

Atypical Antipsychotics: CATIE Study, Drug-Induced Movement Disorder and Resulting Iatrogenic Psychiatric-Like Symptoms, Supersensitivity Rebound Psychosis and Withdrawal Discontinuation Syndromes

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Chronic illness can result in chronicity of clinical practice. As we have moved away from prescribing classical antipsychotics and tricyclic antidepressants, issues remain with the use of atypical antipsychotics and second-generation antidepressants that need to be addressed, namely, iatrogenic discontinuation syndromes and supersensitivity psychiatric symptoms. An optimal maintenance drug treatment consists of regular attempts to reduce the dose by finding a minimal therapeutic dose, regularly asking the question of when to reduce or withdraw treatment and for which patients, and moreover, why it is difficult to decrease a given drug treatment. Recently, Falloon [1] proposed that maintenance pharmacotherapy in schizophrenia will depend on finally finding minimally effective doses through 'extensive training in stress management'. In the long-term treatment of major depression, Fava [2] has hypothesized that antidepressants can aggravate the course of depressive illness. Lambert [3] recently suggested that 'antipsychotic-switching syndromes', which include discontinuation syndromes, are a 'major barrier' to adjusting antipsychotic treatment. In this paper, we propose that to achieve optimal maintenance treatment with antipsychotics, and to reduce or withdraw antipsychotics effectively, we must distinguish syndromes associated with discontinuing antipsychotics, such as supersensitivity psychosis, from true relapse. While the prevalence and incidence of drug-induced

movement disorder(s) (DIMD) has continuously decreased with atypical antipsychotics, DIMD persist as do psychiatric and psychiatric-like symptoms associated with DIMD, and these must also be identified and evaluated. Persistent DIMD have been found to be a predictor of the later emergence of tardive dyskinesia (TD) and supersensitivity psychosis [4]. At present, we need to determine the relative risk of iatrogenic discontinuation syndromes, DIMD and DIMD psychiatric symptoms resulting from atypical antipsychotics.

Although atypical antipsychotics are now most commonly prescribed, a debate has emerged on the differences between classical and atypical antipsychotics following the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [5]. The question that comes to the forefront is why recent studies are no longer finding well-established differences between these two generations in terms of efficacy and DIMD. Reasons to explain why recent schizophrenia studies have found reduced drug and placebo differences were examined at the International Society for CNS Clinical Trials and Methodology Annual Mid-Year Conference [6].

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While the fact must be considered that patients included in recent studies have less severe illness with symptoms that are better controlled than in past studies (likely due to earlier treatment), the issue that psychiatric symptoms specific to schizophrenia are not being adequately measured nor differentiated from psychiatric and psychiatric-like symptoms associated with DIMD is crucial to answering this question. For example, it is hard to believe that in a recent review of psychomotor slowing in schizophrenia, the authors, when evaluating its effect on measurement and treatment research to improve cognition in schizophrenia (MATRICS), nearly completely ignored the influence of akinesia and DIMD on neuropsychological tests in schizophrenia and the importance of accurate DIMD measurements [7]. As we pursue this ongoing discussion, we recommend the discontinuation of all classical antipsychotics due to their neurotoxic association with a high prevalence of DIMD and increases in basal ganglia volumes [8], and now address how to prescribe atypical antipsychotics most effectively, by taking into account DIMD-associated psychiatric symptoms and iatrogenic discontinuation syndromes.

The CATIE Study and DIMD Psychiatric Symptoms

The first widely prescribed atypical antipsychotic, risperidone, was first approved in Canada in 1993 following the publication of the Canadian Multicenter Risperidone Study, which reported clear advantages of risperidone over haloperidol and the placebo, and significantly less appearance of DIMD with risperidone than haloperidol [9]. DIMD includes the 4 types of movement disorders induced by antipsychotics: parkinsonism, dystonia, dyskinesia and akathisia [10]. These findings were confirmed by the American Risperidone Study [11] and several other studies reporting greater efficacy of risperidone over classical antipsychotics in terms of cost-efficiency [12] and the clinical management of patients with schizophrenia [13–17]. However, the CATIE study [5] challenged these results. The CATIE study found that of the 4 atypical antipsychotics studied, olanzapine was the only atypical to be more efficacious than the classical antipsychotic perphenazine, and to be highly superior to risperidone for discontinuation of treatment, due to lack of efficacy [5]. Olanzapine is known to produce less DIMD compared to risperidone, therefore one would expect psychiatric symptoms caused by DIMD to be less frequent with olanzapine than risperidone. The expected higher rate of DIMD-induced emergent psychiatric symptoms associ-

