Movement Disorders Associated With Atypical Antipsychotic Drugs

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Data from clinical trials reviewed in this article fulfill predictions based on preclinical findings that atypical antipsychotic drugs are associated with a reduced potential for inducing extrapyramidal symptoms (EPS) and other movement disorders. Atypical drugs have been shown to reduce all subtypes of acute EPS, the frequency of EPS-related patient dropouts, and the need for concomitant antiparkinsonian drug use. Clozapine remains superior to other atypicals in treating psychosis without worsening motor symptoms in patients with Parkinson's disease. Atypicals may be selectively advantageous in treating schizophrenic patients with a predisposition to catatonia. Although the risk of developing lethal neuroleptic malignant syndrome may be diminished with atypical drugs, clinicians must remain alert to the signs of this disorder. Atypicals have reduced liability for inducing tardive dyskinesia (TD) and show antidyskinetic properties in patients with preexisting TD. Passive resolution of TD may be facilitated in some patients by the use of these agents. Thus, the risk of movement disorders has become only one of several considerations in choosing among antipsychotic drugs.
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The development of atypical antipsychotic drugs represents a significant advance in the treatment of patients with schizophrenia. In comparison with conventional agents, atypical antipsychotics may offer broader efficacy and appear to be better tolerated. Although specific advantages of atypical drugs in terms of efficacy are subject to ongoing research, the reduced potential of atypical drugs for inducing neurologic movement disorders appears to be well established.[1–5] That these agents are less likely to affect extrapyramidal motor function is consistent with and predicted by several findings from preclinical studies: a shift to the right in the dose-response curve for the induction of catalepsy in animals, selective induction of depolarization-inactivation in A10 mesolimbic but not A9 nigrostriatal dopamine neurons in the midbrain, reduced antagonism of apomorphine- and amphetamine-induced stereotypies, and selective expression of the protein product of the early gene c-*fos* in limbic and frontal regions.[6,7]

The importance of sparing neurologic and motor function during the course of antipsychotic pharmacotherapy should not be underestimated. Drug-induced movement disorders can be serious, debilitating, and even life-threatening in the form of neuroleptic malignant syndrome (NMS).[8,9] They also exert a profound effect in diminishing effectiveness by precluding the achievement of adequate doses or duration of treatment during therapeutic trials, by contributing to noncompliance, and by simulating or worsening depression, negative or positive symptoms, and cognitive dysfunction. Finally, acute movement disorders may constitute a risk factor or marker for susceptibility to the development of potentially irreversible movements associated with tardive dyskinesia (TD).

When analyzing or comparing studies of movement disorders associated with atypical antipsychotics, it is important to consider several methodological issues that potentially limit conclusions. For example, the incidence and severity of movement disorders can be affected by the following: drug dose, concomitant administration of antiparkinsonian drugs, the duration of treatment and observation, the extent of prestudy washout periods and carryover effects of prior drug treatment, and the susceptibility of the patient sample (e.g., the elderly, drug-naive or treatment-refractory patients). The design of the study, sensitivity of rating instruments, and statistical analyses are also important. In comparisons with typical agents, it is important to consider studies using low- as well as high-potency drugs as comparators.

Keeping these issues in mind, we provide herein a brief survey of published clinical trials that examined the effect of currently marketed atypical antipsychotics on movement disorders in patients with schizophrenia. For each drug, we chose several domains to evaluate to determine relative liability for inducing movement disorders. First, acute extrapyramidal symptoms (EPS) have been measured by overall incidence rates (derived from either spontaneous patient and clinician report or from categorical identification based on rating scales) and by the incidence of phenomenological subtypes, the percentage of EPS-related patient dropouts, and the frequency of concomitant administration of antiparkinsonian drugs. Second, the effect of a drug on motor symptoms in patients with Parkinson's disease or Lewy body dementia constitutes a very stringent test of EPS liability. Third, the effect of a drug on catatonia should be considered. Although catatonic

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symptoms have been observed in 5% to 10% of psychiatric admissions,[10] and reduced cataleptic potential in animal models is predictive of atypicality, this disorder has been virtually ignored in clinical trials. We considered evidence to determine whether atypical drugs induced, improved, or worsened catatonic symptoms and whether they reduced the risk of precipitating NMS in catatonic patients, which has been reported to occur with the use of typical antipsychotics.[11]

Acute EPS and catatonia are found in combination with and may be precursors of NMS, the most fulminant of drug-induced movement disorders.[8,9] Although uncommon, the occurrence of NMS in relation to atypical drugs can be explored based on data from published clinical reports and from the Neuroleptic Malignant Syndrome Information Service database.[12] Finally, the association between atypical drugs and TD can be examined in terms of incidence rates, subtypes, ability to suppress TD, and the potential for remission of TD during treatment.

