivation in antipsychotic-naive first-episode patients (Caligiuri *et al*. 1993; Chatterjee *et al*. 1995; Fenn *et al*. 1996; Kopala *et al*. 1997; Peralta *et al*. 2000; Honer *et al*. 2005). This would suggest that akinetic signs represent an important extrapyramidal dysfunction associated with schizophrenia. Moreover, evidence that non-akinetic parkinsonism becomes more severe following treatment with antipsychotics than the akinetic type suggests that the former is primarily a drug-induced phenomenon (Peralta *et al*. 2000; Honer *et al*. 2005).

Only two studies to date have investigated extrapyramidal motor system asymmetries in neuroleptic-naive schizophrenic patients (Caligiuri *et al*. 1993; Kopala *et al*. 1997). Both studies reported that patients with parkinsonism showed greater right- than left-side abnormalities, supporting previous evidence of primary asymmetries involving the basal ganglia in schizophrenia. The results are consistent with studies demonstrating greater right-side parkinsonism secondary to antipsychotic treatment (Tomer *et al*. 1987; Caligiuri *et al*. 1989).

Some investigators suggest that the lack of objectivity and sensitivity of clinical ratings could be overridden by the use of automated measures of EPSS. Indeed, studies that have used electromechanical measurements have reported a higher prevalence of instrumental measures of parkinsonian signs than studies using qualitative clinical, observer-based ratings (Caligiuri *et al*. 1993; Cortese *et al*. 2005). For example, in the study of Caligiuri *et al*. (1993), parkinsonian tremor seemed to be subclinical and was evident only with laboratory procedures of force steadiness. The authors noted that instrumental measures of EPSS are less vulnerable to examiner bias, are linearly related to severity, and are more sensitive than observer-based ratings in quantifying subclinical motor dysfunction and asymmetries.

Nonetheless, spontaneous parkinsonian motor signs, particularly rigidity and bradykinesia, are already present in patients at very early stages of the illness. It has been postulated that adaptive brain changes may contribute to the development of parkinsonism as part of an autogenic, compensatory response to a mesolimbic hyperdopaminergic state (Csernansky *et al*. 1991). Furthermore, this underlying neurodysfunction, possibly due to basal ganglia dysregulation, could, at least in part, explain why some patients are more prone to the subsequent emergence of antipsychotic-induced EPSS.

Spontaneous dyskinesia

Far more attention has been paid to the controversy that surrounds the frequency and phenomenology of spontaneous, and tardive, dyskinesia in schizophrenia than to the presence of spontaneous parkinsonism.

Several studies have investigated the presence of abnormal involuntary dyskinetic movements in never-treated patients with chronic schizophrenia. By contrast, only a few report data on first-episode patients.

Of the first-episode studies reviewed here, only 10 have reported data on dyskinesia (Table 1). Abnormal movements were mainly assessed with the application of the Abnormal Involuntary Movement Scale (AIMS; Schooler & Kane, 1982) using the operational criteria of Schooler & Kane for a diagnosis of dyskinesia; hence, dyskinesia is defined as present when there are mild movements in at least two areas, or moderate movements in at least one area. Other scales used include the ESRS (Chouinard *et al*. 1980) and the Tardive Dyskinesia Scale (TDS; Simpson *et al*. 1979).

According to the studies reviewed, the median dyskinesia prevalence rate for antipsychotic-naive patients with first-episode psychosis is 9%. Reported figures ranged from 0% (Chorfi & Moussaoui, 1985) to 14% (Fenn *et al*. 1996), including two negative studies (Chorfi & Moussaoui, 1985; Kopala *et al*. 1997). The variation could be attributed to differences in sample sizes and/or to the use of different scales and thresholds for caseness in the measurement. However, the studies with lower rates do not seem to differ systematically in methodology from the studies reporting higher rates. For example, two studies that included approximately the same number of subjects used the same clinical instrument and indeed the same operational criteria, and still reported different frequencies of 0% and 10% (Chorfi & Moussaoui, 1985; Gervin *et al*. 1998).