ated with risperidone would explain the CATIE results, showing risperidone to be significantly less efficacious than olanzapine [5], despite risperidone being known to be at least as efficacious as olanzapine for true schizophrenic symptoms. Furthermore, the rating scales used to measure DIMD did not find the well-established differences between the 5 antipsychotics for DIMD rates [5]. Thus, we propose that DIMD and DIMD-induced psychiatric symptoms were confounded with true schizophrenic symptoms in the CATIE study. DIMD-associated psychiatric symptoms could be classified into 3 types: (1) emergent psychiatric symptoms caused by DIMD, such as akinesia inducing depression, akathisia inducing anxiety; (2) iatrogenic psychiatric-like symptoms resulting from confounding DIMD with psychiatric symptoms, such as akinesia confounded with psychomotor retardation, akathisia with agitation; (3) supersensitivity psychosis symptoms associated with DIMD. In the CATIE study, quetiapine (mean dose = 543.4 mg/day), which shares a low rate of DIMD with olanzapine, was also found to be significantly less efficacious compared to olanzapine, but in contrast to risperidone, this lack of efficacy could be due to psychiatric symptoms related to supersensitivity psychosis explained by quetiapine's loose binding properties at the D_2 receptor [18]. Patients taking quetiapine had a completion rate of 18% out of 329 patients, whereas in our 3-year prospective study of quetiapine monotherapy with a lower mean dose of 487 mg/day (thus less likely to develop therapeutic tolerance), the completion rate was 21.7% out of 23 patients; 6 of 7 patients who relapsed, after a minimum 3 months of stabilized quetiapine treatment, met the criteria for supersensitivity psychosis [19]. Without distinguishing these DIMD-associated psychiatric symptoms from symptoms due to the original illness, the major impact of atypical antipsychotics is on the reduction of DIMD and TD [10, 20], and their beneficial effects on psychosis are masked by DIMD emergent psychiatric symptoms, including supersensitivity psychosis. We will review 4 multicenter trials, which include a total of 14,497 patients, to illustrate how psychiatric and schizophrenic symptoms are confounded with DIMD-associated psychiatric symptoms.

TD in the Time Period of Classical Antipsychotics

TD epidemiology has changed significantly since the introduction of atypical antipsychotics, with a constant decline in its prevalence [10]. TD, classified as a DIMD, is a hyperkinetic, involuntary and purposeless movement

disorder [10, 20]. Considered as the most significant side effect of classical antipsychotics, TD has been associated with antipsychotics and gastrointestinal neuroleptics, and usually occurs after several years of treatment. Persistent TD can also occur after short-term exposure to classical antipsychotics and gastrointestinal neuroleptics even at low doses and for as few as 2 months [8, 21–23], while reversible and withdrawal dyskinesias share properties with levodopa-induced dyskinesia [24]. We conducted several epidemiological studies of TD [4, 25–27] and in 1975, using the National Institute of Mental Health (NIMH) psychopharmacology criteria, we found a 31% prevalence of TD in 261 outpatients with schizophrenia [25]. We also evaluated these patients according to the Schooler and Kane research diagnostic criteria and found a 22% prevalence of TD. This variability of findings related to defining criteria complicates comparisons across studies [10]. In a 5-year follow-up study of 169 of the same patients [4, 25], 45% met the research diagnostic criteria for TD. In 1975, 131 of the 261 patients did not meet the research diagnostic for TD, and in 1980 treatment-emergent TD was found in 46 of the patients who did not have it in 1975, for a 5-year cumulative incidence rate of 35% and a mean annual incidence rate of 8.4%. When corrected for remissions, the mean annual incidence rate decreased to 2.9%. This incidence rate, which includes both patients who developed and remitted from TD over time, is similar to results found by other studies during the same time period [28, 29]. The cumulative incidence of treatment-emergent TD in the study by Kane et al. [29] was 12% after 4 years and 40% after 8 years of neuroleptic exposure, which is similar to our finding of an annual incidence rate (corrected for remissions) of 3% for classical antipsychotics.

In a study carried out in 130 lithium-treated affective disorder patients previously, but less, exposed to antipsychotics, we found a TD prevalence of 9.2% [26], which was a quarter of the incidence reported in our previous studies on patients with schizophrenia who had greater exposure to antipsychotics. In this time period of classical antipsychotics, 2 meta-analyses (including mostly patients with schizophrenia) reported mean TD prevalences of 23% [30] and 20% [31]. In view of the fact that 58% of patients treated with classical antipsychotics will develop treatment-emergent TD after 10–15 years of treatment [4], and the known beneficial neuroprotective effects of atypical antipsychotics on TD [32] and on increased basal ganglia volumes induced by classical antipsychotics [8], we recommend the discontinuation of all classical antipsychotics due to their neurotoxic effects.

TD in the Time Period of both Classical and Atypical Antipsychotics

In the time period of both classical and atypical antipsychotics, the following multicenter studies ($n = 3,753$) evaluated the incidence and prevalence of TD, using the same definitions, Extrapyramidal Symptom Rating Scale [20] and training videotapes as in the previous time period. In the first study, an annual TD incidence of 0.68% was reported prospectively in 725 patients with schizophrenia, treated with the long-acting injectable atypical antipsychotic risperidone [27, 33]. Treatment-emergent TD was found in 12 of 587 patients without dyskinesia at the baseline [33]; however, 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%) of persistent treatment-emergent TD. Of the patients with baseline dyskinesia, 28.4% improved, no longer met TD criteria and maintained this response [33]. This annual treatment-emergent TD incidence of 0.68% with atypical antipsychotics is only 22% of the annual incidence of 3% reported with classical antipsychotics [4]. In the second study, the Schizophrenia International Suicide Prevention Trial (67 centers in 11 countries) [34], 980 patients with schizophrenia, or schizoaffective disorders, taking an atypical alone (25.6%), a classical alone (31.5%) or both a classical and an atypical antipsychotic (42.9%) were included from March 19, 1998, to February 14, 1999, and TD was found at the baseline in 115 (12%) patients [27, 35]. Thus, after 10 years in the time period of both classical and atypical antipsychotics, the overall prevalence of TD decreased by at least twofold compared to our previous 1979–1988 studies with classical antipsychotics [4, 25], using the same definitions, Extrapyramidal Symptom Rating Scale and training videotapes. In the third study (baseline data from three Ris-Consta multicenter studies) [27, 36] carried out 1 year later, 2,048 patients were included from March 21, 1999, to December 15, 2000, and TD was found at the baseline in 209 patients (10.2%), using the same methodology. This study showed a further decrease in the prevalence of TD after an additional year of atypical use. This changing epidemiology of TD with atypical antipsychotics is confirmed by Correll et al. [37] in a systematic review of 1-year prospective studies with atypical antipsychotics, and by Jeste et al. [38] in a 1-year study of elderly patients treated with risperidone. In conclusion, following the introduction of atypical antipsychotics, the prevalence and incidence of TD have significantly decreased. However, the risk for TD still exists with both