CLOZAPINE

Although first synthesized in the 1950s, the dibenzodiazepine derivative clozapine received renewed attention as the prototype for atypical antipsychotic drugs following the landmark study of refractory patients by Kane et al.[13] in 1988. In this study, the authors found a reduction in EPS, which was significantly greater in patients receiving clozapine compared with those who received chlorpromazine combined with benztropine mesylate. Although not a study of the new onset or actual incidence of EPS, this report nevertheless supported a more favorable reduction in the prevalence of preexisting EPS with clozapine and established a standard paradigm for measuring EPS liability in subsequent clinical trials. Estimates of the true incidence of EPS, unobscured by prior treatment, can be obtained from studies of first-episode, drug-naive patients, but clinicians in "real-world" practice are in fact confronted more often with pretreated and chronically ill patients who are similar to those recruited in most clinical trials.

In other trials of clozapine versus typical antipsychotics, clozapine resulted in a significantly greater reduction in the incidence of acute EPS, in mean rating scores of EPS, in the frequency of patient dropouts, and in the need for anticholinergic drugs or β-adrenergic antagonists.[13–22] Essentially no EPS were observed with clozapine in some studies.[15,17]

Clozapine has been shown to result in a reduction in acute EPS across the phenomenological spectrum in comparison with typical drugs. This effect is particularly striking for the absence of classic parkinsonian features. High ratings found in some studies for bradykinesia and parkinsonism most likely reflect ratings of sedation and hypersalivation, respectively, which are common side effects of clozapine and not measures of movement disorders per se.[20,21]

Using a sensitive case definition, Cohen et al.[23] reported a high rate (39%) of primarily mild akathisia associated with clozapine that was similar to the rate observed with typical drugs (45%). However, diagnosis of moderate-to-severe akathisia in patients treated with clozapine compared with patients treated with typical drugs (9% vs. 14%) approximated akathisia rates reported by Chengappa et al.[24] and other investigators.[13–22] In addition, the dose of clozapine relative to typical antipsychotics in the Cohen et al. study[23] was higher than the ratio used in other trials,[13,18,24] and the absence of a placebo group in these studies makes it difficult to distinguish mild akathisia from psychoticagitation. In other clinical reports, clozapine has been advocated as a selective treatment for patients with chronic, refractory akathisia.[25,26]

Clozapine has been used in over 400 patients with Parkinson's disease in open studies of the treatment of psychosis.[27,28] It has been effective at doses under 50 mg/day in 80% to 90% of patients with minimal effects on motor function. In 2 recent double-blind, placebo-controlled trials, the efficacy and safety in these patients were confirmed.[29,30] In addition to its effects on psychosis, clozapine has been useful in reducing tremors and levodopa-induced dyskinesias in patients with Parkinson's disease.[27,28,31,32]

Biancosino et al.[33] reported the development of catatonia after the initiation of clozapine in a young woman who had no prior history of catatonia despite previous treatment with typical antipsychotics. The dearth of other published reports suggests that clozapine is a rare and unlikely cause of catatonia, and that it could have a selective advantage in treating psychotic patients at risk for catatonia. In fact, Rommel et al.[34] and Lausberg and Hellweg[35] reported resolution of catatonic symptoms after administration of clozapine. Although Povlssen et al.[17] indicated that 16 (7.4%) of 216 patients in their trial had catatonic schizophrenia, the response of this subgroup to treatment with clozapine was not reported. However, there were also no reports of catatonia worsening or progressing to NMS. In the trial by Naber et al.,[19] 55 (11.5%) of 480 patients studied were diagnosed with the catatonic subtype of schizophrenia. These investigators reported a favorable response to clozapine in this subgroup, which was similar to the response found among other subtypes of schizophrenia and for the group as a whole.