The rate of spontaneous dyskinesia for chronically ill patients with schizophrenia has been reported to range even more widely, with the majority of studies suggesting elevated rates. Hence, previous reviews of studies that assessed the prevalence of spontaneous dyskinesia in individuals with chronic schizophrenia have reported different values: 4% (Casey, 1985), 5·8% (Baldessarini, 1988), 12% (Torrey, 2002), and 4–40% (age-adjusted rates) (Fenton, 2000). However, three studies found no evidence of an elevated rate of spontaneous dyskinesia in antipsychotic-naive chronic patients with schizophrenia (Hernan Silva *et al*. 1994; McCreadie & Ohaeri, 1994; Venkatasubramanian *et al*. 2003). Here again, the negative studies do not differ systematically in methodology from the positive studies, except for a tendency of the negative studies to evaluate younger and less chronic patients. The wide prevalence range in chronic patients could reflect variability in the mean age of the patients evaluated. Indeed, spontaneous dyskinesia is known to increase with age (Fenton, 2000). For example, studies have reported a spontaneous dyskinesia prevalence rate of 1–5% for healthy elderly subjects (Klawans & Barr, 1982; Kane *et al*. 1982), 18–32% for geriatric antipsychotic-naive medical patients in nursing homes (Bourgeois *et al*. 1980*a*,*b*; Blowers *et al*. 1981), and 38–100% for elderly drug-naive patients with chronic schizophrenia (Owens *et al*. 1982; McCreadie *et al*. 1996; Waddington & Youssef, 1990). It is possible that an increase in the rates of spontaneous dyskinesia with age reflects an extrapyramidal neurodegenerative process in relation to ageing and organic and psychotic illness progression.

The prevalence rate of tardive dyskinesia in individuals with schizophrenia who have been treated with traditional antipsychotic medications has been estimated to be 15–20% (Kane & Smith, 1982; Gerlach & Casey, 1988). The prevalence and severity of tardive dyskinesia are also related to the time of exposure to antipsychotics. In fact, the incidence of tardive dyskinesia is about 5% per year of exposure to conventional antipsychotic medications (Kane *et al*. 1988). Data from a 4-year follow-up study of first-episode schizophrenia patients showed a cumulative incidence for tardive dyskinesia of 4·8% at 1 year, and 15·6% at 4 years (Chakos *et al*. 1996). However, the incidence and prevalence of tardive dyskinesia seem to have fallen with the use of second-generation atypical antipsychotics (Kane, 2004; Correll *et al*. 2004). Three recent, long-term studies of atypical antipsychotics in first-episode psychosis suggest that these antipsychotic drugs possibly produce less extrapyramidal side-effects and tardive dyskinesia (Green *et al*. 2006; Kopala *et al*. 2006; Schooler *et al*. 2006).

The presence of dyskinesia in patients with schizophrenia constitutes a complex and heterogeneous phenomenon. Thus, some abnormal choreoathetoid movements seem to be intrinsic to the pathogenesis of the illness, occurring spontaneously even at the early stages of the psychotic process. It has been suggested that the presence of such spontaneous abnormal movements is associated with primary alterations in subcortical dopamine neuronal activity, although their aetiopathogenesis remains poorly understood. Medication, ageing and neurodegeneration can further contribute to their emergence or modify their expression.

Akathisia and dystonia

Most studies on antipsychotic-naive patients with psychotic illness have not specifically investigated the presence or correlates of akathisia or dystonia. A few have provided a summary index of the observed rates alongside their main findings on spontaneous dyskinesia or parkinsonism. Scales used for the assessment include the ESRS (Chouinard *et al*. 1980) and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989).

Only six studies have investigated the presence of akathisia in first-episode antipsychotic-naive patients (Table 1). Of these, two studies failed to find any sign of akathisia (Kopala *et al*. 1997; Puri *et al*. 1999), whereas the remaining four studies reported prevalence figures ranging between 5·5% (Chatterjee *et al*. 1995) and 8% (Kopala *et al*. 2006). Again, these findings should be interpreted with caution. The ESRS, which was used by the majority of the studies reviewed, contains only one item to assess akathisia, in contrast to the more comprehensive BARS, which was designed specifically for this purpose. Dystonia was evaluated in only two first-episode studies (Table 1). The first one reported a low rate of dystonia (2·4%; Honer *et al*. 2005) and the second was negative (Kopala *et al*. 2006). To our knowledge, there are no studies evaluating akathisia or dystonia rates in chronically ill, never-treated patients with schizophrenia. Consequently, the evidence supporting the occurrence or absence of both akathisia and dystonia in psychotic patients never exposed to antipsychotic medication is, at present, weak and inconclusive.

Follow-up studies of never-treated patients with first-episode psychosis

Follow-up studies provide the potential to address the following important questions: (1) Is the presence of pretreatment EPSS related to an increased risk of subsequent drug-related parkinsonism and/or dyskinesia? (2) What is the impact of different types of medication, that is typical *versus* atypical antipsychotics, on pre-existing EPSS? (3) Is the occurrence of spontaneous EPSS affecting illness outcome?