atypical and classical antipsychotics, and there is a need for continued surveillance of emerging cases of TD in patients taking antipsychotics [39], especially as the current debate continues on the differences in efficacy between these two generations of antipsychotics following results from studies such as the CATIE [5, 39]. Furthermore, Kane [39] has pointed out that newly trained clinicians using mostly atypical antipsychotics may not have had the same exposure to TD as previously trained clinicians.

DIMD and DIMD-Associated Psychiatric Symptoms in the Time Period of both Classical and Atypical Antipsychotics

A high prevalence of all 4 types of DIMD (parkinsonism, dystonia, dyskinesia and akathisia) remains. In the Schizophrenia International Suicide Prevention Trial (n = 980), a prevalence of 57.5% of DIMD (n = 551 patients) was found [27, 35]. In the Ris-Consta studies (n = 2,048) [27, 36], 970 patients (47.4%) had DIMD at the baseline, which consisted of 778 patients with parkinsonism (38.0%), 285 patients with akathisia (14%) and 209 patients with TD (10.2%). Thus, nearly 1 patient out of 2 had a definite DIMD in this time period of classical and atypical antipsychotics. In addition, DIMD have been consistently associated with significant psychiatric symptoms as measured by the positive and negative syndrome scale (PANSS) [40, 41]. In the InterSept study (n = 980), which included patients with schizophrenia and schizoaffective disorder who were at risk of suicide, suicidality was associated at baseline with DIMD, parkinsonism, TD and akathisia, and depression was associated with TD and akathisia [27, 35]. Based on these results, we recommend routinely assessing DIMD in patients with schizophrenia with suicidal and depressive symptoms. In the Ris-Consta studies (n = 2,048), baseline DIMD were also significantly associated with the PANSS total score, positive, negative and anxiety/depression symptoms [27, 36]. Greater anxiety and depression were seen in patients with severer DIMD, akathisia and parkinsonism. Higher PANSS negative symptom rating was associated with parkinsonism and higher PANSS total scores were associated with akathisia. In this time period, these last two studies (n = 3,028) show that DIMD persists with atypical antipsychotics, and that patients with DIMD have significantly higher PANSS scores compared to patients without DIMD.

These results are in agreement with findings from 2 other multicenter studies: the American CATIE study [5] and the European Schizophrenia Outpatient Health Outcomes (SOHO) study [42]. In the CATIE baseline data, patients with TD (n = 212) were found to have significantly more psychopathology than patients without TD (n = 1,098) as measured by the PANSS total score and PANSS general psychopathology subscale [43]. In the 3-year prospective SOHO study, emergent cases of TD were associated with greater overall psychopathology. An increase in clinical global impression overall symptom severity was longitudinally associated with new cases of TD (5.7%) in patients without TD at the baseline (n = 8,620) [44]. The SOHO and the CATIE studies have also examined other predictors for TD. Both the CATIE and SOHO studies found that other DIMD were associated with TD [43, 45]: the CATIE study showed that patients with TD had more parkinsonism and/or akathisia [43] while the SOHO study found that baseline extrapyramidal symptoms predicted TD [45], confirming our 1988 findings in a prospective study of TD [4]. In addition to reporting that the incidence of TD was lower in patients taking atypical compared to classical antipsychotics after 6 months [46], the SOHO study showed that the incidence of TD was associated with the incidence of prolactin-related sexual disturbances, independent of drug-induced changes in prolactin concentrations [47, 48].

It is crucial to acknowledge that there is a persistence of DIMD with atypical antipsychotics, which are not recognized and confounded with psychiatric symptoms [27]. Several rating scales used routinely in clinical trials to detect DIMD do not differentiate DIMD from psychiatric symptoms [20]. Results from the 4 multicenter trials (n = 14,497 patients) looking into this issue, the CATIE [43], the InterSePT [27, 35], the Ris-Consta [27, 36] and the SOHO studies [44], have all confirmed the strong association of DIMD with psychiatric symptoms. Since most of the studies included in this paper measure psychiatric symptoms according to the PANSS, we propose the following classification of PANSS psychiatric symptoms associated with DIMD: first, emergent psychiatric symptoms caused by DIMD, such as anxiety, depression and suicidality (for example, akinesia is known to produce depression, fatigue, psychomotor retardation and suicidal ideation, while akathisia induces anxiety, psychomotor agitation, aggression, insomnia and suicidal ideation [49–52] and TD is also associated with suicidal ideation [52]); second, iatrogenic psychiatric-like symptoms resulting from confounding and misidentifying DIMD with psychiatric symptoms, such as confounding

bradykinesia and facial mask with blunted affect and motor retardation, akathisia with agitation, anxiety and insomnia and dystonias and dyskinesias with mannerisms and schizophrenic motor disturbances [20]; third, psychiatric schizophrenic symptoms associated with DIMD caused by supersensitivity psychosis, which we are now going to review.