In a recent review, we found 19 published cases of NMS associated with clozapine.[12] In 2 reported surveys,[36,37] the incidence of NMS in patients treated with clozapine was reported as 0.2%, which is similar to the incidence associated with typical drugs.[8,9] However, a comparative, naturalistic, and open study revealed a significantly reduced incidence of NMS with clozapine compared with high-potency typical agents (0% vs. 0.6%; p = .05).[38] NMS due to clozapine appears to be phenomenologically similar to classic descriptions of the syndrome, except that tremors, rigidity, and extreme temperatures have been described less often.[12] Although the reduction in EPS associated with NMS appears to be unique to clozapine, greater awareness of the syndrome among clinicians may have already reduced the occurrence of extreme and advanced hyperthermic cases of NMS even with typical drugs.[12] In reports of patients who recovered from NMS, rechallenge with clozapine resulted in recurrence of NMS symptoms in up to 30% of cases, not significantly different from reports using typical agents.[12]

Another important advantage of clozapine is the promise of a reduced incidence of TD. In several long-term trials, there were no reports of TD.[14,16,17,24,39] However, other investigators have reported possible new-onset or worsening cases of TD, although

the effect of prior treatment in these cases could not be excluded.[20,21,40]

It is instructive to compare the minimal risk of TD with clozapine with the rate of spontaneous dyskinesias reported in untreated populations of schizophrenic patients.[41–43] Fenton[42] and others[41,43] have reported a prevalence rate of 4% to 7% of spontaneous dyskinesias among schizophrenic patients, which increases with age and chronicity. These findings suggest that the reduced and minimal incidence of TD associated with clozapine and other atypical drugs may be difficult to distinguish from the expected background rate of dyskinesias in this population.

Since diabetes has been proposed as a risk factor for TD,[44] it is interesting to speculate whether clozapine and other atypicals, which have been associated with glucose dysregulation, may increase the risk of TD; however, this is not borne out by the extremely low risk for TD among patients treated with these drugs.

Given its relatively weak affinity for D_2 receptors, clozapine is surprisingly more effective in suppressing signs of TD in comparison to typical antipsychotics in most studies.[14,20,22,39,45–49] It is especially effective in suppressing tardive dystonia.[39] Lieberman et al.[39] reported at least a 50% decrease in symptom severity in 43% of patients with TD who were followed for up to 3 years on clozapine treatment. The mechanism underlying this preferential effect is unclear.

Remission of TD in up to 34% of cases has been reported in relation to treatment with clozapine.[39,45,50] Gerbino et al.[50] reported that remission of TD persisted in 60% of cases despite reduction in clozapine dosage, and in 12% after clozapine discontinuation. This suggests resolution of TD in some patients rather than mere suppression. The inference that resolution of TD during clozapine treatment reflects passive or spontaneous recovery rather than a specific active effect of the drug derives from similar remission rates of 14% to 36% reported in previous studies with typical drugs.[41,51–53]

However, a unique study by Tamminga et al.[45] supported a more specific advantage for clozapine in the remission of TD compared with haloperidol. Among 32 schizophrenic patients with TD followed for 12 months, patients receiving clozapine showed a significantly greater reduction in dyskinesia scores compared with those receiving haloperidol. More interestingly, only clozapine-treated patients showed a loss of drug withdrawal–induced worsening of dyskinesias after 12 months, suggesting resolution of the underlying dyskinetic process. In contrast to data from Gerbino et al.[50] and Tamminga et al.,[45] other investigators have documented withdrawal dyskinesias, sometimes severe, following discontinuation of clozapine.[47,48,54]

RISPERIDONE

Risperidone, a benzisoxazole compound, was the first of the new atypical antipsychotics to be introduced. In clinical trials, risperidone resulted in a significantly lower incidence of acute EPS, greater reductions in EPS rating scores, fewer dropouts, and less frequent use of anticholinergic drugs compared with haloperidol.[55–65] In a small study of first-episode schizophrenics, risperidone-treated patients experienced one fourth the incidence of parkinsonism and concurrent anticholinergic use compared with patients receiving typical antipsychotics.[66]

However, postmarketing studies and closer inspection of clinical trial data indicated that EPS liability was dose dependent.[55–65,67] Advantages of risperidone diminished if doses above 6 mg/day were prescribed or if lower doses of haloperidol or less potent drugs were used in comparison.[56,62–65] In another study of first-episode, drug-naive patients, Kopala et al.[68] found no EPS when doses of 2 to 4 mg/day of risperidone were used, whereas 17% of patients developed rigidity and 32% developed mild akathisia when doses of 5 to 8 mg/day were administered. Thus, no additional benefit accrues, but the risk of EPS rises when doses above approximately 6 mg/day of risperidone are prescribed.

