# Interrelations between psychiatric symptoms and drug-induced movement disorder

**Guy Chouinard, MD**

Fernand-Seguin Research Centre, Louis-H. Lafontaine Hospital; Department of Psychiatry, Université de Montréal; Clinical Psychopharmacology Unit, Allan Memorial Institute, McGill University Health Centre; and Department of Psychiatry, McGill University, Montréal, Que.

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After 30 years of clinical research into drug-induced movement disorder (DIMD), we are still facing unresolved issues regarding the interrelations between psychiatric symptoms and DIMD. Recently, I proposed a new classification of DIMD that includes abnormal movements previously labelled extrapyramidal symptoms. DIMD caused by psychotropic drugs is still confused with psychiatric symptoms treated by the same drugs. The results from 2 international multicentre trials, the InterSePT and the Ris-Consta Studies, conducted in the era of both typical and atypical antipsychotic agents, which included over 3000 patients with schizophrenia and schizoaffective disorder worldwide, still showed a high, but decreasing, incidence of pretreatment DIMD, which varied from 57.5% (1998–1999) to 47.4% (1999–2000), and a decreasing incidence of tardive dyskinesia, which varied from 12% (1998–1999) to 10.2% (1999–2000), reflecting the greater use of atypical antipsychotic drugs. Furthermore, in both studies, psychiatric symptoms as measured by the Positive and Negative Symptom Scale (PANSS) were significantly correlated with DIMD and DIMD subtypes, thus suggesting the need for additional measurement instruments in schizophrenia and related psychoses.

Après 30 ans de recherche clinique sur les troubles du mouvement d'origine médicamenteuse (TMOM), il reste encore des questions non résolues en ce qui concerne les corrélations entre les symptômes psychiatriques et les TMOM. J'ai proposé récemment une nouvelle classification des TMOM qui comprend les mouvements anormaux auparavant appelés symptômes extrapyramidaux. On continue à confondre les TMOM causés par les psychotropes et les symptômes psychiatriques traités par les mêmes médicaments. Les résultats de deux études multicentriques internationales, les études InterSePT et Ris-Consta, portant sur les antipsychotiques typiques et atypiques, qui visaient plus de 3000 patients atteints de schizophrénie et de troubles schizoaffectifs dans le monde, ont révélé une incidence élevée mais à la baisse de TMOM avant le traitement, qui est passée de 57,5 % (1998–1999) à 47,4 % (1999–2000), ainsi qu'une incidence à la baisse de dyskinésie tardive, qui est passée de 12 % (1998–1999) à 10,2 % (1999–2000), ce qui reflète l'utilisation plus répandue des antipsychotiques atypiques. De plus, dans les deux études, on a établi une corrélation importante entre les symptômes psychiatriques mesurés par l'échelle des symptômes positifs et négatifs (Positive and Negative Symptom Scale [PANSS]) et les TMOM et sous-types de TMOM, ce qui indique qu'il faut d'autres instruments de mesure pour la schizophrénie et les psychoses connexes.

## Introduction

After 30 years of clinical investigation of drug-induced movement disorder (DIMD), we remain without a clear consensus about the definition and classification of these movement disorders. Research toward understanding this phenomenon has thus far focused on antipsychotic agents, but DIMD is also being described with mood stabilizers, anticonvulsants, antihistamines and antidepressants, especially when given concomitantly with antipsychotics.[1]

Movement and posture disorders can be classified as pathophysiological movement disorders and DIMD. The

**Correspondence to: Dr. Guy Chouinard, Clinical Psychopharmacology Unit, Allan Memorial Institute, MUHC, 1025 Pine Ave. W, Montréal QC H3A 1A1; fax 514 982-6620; va.chouinard@gmail.com**

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pathophysiological movement disorders can be broken down into spontaneous movement disorders, neurodegenerative movement disorders, hereditary movement disorders, movement disorders consequent upon metabolic abnormalities and idiopathic movement disorders. I proposed a novel classification system, defining these movement disorders as reversible or persistent, hypokinetic or hyperkinetic, and dystonic or nondystonic. DIMD can be classified into reversible or persistent and hyperkinetic or hypokinetic DIMD.[1]

Parkinsonian symptoms are known to impair cognition, cognitive functions and rehabilitation, and drug-induced parkinsonian symptoms are similar to negative symptoms seen in psychotic illness. For example, parkinsonian bradykinesia and facial mask are similar to blunted affect and motor retardation, whereas akathisia resembles agitation, anxiety and insomnia, and dystonias and dyskinesias resemble mannerisms typical of schizophrenia and schizophrenic motor disturbances. Furthermore, tardive dyskinesia (TD) and akathisia have been shown to be associated with suicidality in schizophrenia.[2] Patients treated with antipsychotic drugs need to be evaluated for treatment-emergent DIMD by using a standardized rating scale[3,4] because of these confounding features between DIMD and psychotic symptoms. Standardized rating scales have advanced our evaluation of antipsychotic agents and DIMD by using disease-state categories, but the use of these rating scales still deserves re-evaluation.