Supersensitivity Withdrawal Syndromes and Supersensitivity Rebound Psychosis

We first reported drug-induced psychotic relapses associated with TD [53–55], a fall in prolactin [53] and increased dopamine receptor bindings [56] after long-term treatment with classical antipsychotics, and we labeled this phenomenon supersensitivity psychosis. We observed that TD and supersensitivity psychosis appeared with the decrease or withdrawal of an antipsychotic, but, given differing risk factors, not necessarily together and at the same time. The debate continues on how to most effectively withdraw antipsychotic [1] and antidepressant drugs [2], and avoid psychiatric syndromes associated with discontinuation. Three different types of syndromes have been described with the discontinuation of psychotropic drugs: (1) withdrawal syndromes (minor and major new symptoms) [57]; (2) rebound syndromes (rebound insomnia [58], rebound anxiety [59, 60] and rebound panic [61]), which have been reported with benzodiazepines [62] and selective serotonin reuptake inhibitors (SSRIs) [63]; (3) supersensitivity syndromes such as TD and supersensitivity psychosis [53, 54, 64]. These discontinuation syndromes all produce psychiatric symptoms that can be confounded with true relapse of the original illness. In a recent review of the literature on rapid-onset psychosis (supersensitivity psychosis), Moncrief [65, 66] also argues the importance of differentiating between antipsychotic withdrawal effects related to the course of the original illness and drug-induced effects such as supersensitivity psychosis. If morbidity due to the discontinuation of a psychotropic drug can be differentiated from the course of original illness and more effectively treated, long-term maintenance treatment could be reduced and avoided in some patients [65]. The long-term maintenance with second-generation antidepressants and subsequent relapse of a major depressive disorder [67–69] is another example of the difficulty encountered in decreasing and withdrawing psychotropic drugs during long-term maintenance treatment. The SSRI paroxetine has also recently been shown to produce a new persistent re-

bound panic disorder following withdrawal [61, 70], thought to be related to noradrenergic supersensitivity [61]. When discontinuing antipsychotics and antidepressants, the phenomena of supersensitivity syndromes and other iatrogenic discontinuation syndromes must be recognized to avoid giving unnecessarily high doses or prolonged treatment.

A cross-sectional survey of 224 outpatients (113 men and 111 women) with schizophrenia treated with a standardized single classical antipsychotic treatment (which also included 1 antiparkinsonian, but no antidepressants, no mood stabilizers and no benzodiazepines) showed a prevalence of 22% for supersensitivity psychosis [55]. The prevalence of TD (45%), using Schooler and Kane criteria, was twice that found for supersensitivity psychosis. Including borderline cases of supersensitivity psychosis increased the prevalence of supersensitivity psychosis to 43%. Supersensitivity psychosis was associated with a higher maintenance dose of classical antipsychotics, high prolactin levels and schizophrenia with a 'good' prognosis. The higher antipsychotic dose and higher prolactin levels associated with supersensitivity psychosis lend support to the theory of dopamine supersensitivity and these results suggest that lower doses of antipsychotics could prevent the appearance of supersensitivity psychosis. In this study, there was no relationship found between TD and supersensitivity psychosis, perhaps due to TD being associated with poor-prognosis schizophrenia and supersensitivity psychosis with good-prognosis schizophrenia. A higher antipsychotic dose was not shown to be a risk factor for TD, whereas increased age was associated with TD but not associated with supersensitivity psychosis. It is worth noting that most patients in this study were treated with fluphenazine which has a high affinity for the D₂ receptor, which could lead to both a high incidence of supersensitivity psychosis and DIMD [71], as the drug is known to produce a high incidence of parkinsonian symptoms [72].

Supersensitivity psychosis, in its masked and withdrawal forms, is known to occur within 6 weeks following the decrease or withdrawal of an oral antipsychotic or within 3 months for a long-acting injectable antipsychotic. We have proposed that TD and supersensitivity psychosis can result from the loss of cholinergic interneurons in the neostriatum [73] caused by prolonged overactivation following antipsychotic-induced elevations in D₂ High (D₂ receptors with functional high affinity for dopamine) [74]. The developments of supersensitivity psychosis and TD share many characteristics. They can both occur after long-term use of antipsychotics and can be-