Follow-up studies of patients who were naive at first presentation, and who were reassessed following treatment with antipsychotic, showed no significant differences in the frequency of dyskinesia before and after commencing antipsychotic treatment (Chatterjee *et al*. 1995; Kopala *et al*. 1997; Jager, 2000; Peralta *et al*. 2000; Cortese *et al*. 2005). However, it should be noted that the follow-up duration of these studies was on average short (3 weeks to 6 months) and a wide variety of antipsychotics were prescribed. Some authors have previously reported a relationship between the appearance of drug-induced EPSS and the subsequent development of persistent tardive dyskinesia (Crane, 1978; Tenback *et al*. 2006). It is possible that the follow-up periods of the above studies were too short for tardive dyskinesia to develop in patients at increased risk.

Of interest, patients with SMDs in the study by Chatterjee *et al*. (1995) were more likely to develop parkinsonism within the first 8 weeks of antipsychotic treatment. Similarly, Caligiuri & Lohr (1997) found that pre-existing extrapyramidal motor signs, especially rigidity, were risk factors for the development of antipsychotic-induced EPSS in a mixed sample of first-episode and chronically ill patients with schizophrenia. The reason for this is unclear, but the authors hypothesized that because the presence of spontaneous EPSS indicates some degree of nigrostratial compromise, these patients may be especially vulnerable to parkinsonian side-effects of treatment. It is of note that in the study of Chatterjee *et al*. (1995), patients with SMDs were more severely ill and less responsive to treatment with typical antipsychotics than patients without pretreatment extrapyramidal signs. The two groups were similar with respect to the mean doses of antipsychotic medication they received. According to the investigators, the presence of SMDs seems to have prognostic significance, being linked with a poorer outcome and with a longer time to remission. By contrast, in the study by Chakos *et al*. (1996), treatment-related EPSS were associated with greater baseline psychopathology but with superior symptom response in first-episode patients treated with typical antipsychotics. Symptomatic response to atypical antipsychotics seemed to be unrelated to the presence of pretreatment extrapyramidal disorder (Kopala *et al*. 1997; Peralta *et al*. 2000). Of particular clinical relevance was the finding that treatment with risperidone resulted in a reduction of pre-existing EPSS (Kopala *et al*. 1997). Although this report comes from a single study, it would suggest that careful examination of pretreatment movement disorders might be advisable. This would help to establish a baseline severity and avoid possible misattribution to subsequent medication. Furthermore, it would help to establish whether atypical antipsychotics ameliorate existing spontaneous abnormal movements.

In conclusion, the predictive value of motor examination before antipsychotic treatment in identifying patients at risk for later development of acute EPSS remains unclear, and the question of whether pretreatment extrapyramidal side-effects are associated with better or worse treatment outcome awaits further study.

SMDs, demographic characteristics and clinical correlates

The evaluation of the relationship between motor dysfunction and clinical or demographic characteristics of schizophrenia may contribute to the understanding of the biological underpinnings of this dysfunction. The studies of patients with first-episode psychosis reviewed did not identify any relationship between the presence of SMDs and age. This finding is not surprising in these populations of relatively young

and age-homogeneous patients. Similarly, there was no correlation between the presence of SMDs and gender, age at onset, and duration of untreated illness.

As mentioned earlier, spontaneous dyskinesia rates seem to increase with age in studies of chronically ill patients with schizophrenia, although some studies failed to replicate these findings. For example, a large study of never-treated patients with schizophrenia of all age groups did not find a significant change in the rates of spontaneous dyskinesia or parkinsonism in association with age, gender, duration of illness or age at onset of psychosis (McCreadie *et al*. 2005). Increasing age, female gender and young age at illness onset have been reported as predisposing factors for tardive dyskinesia (Kane & Smith, 1982; Waddington & Youssef, 1985) and drug-induced parkinsonism (Sandyk & Kay, 1991*a*; Montastruc *et al*. 1994), although this also has not always been confirmed. The presence of drug-induced EPSS and neurological soft signs, which are minor neurological abnormalities in motor and sensory performance often described in patients with schizophrenia, may also be predictive of tardive dyskinesia (Emsley *et al*. 2005). Nonetheless, the association between increasing age and spontaneous involuntary movements is perhaps the most robust finding across studies in samples including subjects of different ages, and merits consideration as a potential confounding factor when comparing rates among study groups or examining clinical correlates.