More limited data are available for risperidone on the incidence of subtypes of EPS because most original trials focused on overall changes in EPS rating scores as the primary measure of neurologic side effects. Nevertheless, the occurrences of EPS subtypes associated with doses of risperidone less than 6 mg were similar to placebo and significantly less than haloperidol in some studies. Apart from 1 case of parkinsonism, Malla et al.[66] found no cases of dystonia, akathisia, or dyskinesia in 19 first-episode patients treated with risperidone for at least 1 year.

Open studies of risperidone in the treatment of psychosis in patients with Parkinson's disease have shown that 77% improved, but 28% developed significant motor worsening.[27,28] Risperidone does not appear to be an advantageous substitute for clozapine in this population.

Sporadic and conflicting case reports of the association between risperidone and catatonia have been published. In 2 cases, risperidone was associated with the onset of catatonia[69,70]; in 1 of these, catatonia subsided when risperidone was switched to clozapine.[69] In 6 other cases, risperidone was beneficial in treating catatonia.[71–75] In the North American trial of risperidone, 5% of the patients were diagnosed with catatonic schizophrenia, but outcome data were not reported for this particular subgroup. However, no instances of catatonia progressing to NMS were reported.[58]

Jeste et al.[60] reported 1 case of probable NMS (0.1%) in a sample of 842 patients receiving risperidone. In a review of 21 cases of NMS associated with risperidone obtained from the literature and the Neuroleptic Malignant Syndrome Information Service database, we found that risperidone-induced NMS met published diagnostic criteria and was similar in clinical presentation to previous descriptions, except for a reduced occurrence of cases with extreme hyperthermia.[12] Recurrences of NMS symptoms have been reported in 5 of 7 patients who were rechallenged with risperidone.[12]

Although isolated cases of TD have been reported with risperidone, data from long-term trials suggest that the annual risk of TD with risperidone may be one sixth the risk with haloperidol.[57,76,77] Although the risk rises in elderly patients, it remains about one sixth to one tenth that of conventional drugs.[78,79] Jeste et al.[79] reported a 2.6% annual risk of TD in elderly patients with dementia. However, in an earlier study by this group, all 3 cases of dyskinesia associated with risperidone treatment in elderly

patients occurred during the first 3 months of therapy, suggesting they were actually withdrawal dyskinesias stemming from previous treatment with typical antipsychotics.[78] No instances of new dyskinesias were observed after 3 months on risperidone treatment, in contrast to the cumulative incidence of TD in patients receiving haloperidol.

In an 8-week trial, Chouinard et al.[58,80] reported that patients with TD had lower mean change scores in dyskinesia ratings when treated with risperidone compared with haloperidol or placebo, although this reached significance only for the 6-mg and 10-mg doses of risperidone. Similarly, Jeste et al.[60] found significant decreases in dyskinesia scores with risperidone. However, Claus et al.[63] found no significant difference in dyskinesia scores between haloperidol and risperidone; in fact, only haloperidol showed significant suppression of TD in this study. Apart from case reports, there are no studies of remission of TD with risperidone.

OLANZAPINE

Olanzapine, a thienobenzodiazepine derivative, has been extensively studied in relation to movement disorders. Data from clinical trials have demonstrated significant reductions in the incidence of acute EPS, mean rating scores, frequency of dropouts, and use of anticholinergic drugs with olanzapine in comparison with chlorpromazine and haloperidol.[81–87] Olanzapine appears to reduce the rate of acute EPS across all phenomenological subtypes. Similar to clozapine, olanzapine is associated with a marked diminution in parkinsonian features. But as an advantage over clozapine, olanzapine causes significantly less sedation and hypersalivation, resulting in significantly lower ratings of bradykinesia and parkinsonism. In a study of 83 first-episode patients, Sanger et al.[86] found significantly less parkinsonism and akathisia in association with olanzapine compared with haloperidol.

Olanzapine has been tried in open studies to treat psychosis in patients with Parkinson's disease.[27,28] In addition, 2 small trials of olanzapine versus clozapine[88] and placebo,[89] in the treatment of hallucinations and levodopa-induced dyskinesias, respectively, have been reported. Although improvement in psychosis has been reported in 70% of Parkinson's disease patients receiving olanzapine in open studies, worsening of motor symptoms occurred in 38% of patients. Motor worsening led to early termination of 1 controlled trial.[88] Even at low doses, olanzapine may result in increased parkinsonism and "off-time" in these patients.