come irreversible and difficult to control with readministration of the offending antipsychotic [73]. Emotional stress worsens both TD and supersensitivity psychosis [64], and both can be temporarily exacerbated by central anticholinergics and acutely improved by cholinomimetics and anticholinesterases [73]. TD was shown to be the best predictor of supersensitivity psychosis in our 5- and 10-year follow-up study of supersensitivity psychosis [4, 75]. TD and supersensitivity psychosis may or may not occur together in the same time frame, but TD is often associated with supersensitivity psychosis when it occurs during withdrawal of antipsychotics [53, 54]. These two supersensitivity syndromes have been difficult to study due to the fact that antipsychotics can mask their appearance [73]. A further difficulty with identifying supersensitivity psychosis is that symptoms resemble the original illness and true relapse; however, supersensitivity psychosis can be distinguished as it improves more quickly after readministration of the antipsychotic than true relapse, occurs with continuous high doses of antipsychotics and not with noncontinuous antipsychotic treatment and shows therapeutic tolerance to antipsychotic treatment after having shown good drug response [64]. Over time, as therapeutic tolerance increases, there is further development of dopamine supersensitivity [74] and further cholinergic cell loss. Supersensitivity syndromes, like TD, can be: (1) masked, overt (treatment-emergent) or mixed; (2) transient, persistent or mixed; (3) irreversible, reversible (hump course) or mixed [71]. Supersensitivity symptoms can persist for several months or years and can still be reversible or potentially irreversible. When they become persistent and irreversible, supersensitivity symptoms resemble rebound symptoms, being severer than the original symptoms, but these supersensitivity symptoms persist in contrast to rebound symptoms and may include new psychotic symptoms [64].

For atypical antipsychotics, it has been proposed that supersensitivity psychosis occurs more frequently with antipsychotics with fast dissociation from the D₂ receptor [76]. The 2 atypical antipsychotics most often associated with supersensitivity psychosis are quetiapine and clozapine [77] which both have loose binding properties at the D₂ receptor [18, 76]. An additional factor which produces rapid and severe relapse in the withdrawal of clozapine is its effect as an M₄ cholinergic receptor agonist. Thus, for clozapine the rapid relapse upon withdrawal would additionally be exacerbated by the M₄ receptor downregulation following chronic administration of agonists at this receptor. After drug withdrawal, in the absence of the M₄ agonist, cAMP production undergoes a

dramatic rebound, and florid psychosis results [78]. Some cases of supersensitivity psychosis have also been reported with olanzapine [79]. Supersensitivity psychosis was found to be associated with quetiapine in our 3-year open label study of quetiapine in 23 stable male outpatients with schizophrenia and schizoaffective disorder who had previously been treated with classical antipsychotics and/or risperidone, and had shown interepisode residual symptoms and complained of side effects [19]. As mentioned in our discussion of the CATIE study, 7 patients relapsed after a minimum of 3 months of stabilized treatment and 6 of these patients met the criteria for supersensitivity psychosis [19]. Throughout the trial, 11 of 14 patients with baseline TD (78.6%) relapsed, supporting the idea that TD predisposes to supersensitivity psychosis relapse.

Anticonvulsants (valproic acid, lamotrigine and gabapentin) have been shown to be efficacious in approximately 50% of patients with supersensitivity psychosis [64, 80]. We also recommend the use of anticonvulsants in supersensitivity panic and generalized anxiety disorder induced by the discontinuation of SSRIs, particularly the anticonvulsant gabapentin. An anticonvulsant can be used in conjunction with an antipsychotic or an SSRI in order to more effectively decrease or withdraw these psychotropic drugs and find the minimal therapeutic dose for patients who still need long-term treatment. Finding a minimal therapeutic dose with an anticonvulsant has an additional advantage for a drug like olanzapine, as decreasing the dose will avoid significant metabolic side effects. In 2001, in the New York State Office of Mental Health psychiatric centers, 35% of patients with a diagnosis of schizophrenia received valproate, and approximately 10% received gabapentin [81]. For severe cases of schizophrenia, the use of valproic acid or lamotrigine [82, 83] is preferred in order to prevent drug tolerance to antipsychotic effects. While gabapentin is less potent than valproic acid or lamotrigine, it is superior to them for reducing anxiety [84] and thus facilitates the achievement of optimal minimal maintenance drug treatment. One proposed mechanism explaining the beneficial results of anticonvulsant adjunctive treatment in schizophrenia is their antikindling effect [80]. We have also related their beneficial effects to an antagonism of a calcium-dependent process [73]. We recommend adjunctive gabapentin treatment as a first choice for desensitization from SSRI treatment, although lamotrigine can also be prescribed as adjunctive therapy with SSRIs as it has a mood-stabilizing effect. In a review, Goldberg and Burdick [85] concluded that lamotrigine and gabapentin had fewer ad-

verse cognitive events than other anticonvulsants, and, in addition, emerging evidence suggests that lamotrigine may improve DIMD [86, 87]. Lamotrigine has also been shown to be effective as an adjunctive to antipsychotic monotherapy in first-episode patients with schizophrenia who become treatment resistant [88]. We estimate that 50% of cases of treatment-resistant schizophrenia can be related to supersensitivity psychosis. In patients for whom maintenance treatment is necessary, a minimal therapeutic dose can be established with the use of an anticonvulsant that will desensitize patients from chronic antipsychotic or SSRI administration.