The incidence of TD in patients with schizophrenia and schizoaffective disorder treated with long-acting, atypical, injectable antipsychotic risperidone was investigated in a 1-year, open-label international trial in 725 stable adult patients with schizophrenia or schizoaffective disorder.[5] Patients received long-acting injectable risperidone at doses of 25 mg, 50 mg or 75 mg every 2 weeks, for up to 50 weeks, and regular assessments including the Extrapyramidal Symptom Rating Scale (ESRS).[3] The TD research criteria used were the following: for baseline TD, a score of 3 or more on 1 item, or a score of 2 on 2 ESRS dyskinetic items; for emergent TD, an increase of 2 points on 2 items of the ESRS dyskinetic subscale at any time point, or an increase from baseline of 3 points or more on 1 item; for persistent TD, emergent TD on 2 or more consecutive visits; and for resolved or remitted TD, score improvement at end point that resulted in no longer fulfilling the criteria for baseline dyskinesia.

ESRS data were available for 696 of the 725 patients and showed that 84% had no dyskinesia at baseline, whereas 16% did. On the parkinsonism examination, the improvement of DIMD with risperidone was demonstrated by a significant decrease in ESRS scores (items 13–30) compared with baseline. On the dyskinesia examination, mean ESRS scores (items 51–57) also decreased significantly compared with baseline.[5] Persistent TD was found in 12 of 587 patients without dyskinesia at baseline.[5] Expert case assessment determined 7 cases (1.19%) of withdrawal dyskinesia (3 cases resolved, 4 cases unchanged), 1 case (0.17%) of reversible dyskinesia and 4 cases (0.68%), versus 3% with typical antipsychotic drugs,[6] of persistent emergent TD. In patients with dyskinesia at baseline, ESRS dyskinesia scores significantly improved with long-acting risperidone. The condition of 28.4% of patients with baseline dyskinesia improved so that they did not meet TD criteria and maintained this response.[5] This rate of remission was much higher than the 5.5% annual remission rate reported with typical antipsychotic drugs.[6,7]

Compared with other rating scales, such as the Simpson–Angus Scale[8] and the Abnormal Involuntary Movement Scale (AIMS),[9] the ESRS measures all subtypes of DIMD, thus permitting the evaluation of mixed DIMD syndromes that should be recognized in diagnostic and rating procedures. A criticism of several studies of TD has been the neglected rating of drug-induced parkinsonism and chronic dystonia, which can be confused with TD.[1]

### *Relations between suicide/depressive symptoms and DIMD*

The ESRS has been found to specifically measure DIMD, independent of changes in psychopathology as measured by the Positive and Negative Symptom Scale (PANSS).[10,11] However, to illustrate the difficulty in differentiating between psychiatric symptoms and DIMD, we will consider DIMD in the International Suicide Prevention Trial (InterSePT).[12,13] In the multicentre (67 centres from 11 countries) InterSePT, which included ESRS data for 958 patients included from Mar. 19, 1998, to Feb. 14, 1999, we found DIMD in 551 (57.5%) and TD in 115 (12%) patients.[14] Fewer patients who were taking an atypical antipsychotic alone (25.6%) or an atypical antipsychotic and a conventional antipsychotic together (42.9%) had DIMD than patients taking a conventional antipsychotic alone (31.5%). It is worth noting the high incidence (57.5%) of DIMD in this worldwide sample of patients with schizophrenia and schizoaffective disorder at high risk for suicide.

The relations between DIMD and subtypes of DIMD (TD, parkinsonism and akathisia) and measures of suicidality and depression were examined. Parkinsonism, TD and akathisia were significantly correlated with suicidality, as measured by the InterSePT Scale for Suicidal Thinking (ISST).[14] Multiple linear regression analysis further indicated that greater overall severity of DIMD was correlated with increasing age, diagnosis of schizophrenia and higher Clinical Global Impression Scale for Severity of Suicidality (CGI-SS) score.[12] Greater severity of TD was significantly correlated with increasing age and duration of illness, history of alcohol abuse, higher baseline PANSS anxiety/depression and higher baseline CGI-SS score. Greater severity of parkinsonism was significantly correlated with increasing age and duration of illness, male sex, diagnosis of schizophrenia and higher CGI-SS score. Greater severity of akathisia was significantly correlated with diagnosis of schizophrenia, higher PANSS anxiety/depression factor and higher CGI-SS score.