In addition to a single report of the successful use of olanzapine in a case of catatonia,[90] Martenyi et al.[91] published the results of a unique attempt to retrospectively analyze data on catatonia derived from trials of olanzapine. They found a reduction in subscores on general rating scales of psychotic symptoms, which they felt mirrored a possible ameliorative effect of olanzapine on catatonic symptoms. Methodological limitations of this analysis should raise cautions concerning any conclusions as to the benefits of olanzapine or any antipsychotic in catatonia. Perhaps more significantly, these investigators did not document any induction or worsening of catatonia, or progression of catatonia to NMS, as has been proposed to occur with typical antipsychotics.[11] However, Segal et al.[92] recently reported the possible induction of NMS in a patient with relapsing catatonia.

There are no data on the incidence of NMS with olanzapine. In our review, we found 9 cases of NMS that met diagnostic criteria in patients receiving olanzapine.[12] In addition, there are reports of recurrence of NMS symptomatology in 4 of 6 patients rechallenged with olanzapine.[12]

The risk of TD with olanzapine has been estimated to be about one twelfth the risk associated with haloperidol.[93,94] In long-term studies, Beasley et al.[94] demonstrated a significant decrease in the risk of TD with olanzapine. Beyond the initial 6-week observation period, during which withdrawal dyskinesias from prior antipsychotic drugs may have occurred, the 1-year risk of TD for all patients was calculated to be 0.52% with olanzapine and 7.45% with haloperidol. In fact, when analyzed beyond the initial withdrawal period, no new cases of TD were observed among 375 olanzapine-treated patients who had no evidence of dyskinesias at baseline, compared with 3 new cases of TD among 83 patients treated with haloperidol. When compared with a rate of 4% to 7% in the prevalence of spontaneous dyskinesias among schizophrenic patients,[41–43] these data suggest that the rate of dyskinesias with olanzapine as with other atypicals may be no greater than among untreated patients.

Kinon et al.[95] reported a persistent reduction of up to 71% in dyskinesia scores in patients with TD who received olanzapine. In a subsequent study, Kinon et al.[96] reported that 70% of patients with TD no longer met criteria for the disorder after 8 months of treatment with olanzapine.[4] Furthermore, no significant rebound worsening of dyskinesias was observed after a reduction of 75% in drug dosages, which suggested an ameliorative rather than a simple suppressive effect on TD.

Suppression of TD is presumably related to D_2-receptor blockade by olanzapine, whereas anticholinergic effects of the drug would be expected to worsen dyskinesias. However, recent data suggesting procholinergic properties of olanzapine may offer an alternative mechanism for effects on TD.[97] A recent study by our group has suggested a potential antidyskinetic effect for drugs with postsynaptic cholinergic activity.[98]

QUETIAPINE

Quetiapine, a dibenzothiazepine compound, has been associated with significant reductions in the incidence, rating scores, dropouts, and use of anticholinergic drugs in relation to acute EPS compared with typical antipsychotics.[99–108] The incidence of acute EPS with quetiapine has been comparable to placebo across the therapeutic dosage range of this drug. However, in a study by Peuskens and Link,[103] the use of anticholinergic drugs was similar between patients receiving quetiapine or chlorpromazine. Similar to olanzapine, reductions in EPS during treatment with quetiapine occurred across the phenomenological spectrum of EPS, and ratings of bradykinesia due to sedation and parkinsonism due to hypersalivation were significantly less than with clozapine.

In open studies of patients with Parkinson's disease, quetiapine resulted in improvement in psychosis in 85% of patients,

and motor worsening was observed in only 13%, suggesting selective advantages of quetiapine in this population.[27,28] However, Fernandez et al.[109] reported that treatment of psychosis with quetiapine was ineffective in 6 of 11 Parkinson's disease patients, who had to be switched back to clozapine or olanzapine to reattain symptom control.

There are no reports of catatonia in the context of treatment with quetiapine. The manufacturer has reported 2 possible cases of NMS (0.1%) among 2387 patients involved in premarketing studies,[110] which is similar to the rate of NMS reported with typical drugs.[12] There are only 3 published case reports of NMS due to quetiapine,[111–113] 2 of which included treatment with other antipsychotic drugs.[112,113] Rechallenge with quetiapine resulted in recurrent NMS symptoms in one case,[114] but not in another.[115]

Glazer et al.[116] and others[107,117,118] have reported that the rate of TD with quetiapine was similar to olanzapine and significantly less than haloperidol in all age groups. Although quetiapine treatment was associated with almost complete remission of TD in one case report,[119] mean dyskinesia ratings have not been reported to change significantly in published trials of quetiapine.[102,120] Further investigations of quetiapine in the treatment of patients with preexisting TD would be worthwhile.