In conclusion, overlooking DIMD-induced psychiatric symptoms and supersensitivity syndromes will continue to lead to results such as those found in the CATIE study which show that olanzapine is the only atypical antipsychotic more efficacious than a classical antipsychotic. The proposed classification for psychiatric and psychiatric-like symptoms associated with DIMD may help to avoid the prescription of all classical antipsychotics and

prevent the use of higher doses and longer treatments than necessary of atypical antipsychotics. Further research is needed in order to develop appropriate strategies to distinguish between true relapse and iatrogenic discontinuation syndromes and to elaborate methods to more effectively withdraw antipsychotics and antidepressants by preventing and treating supersensitivity syndromes, particularly for the antipsychotics clozapine and quetiapine and for the SSRI paroxetine. Pharmacogenetics may contribute to further prevention of DIMD, TD and supersensitivity psychosis as we begin to understand more about individual differences in the metabolism of psychotropic drugs [89]. As most plasma concentrations of antipsychotics and second-generation antidepressants are not routinely available or unreliable, except for clozapine, knowing more about genetic differences in psychotropic drug metabolism will also allow to prescribe minimal therapeutic doses of antipsychotics and antidepressants for greater efficacy and better prevention in the maintenance treatment.

References

- Falloon IR: Antipsychotic drugs: when and how to withdraw them? *Psychother Psychosom* 2006;75:133–138.
- Fava GA: Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry* 2003;64:123–133.
- Lambert TJ: Switching antipsychotic therapy: what to expect and clinical strategies for improving therapeutic outcomes. *J Clin Psychiatry* 2007;68:10–13.
- Chouinard G, Annable L, Ross-Chouinard A, Mercier P: A 5-year prospective longitudinal study of tardive dyskinesia: factors predicting appearance of new cases. *J Clin Psychopharmacol* 1988;8(suppl):S21–S26.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–1223.
- ISCTM Third Annual Mid-Year Conference. Brussels, 17–18 September 2007.
- Morrens M, Hulstijn W, Sabbe B: Psychomotor slowing in schizophrenia. *Schizophr Bull* 2007;33:1038–1053.
- Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R: Tardive dyskinesia in the era of typical and atypical antipsychotics. 1. Pathophysiology and mechanisms of induction. *Can J Psychiatry* 2005;50:541–547.
- Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, Labelle A, Beauclair L, Arnott W: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993;13:25–40.
- Chouinard G: New nomenclature for drug-induced movement disorders including tardive dyskinesia. *J Clin Psychiatry* 2004;65(suppl):S9–S15.
- Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994;151:825–835.
- Chouinard G, Albright PS: Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. *J Clin Psychopharmacol* 1997;17:298–307.
- Addington DE, Jones B, Bloom D, Chouinard G, Remington G, Albright P: Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. *Clin Ther* 1993;15:917–926.
- Chouinard G, Arnott W: Clinical review of risperidone. *Can J Psychiatry* 1993;38 (suppl 3):S89–S95.
- Chouinard G, Kopala L, Labelle A, Beauclair L, Johnson SV, Singh KI: Phase-IV multicentre clinical study of risperidone in the treatment of outpatients with schizophrenia. The RIS-CAN-3 Study Group. *Can J Psychiatry* 1998;43:1018–1025.
- Marder SR, Davis JM, Chouinard G: The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997;58:538–546.
- Moller HJ, Muller H, Borison RL, Schooler NR, Chouinard G: A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. *Eur Arch Psychiatry Clin Neurosci* 1995;245:45–49.
- Seeman P, Tallerico T: Rapid release of antipsychotic drugs from dopamine D₂ receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *Am J Psychiatry* 1999;156:876–884.
- Margolese HC, Chouinard G, Beauclair L, Belanger MC: Therapeutic tolerance and rebound psychosis during quetiapine maintenance monotherapy in patients with schizophrenia and schizoaffective disorder. *J Clin Psychopharmacol* 2002;22:347–352.
- Chouinard G, Margolese HC: Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res* 2005;76:247–265.
- Chouinard G, Boisvert D, Bradwejn J: Tardive dyskinesia in a nonpsychiatric patient due to short-term use of a neuroleptic/anticholinergic combination drug. *Can Med Assoc J* 1982;126:821–822, 827.