Several first-episode studies have investigated whether SMDs are associated with a specific symptom profile or dimension of schizophrenia. Cortese *et al*. (2005) showed a positive association between spontaneous dyskinesia and positive symptoms, and also between spontaneous parkinsonism and multiple dimensions of psychopathology, including disorganization, positive and negative symptoms. An association between negative symptoms and spontaneous parkinsonism has been reported in the majority of first-episode studies that have addressed the issue. One study indicated a significant correlation between severity of negative symptoms and severity of akinetic parkinsonism (Peralta *et al*. 2000). Four additional studies reported that patients with extrapyramidal disorders at illness onset had higher mean negative symptoms (Chatterjee *et al*. 1995; Fenn *et al*. 1996; Kopala *et al*. 1997; Honer *et al*. 2005). Only one first-episode study failed to confirm the above correlation between parkinsonism and psychopathology. The authors speculated that the lack of any significant relationship between extrapyramidal motor scores (clinical or instrumental) and severity of negative symptoms might have been due to the insensitivity of the instrument used to measure psychopathology (Caligiuri *et al*. 1993).

The association between negative symptoms and spontaneous parkinsonism might reflect either overlapping definitions among constructs or shared pathological mechanisms. Phenomenological similarities between certain negative symptoms (affective flattening, alogia) and certain parkinsonian symptoms (akinesia) may explain their association (Brown & White, 1992; Peralta & Cuesta, 1999). Alternatively, parkinsonian signs in schizophrenia may reflect frontostriatal hypodopaminergia intrinsic to the illness (Caligiuri *et al*. 1993).

Previous studies on unmedicated patients at different stages of their illness have also investigated the relationship between SMDs and psychopathology, with inconsistent results. Some studies found a positive correlation between spontaneous dyskinesia and negative symptoms (Fenton *et al*. 1994; McCreadie *et al*. 1997) whereas others failed to reveal any relationship between SMDs and psychopathology in chronic patients with schizophrenia (McCreadie *et al*. 2005). In medicated patients, tardive dyskinesia has been associated with both positive (Sandyk & Kay, 1991*b*; White *et al*. 1991) and negative symptoms (Waddington *et al*. 1987). Drug-induced parkinsonism has been mainly associated with negative symptoms and described as a 'negative movement disorder' (Sandyk & Kay, 1992).

Finally, possible associations have been reported between SMDs and impaired pre-morbid functioning (Honer *et al*. 2005) and poorer outcome (Chatterjee *et al*. 1995), as well as between spontaneous dyskinesia and lower educational achievement (Gervin *et al*. 1998) in first-episode patients. Fenton *et al*. (1994) reported an association between spontaneous dyskinesia and both a more severe course and a lower IQ among never-treated chronically ill patients with schizophrenia. Of potential relevance, poor childhood performance predisposed to developing tardive dyskinesia in first-episode patients following exposure to typical antipsychotics (Chakos *et al*. 1996). Nevertheless, there is an extensive literature supporting an association between tardive dyskinesia and cognitive dysfunction (Waddington *et al*. 1993).

The association between SMDs, cognitive dysfunction and negative symptoms indicates that this triad, also known as the 'deficit syndrome', may have a common pathophysiology, and is possibly related to a poorer outcome (Crow, 1985).

Discussion

The studies reviewed confirm that dyskinesia and parkinsonism are already evident in antipsychotic-naive patients suffering their first episode of schizophrenia or psychosis. These findings give support to

the hypothesis that SMDs represent a neuromotor component of schizophrenia.