Overall, suicidality was associated more frequently with DIMD, parkinsonism, TD and akathisia, and depressive symptoms were significantly associated with both TD and severity of akathisia. We concluded that an association exists between some measures of suicidality and depression and DIMD and its subtypes in patients with schizophrenia and schizoaffective disorder who are at high risk for suicide. Our findings showed that patients with schizophrenia with

depression and suicidality need to be assessed for DIMD in the era of atypical antipsychotic drugs.

*Relations between PANSS psychiatric symptoms and DIMD*

To further understand how DIMD can be confused with psychiatric symptoms in schizophrenia and schizoaffective disorders, we analyzed pretreatment DIMD from 3 multicentre studies of long-acting, injectable risperidone ($n$ = 2048), with the first patient included on Mar. 21, 1999, and the last patient on Dec. 15, 2000, and investigated the relations between patient characteristics, the PANSS factors and DIMD.[15] Our aim was to characterize the presence and severity of DIMD with severity of psychiatric disturbance as reflected by the PANSS.[16,17] A study of association between severity of movement disorders and worsening of psychopathology is important, because the presence of movement disorders can lead to difficulty in assessing therapeutic effects and emerging side effects. Data at pretreatment from the 3 pivotal long-acting risperidone multicentre trials were combined.[18–20] Subjects were adults aged between 18 and 65 years, with primary diagnoses of either schizophrenia or schizoaffective disorder as determined by DSM-IV criteria.[21] The variables examined included patient characteristics (age, sex, ethnic origin and diagnosis); total, positive, negative and anxiety–depression factors of the PANSS; and total, akathisia, parkinsonism and tardive dyskinesia components of the ESRS. We found that 970 patients (47.4%) had DIMD, as defined according to the criteria of the ESRS manual,[3] 778 had parkinsonism (38.0%), 285 had akathisia (14.0%) and 209 had TD (10.2%) at pretreatment.[15]

Patients with DIMD had significantly higher total PANSS positive, negative and anxiety/depression subscores, and scores were higher in patients with some DIMD subtypes. PANSS total, positive and anxiety/depression factor scores were higher in patients with DIMD, akathisia and parkinsonism, but not in those with TD. PANSS negative scores were also higher in patients with DIMD and parkinsonism, but not akathisia and TD. A higher PANSS negative score was associated with parkinsonism, whereas a higher PANSS total score was associated with akathisia. Patients with more severe anxious and depressive symptoms were more likely to have more severe DIMD, akathisia and parkinsonism, but not TD. It is worth noting that the presence of TD was not correlated with higher PANSS scores.

Significant relations were found between ESRS scores and PANSS and demographic factors. Subjects with TD were more likely to be older, female and of Asian descent. Subjects with akathisia were more likely to be female, have schizoaffective disorders and have higher anxiety–depressive PANSS scores. Patients with parkinsonism were more likely to be older and not black, have schizoaffective disorder and rate higher on the negative and anxiety–depressive scores of the PANSS. Thus, we concluded that the presence and severity of DIMD were associated with significantly higher PANSS positive, negative and anxiety/depression symptoms, and especially with parkinsonism and akathisia. These data suggest a relation between DIMD and schizophrenic symptoms, as measured by the PANSS, despite the sensitive discrimination by the ESRS between DIMD and positive and negative symptoms of schizophrenia.[3,10,11]

In conclusion, the 3 Ris-Consta pivotal studies[22] and the international multicentre InterSePT study, conducted in the era of both typical and atypical antipsychotic agents, which included over 3000 patients worldwide, showed a decreasing incidence of pretreatment DIMD, which varied from 57.5% (1998–1999) to 47.4% (1999–2000), and decreasing incidence of TD, which varied from 12% (1998–1999) to 10.2% (1999–2000).[3] Furthermore, in a 1-year study, long-acting injectable risperidone was associated with a low annual rate (0.68%) of new emergent TD.[5] Improvement in the severity of pre-existing dyskinesia confirmed the beneficial effects of oral risperidone. Thus, prevalence of TD was found in a study in 2002 to be 4 times lower than the prevalence found in depot typical antipsychotic drugs (43.2%, $n$ = 605/1400).[1] However, despite the decreased incidence of DIMD and TD with atypical antipsychotic drugs, we found a consistent relation between psychiatric symptoms and movement disorders, thus showing the continuous need to measure DIMD in schizophrenia and schizoaffective disorders in the era of atypical antipsychotic drugs and to develop additional symptom measures for schizophrenia and related psychoses.

**Competing interests:** Dr. Chouinard has acted as a consultant for Solvay, Organon, Pfizer, Schering-Plough and Neuro3d.

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