- 22 Chouinard G, Jones BD: Early onset of tardive dyskinesia: case report. *Am J Psychiatry* 1979;136:1323-1324.
- 23 Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R, Annable L: Tardive dyskinesia in the era of typical and atypical antipsychotics. 2. Incidence and management strategies in patients with schizophrenia. *Can J Psychiatry* 2005;50:703-714.
- 24 Chouinard G, Steinberg S: Type I tardive dyskinesia induced by anticholinergic drugs, dopamine agonists and neuroleptics. *Prog Neuropsychopharmacol Biol Psychiatry* 1982;6:571-578.
- 25 Chouinard G, Annable L, Ross-Chouinard A, Nestoros JN: Factors related to tardive dyskinesia. *Am J Psychiatry* 1979;136:79-82.
- 26 Ghadirian AM, Annable L, Belanger MC, Chouinard G: A cross-sectional study of parkinsonism and tardive dyskinesia in lithium-treated affective disordered patients. *J Clin Psychiatry* 1996;57:22-28.
- 27 Chouinard G: Interrelations between psychiatric symptoms and drug-induced movement disorder. *J Psychiatry Neurosci* 2006; 31:177-180.
- 28 Barnes TR, Kidger T, Gore SM: Tardive dyskinesia: a 3-year follow-up study. *Psychol Med* 1983;13:71-81.
- 29 Kane JM, Woerner M, Borenstein M, Wegner J, Lieberman J: Integrating incidence and prevalence of tardive dyskinesia. *Psychopharmacol Bull* 1986;22:254-258.
- 30 Yassa R, Jeste DV: Gender differences in tardive dyskinesia: a critical review of the literature. *Schizophr Bull* 1992;18:701-715.
- 31 Kane JM, Smith JM: Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry* 1982;39:473-481.
- 32 Chouinard G: Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. *J Clin Psychopharmacol* 1995;15(suppl 1):S36-S44.
- 33 Chouinard G, Lasser R, Bossie C, Zhu Y, Gharabawi G: Does a long-acting atypical antipsychotic offer a low risk of tardive dyskinesia in patients with schizophrenia? *Schizophr Res* 2003;60:277.
- 34 Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S: Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003;60:82-91.
- 35 Chouinard G, Margolese H, Alphas L, Larach-Walters V, Beauclair L, Anand R: Relationship between baseline extrapyramidal symptoms and suicidality in schizophrenic subjects included in the InterSePT trial. *Biol Psychiatry* 2002;51(suppl):S20-S21.
- 36 Chouinard G, Bhanji NH, Light M, Margolese HC: Patient characteristics, symptom severity, and movement disorders in patients with schizophrenia and schizoaffective disorder. *Biol Psychiatry* 2003;53(suppl):S21.
- 37 Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004;161:414-425.
- 38 Jeste DV, Okamoto A, Napolitano J, Kane JM, Martinez RA: Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. *Am J Psychiatry* 2000;157:1150-1155.
- 39 Kane JM: Tardive dyskinesia circa 2006. *Am J Psychiatry* 2006;163:1316-1318.
- 40 Kay SR, Opler LA, Lindenmayer JP: The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989;7:59-67.
- 41 Kay SR, Opler LA, Lindenmayer JP: Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1988;23:99-110.
- 42 Haro JM, Edgell ET, Jones PB, Alonso J, Gavart S, Gregor KJ, Wright P, Knapp M: The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment. *Acta Psychiatr Scand* 2003;107:222-232.
- 43 Miller DD, McEvoy JP, Davis SM, Caroff SN, Saltz BL, Chakos MH, Swartz MS, Keefe RS, Rosenheck RA, Stroup TS, Lieberman JA: Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CAT-IE schizophrenia trial. *Schizophr Res* 2005; 80:33-43.
- 44 Tenback DE, van Harten PN, Slooff CJ, van Os J: Worsening of psychosis in schizophrenia is longitudinally associated with tardive dyskinesia in the European Schizophrenia Outpatient Health Outcomes study. *Compr Psychiatry* 2007;48:436-440.
- 45 Tenback DE, van Harten PN, Slooff CJ, van Os J: Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: a prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Am J Psychiatry* 2006;163:1438-1440.
- 46 Tenback DE, van Harten PN, Slooff CJ, Belger MA, van Os J: Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *J Clin Psychiatry* 2005;66: 1130-1133.
- 47 Tenback DE, van Harten PN, Slooff CJ, van Os J: Tardive dyskinesia in schizophrenia is associated with prolactin-related sexual disturbances. *Neuropsychopharmacology* 2006;31:1832-1837.
- 48 Ghadirian AM, Chouinard G, Annable L: Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients. *J Nerv Ment Dis* 1982;170:463-467.
- 49 Van Putten T, Mutalipassi LR, Malkin MD: Phenothiazine-induced decompensation. *Arch Gen Psychiatry* 1974;30:102-105.
- 50 Van Putten T, May RP: 'Akinetic depression' in schizophrenia. *Arch Gen Psychiatry* 1978; 35:1101-1107.
- 51 Rifkin A, Quitkin F, Klein DF: Akinesia: a poorly recognized drug-induced extrapyramidal behavioral disorder. *Arch Gen Psychiatry* 1975;32:672-674.
- 52 Margolese HC, Chouinard G, Walters-Larach V, Beauclair L: Relationship between antipsychotic-induced akathisia and tardive dyskinesia and suicidality in schizophrenia: impact of clozapine and olanzapine. *Acta Psychiatr Belg* 2001;101:128-144.
- 53 Chouinard G, Jones BD, Annable L: Neuroleptic-induced supersensitivity psychosis. *Am J Psychiatry* 1978;135:1409-1410.
- 54 Chouinard G, Jones BD: Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *Am J Psychiatry* 1980;137:16-21.
- 55 Chouinard G, Annable L, Ross-Chouinard A: Supersensitivity psychosis and tardive dyskinesia: a survey in schizophrenic outpatients. *Psychopharmacol Bull* 1986;22:891-896.
- 56 Chouinard G, Creese I, Boisvert D, Annable L, Bradwejn J, Jones B: High neuroleptic plasma levels in patients manifesting supersensitivity psychosis. *Biol Psychiatry* 1982; 17:849-852.
- 57 Chouinard G, Bradwejn J, Annable L, Jones BD, Ross-Chouinard A: Withdrawal symptoms after long-term treatment with low-potency neuroleptics. *J Clin Psychiatry* 1984; 45:500-502.
- 58 Kales A, Scharf MB, Kales JD: Rebound insomnia: a new clinical syndrome. *Science* 1978;201:1039-1041.
- 59 Fontaine R, Chouinard G, Annable L: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry* 1984;141:848-852.
- 60 Chouinard G: Rebound anxiety: incidence and relationship to subjective cognitive impairment. *J Clin Psychiatry Monogr* 1986;4: 12-16.
- 61 Bhanji NH, Chouinard G, Kolivakis T, Margolese HC: Persistent rebound panic disorder, rebound anxiety and insomnia following paroxetine withdrawal: a review of rebound-withdrawal phenomena. *Can J Clin Pharmacol* 2006;13:e69-e74.
- 62 Chouinard G: Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry* 2004;65(suppl 5):7-12.
- 63 Fava GA, Bernardi M, Tomba E, Rafanelli C: Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. *Int J Neuropsychopharmacol* 2007;10:835-838.