Unfortunately, the structural and functional neurobiological basis of SMDs in schizophrenia remains poorly understood. It has been suggested that the presence of spontaneous movements reflects regionally specific alterations in subcortical dopamine neuronal activity. Thus, schizophrenia in some patients may be associated with striatal dopamine hypoactivity independently from, or as a compensatory mechanism for, increased mesolimbic dopamine transmission (Caligiuri *et al*. 1993). Evidence for the coexistence of motor disorders and functional and neurocognitive deficits in schizophrenia suggest that the neurobiological mechanisms involved in these deficits are more complex than simple hypo- or hyperdopaminergia (Graybiel, 1997; Andreasen *et al*. 1999). In this respect, neuromotor dysfunction in schizophrenia may involve multiple frontal–subcortical brain pathways responsible not only for motor but also for emotional, cognitive and affective behaviour (Andreasen *et al*. 1998). At the subcortical level, the basal ganglia have been implicated in the pathogenesis of schizophrenia, and have been suggested to play a crucial role in the origin of the motor dysfunction observed in this disorder. In fact, the basal ganglia constitute an essential integrative forebrain system that collects signals from the entire cerebral cortex (sensory, motor, association and limbic areas), redistributes these signals with respect to one another, and sends their outputs back to the frontal lobes and brainstem, through the thalamus. They include five subcortical nuclei: the caudate and putamen (which together form the striatum), the globus pallidus, the subthalamic nucleus and the substantia nigra. There are both parallel and integrative networks in corticobasal ganglia pathways, maintained and modulated through trans-thalamic circuits (Draganski *et al*. 2008). The caudate is thought to play a role in cognitive function, the ventral striatum is involved in reward and reinforcement, and the putamen is known to be responsible for motor control. Symptom distribution in various neurological and psychiatric conditions and also in neuropsychological models and neuropathological data are primarily supportive of this model (Utter & Basso, 2008). The perturbed connectivity between these structures and the cortex, which putatively underlies psychotic disorders, could be the substrate for motor disorders. This notion finds further support in recent neuropsychiatric imaging data. Studies on antipsychotic-naive patients and subjects at high risk have shown a reduced size of basal ganglia structures as compared to healthy controls (Keshavan *et al*. 1998; Lawrie *et al*. 2001). Furthermore, higher rates of neurological abnormalities, including motor signs, have been associated with a reduction of basal ganglia volumes in first-episode psychosis patients (Keshavan *et al*. 2003; Dazzan *et al*. 2004), and with a reduction of specific frontal and temporal cortical areas in both healthy and psychotic subjects (Dazzan *et al*. 2006). Schröder *et al*. (1991) reported a similar association between motor coordination and reduced basal ganglia and thalamus volume in patients with schizophrenia. In a functional magnetic resonance imaging (fMRI) fingertapping study, significant activation was found in cortical and subcortical motor areas such as the pre-motor cortex and putamen in both patients with schizophrenia and parkinsonism (Müller *et al*. 2003). Two studies also reported a motor-induced overactivation of the pre-motor cortex using single photon emission computed tomography (SPECT) in untreated patients with schizophrenia (Gur *et al*. 1985; Günther *et al*. 1991). In another fMRI study, patients with schizophrenia showed alterations in the activation patterns of basal ganglia and the thalamus during a motor sequencing task relative to healthy controls (Menon *et al*. 2001). Of interest, antipsychotic agents have been shown to modulate the activity of basal ganglia and/or their associated neuronal networks. In a positron emission tomography (PET) study in patients with first-episode schizophrenia, the observed primary overactivation of the cortico-striato-thalamic-cortical loop was reduced under treatment with risperidone (Liddle *et al*. 2000). Furthermore, antipsychotic drugs have been found to reduce basal ganglia activity and enhance thalamus activity (Liddle *et al*. 2000). These data would suggest that antipsychotic treatment may in fact interact with an underlying disease-mediated process to bring about and accentuate the simple and complex motor abnormalities observed in schizophrenia.

In contrast with prevailing clinical practice, not all abnormal movements should be explained away as a consequence of antipsychotic use, and a baseline examination of SMDs, conducted before antipsychotic treatment administration, can be informative. Future first-episode, longitudinal, follow-up studies, assessing patients before and after antipsychotic treatment may be able to determine what proportion of movement disorders in patients with schizophrenia is intrinsic to schizophrenia, iatrogenic, or the result of an interaction between the two. Indeed, there is preliminary evidence that pre-existing abnormal movements increase the risk of subsequent EPSS. Therefore, early treatment of schizophrenia may provide an opportunity to prevent the development of the component of abnormal movements attributable to the disease process itself. Furthermore, first-episode studies support an association between motor abnormalities and negative symptoms, cognitive dysfunction, poor

outcome and possibly positive family history. SMDs may therefore be trait characteristics of either a distinct 'motor' type of schizophrenia (similar to the parakinetic schizophrenia described in the past) or part of a more severe form of the illness.

The findings reviewed support the notion that the SMDs observed in first-episode patients are part of a neurodysfunction related to the pathogenesis underlying the illness, rather than the consequences of neurodegenerative processes. Future studies should attempt to provide a greater insight into the role of basal ganglia structures and extrapyramidal pathways in the pathophysiology of schizophrenia.

Declaration of Interest

None

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