- 64 Chouinard G: Severe cases of neuroleptic-induced supersensitivity psychosis. Diagnostic criteria for the disorder and its treatment. *Schizophr Res* 1991;5:21–33.
- 65 Moncrieff J: Why is it so difficult to stop psychiatric drug treatment? It may be nothing to do with the original problem. *Med Hypotheses* 2006;67:517–523.
- 66 Moncrieff J: Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand* 2006;114:3–13.
- 67 Fava M, Schmidt ME, Zhang S, Gonzales J, Raute NJ, Judge R: Treatment approaches to major depressive disorder relapse. 2. Reinitiation of antidepressant treatment. *Psychother Psychosom* 2002;71:195–199.
- 68 Baldessarini RJ, Ghaemi SN, Viguera AC: Tolerance in antidepressant treatment. *Psychother Psychosom* 2002;71:177–179.
- 69 Schmidt ME, Fava M, Zhang S, Gonzales J, Raute NJ, Judge R: Treatment approaches to major depressive disorder relapse. 1. Dose increase. *Psychother Psychosom* 2002;71:190–194.
- 70 Shoenberger D: Discontinuing paroxetine: a personal account. *Psychother Psychosom* 2002;71:237–238.
- 71 Chouinard G, Jones B: Neuroleptic-induced supersensitivity psychosis, the ‘hump course’ and tardive dyskinesia (letter). *J Clin Psychopharmacol* 1982;2:143–144.
- 72 Chouinard G, Annable L, Ross-Chouinard A: Fluphenazine enanthate and fluphenazine decanoate in the treatment of schizophrenic outpatients: extrapyramidal symptoms and therapeutic effect. *Am J Psychiatry* 1982;139:312–318.
- 73 Miller R, Chouinard G: Loss of striatal cholinergic neurons as a basis for tardive and L-dopa-induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. *Biol Psychiatry* 1993;34:713–738.
- 74 Seeman P, Schwarz J, Chen JF, Szechtman H, Perreault M, McKnight GS, Roder JC, Quirion R, Boksa P, Srivastava LK, Yanai K, Weinschenker D, Sumiyoshi T: Psychosis pathways converge via D₂ high dopamine receptors. *Synapse* 2006;60:319–346.
- 75 Chouinard G, Annable L, Ross-Chouinard A, Holobow N: A ten year follow-up of supersensitivity psychosis. *Biol Psychiatry* 1990;27:110A.
- 76 Kapur S, Seeman P: Does fast dissociation from the dopamine D₂ receptor explain the action of atypical antipsychotics? A new hypothesis. *Am J Psychiatry* 2001;158:360–369.
- 77 Ekblom B, Eriksson K, Lindstrom LH: Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. *Psychopharmacology (Berl)* 1984;83:293–294.
- 78 Miller R: *A Theory of the Basal Ganglia and Their Disorders*. Boca Raton, CRC Press, 2008.
- 79 Llorca PM, Vaiva G, Lancon C: Supersensitivity psychosis in patients with schizophrenia after sudden olanzapine withdrawal. *Can J Psychiatry* 2001;46:87–88.
- 80 Chouinard G, Sultan S: Treatment of neuroleptic-induced supersensitivity psychosis with antiepileptic drugs: report of a series of 43 cases. *Psychopharmacol Bull* 1990;26:337–341.
- 81 Citrome L, Jaffe A, Levine J, Allingham B: Use of mood stabilizers among patients with schizophrenia, 1994–2001. *Psychiatr Serv* 2002;53:1212.
- 82 Kremer I, Vass A, Gorelik I, Bar G, Blanaru M, Javitt DC, Heresco-Levy U: Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004;56:441–446.
- 83 Dursun SM, McIntosh D, Milliken H: Clozapine plus lamotrigine in treatment-resistant schizophrenia. *Arch Gen Psychiatry* 1999;56:950.
- 84 Chouinard G, Beauclair L, Belanger MC: Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders. *Can J Psychiatry* 1998;43:305.
- 85 Goldberg JF, Burdick KE: Cognitive side effects of anticonvulsants. *J Clin Psychiatry* 2001;62(suppl 14):S27–S33.
- 86 Large CH, Webster EL, Goff DC: The potential role of lamotrigine in schizophrenia. *Psychopharmacology (Berl)* 2005;181:415–436.
- 87 Zipp F, Burklin F, Stecker K, Baas H, Fischer PA: Lamotrigine in Parkinson’s disease – a double blind study. *J Neural Transm Park Dis Dement Sect* 1995;10:199–206.
- 88 Kolivakis TT, Beauclair L, Margolese HC, Chouinard G: Long-term lamotrigine adjunctive to antipsychotic monotherapy in schizophrenia: further evidence. *Can J Psychiatry* 2004;49:280.
- 89 Malhotra AK, Murphy GM Jr, Kennedy JL: Pharmacogenetics of psychotropic drug response. *Am J Psychiatry* 2004;161:780–796.