ZIPRASIDONE

Ziprasidone, a benzothiazolyl piperazine derivative, has been associated with significant reductions across the therapeutic dosage range in the incidence of acute EPS, mean rating scores, dropouts, and the use of anticholinergic drugs and β-adrenergic antagonists compared with haloperidol.[121–125] The reduction in acute EPS has been observed for all EPS subtypes.

Given that ziprasidone has only recently been introduced, there are insufficient published clinical trials and experience to comment on effects of the drug in relation to TD, Parkinson's disease, catatonia, and NMS. In short-term trials, ziprasidone has resulted in diminished dyskinesia ratings, although not significantly different from the effects of haloperidol and placebo.[121–125]

COMPARATIVE STUDIES AND META-ANALYSES

In addition to published trials of atypical antipsychotics compared with placebo or typical agents, there are a number of head-to-head comparisons or switching studies between atypical drugs.[126–137] Among 12 such studies, 11 compared risperidone with other atypicals. Of these, 2 using clozapine[126,127] and 2 using olanzapine[132,133] showed similar effects on EPS compared with risperidone. Seven other studies showed reduced liability with other atypicals compared with risperidone.[128–131,134–136] In another study by Tollefson et al.[137] in treatment-resistant patients, there was no difference between olanzapine and clozapine in the frequency of acute EPS. However, similar to placebo-controlled trials, these comparative studies must be individually examined for the same confounding and biased effects of dosages, assessment instruments and techniques, research design, and validity of statistical analyses.

Assuming these methodological issues are considered, meta-analyses of clinical trials provide another method for comparing effects of atypical and typical antipsychotics on movement disorders and the extrapyramidal motor system.[1–5] Although contrasting results have been obtained concerning measures of efficacy, all published meta-analyses yield one consistent conclusion, i.e., that atypical antipsychotics as a group represent a significant advance over earlier antipsychotics in sparing the extrapyramidal system and reducing the risk of drug-induced movement disorders.

CONCLUSION

Data from clinical trials fulfill expectations and predictions based on preclinical findings; all of the atypical antipsychotic drugs show a significantly reduced potential in causing acute EPS and other movement disorders. Acute EPS are reduced across the phenomenological spectrum, with the most improvement observed in relation to classic parkinsonian signs and symptoms. Combining data from many studies, the relative risk of drug-induced acute EPS may be expressed in descending order by the following tentative formula: typical antipsychotics (high potency > midrange > low potency) > atypical antipsychotics (risperidone > ziprasidone ≥ olanzapine > quetiapine ≥ clozapine). Provided that dosage guidelines are followed, the differences in EPS liability among the atypicals may be clinically significant primarily when they are used in high-risk populations.

In the treatment of psychosis in patients with Parkinson's disease, low-dose clozapine remains the antipsychotic drug with a safety and efficacy profile that is best supported by scientific evidence. However, quetiapine appears promising as a well-tolerated alternative, provided that controlled trials substantiate its efficacy.

Unfortunately, there are few definitive studies or reports of catatonia and atypical antipsychotics. This may imply that atypicals infrequently induce catatonia, in contrast to typical drugs and in keeping with their reduced cataleptic potential in preclinical studies as a defining property of atypicality. Many catatonic patients may have been excluded from clinical trials of atypicals in schizophrenic patients because of primary mood disorders or difficulties obtaining consent. However, several large trials of atypicals included catatonic schizophrenics but did not separately report outcomes in this subgroup. Investigations of patients with catatonic schizophrenia afford an important opportunity to determine whether patients with a predisposition to develop catatonia represent a high-risk group for whom atypical agents offer effective antipsychotic therapy without the dangers of inducing or worsening catatonic symptoms and possibly precipitating NMS.

On the other hand, it is clear that clozapine, risperidone, olanzapine, and possibly quetiapine have been associated with isolated cases of NMS that meet accepted diagnostic criteria. Because NMS is uncommon, and because the incidence and severity of cases may have already declined as a result of more conservative dosing practices and greater awareness of the diagnosis, the relative risk of NMS and differences in its clinical presentation with atypicals compared with typical drugs are difficult to ascertain. Although the chances of developing fulminant and lethal NMS may be

diminished in association with the use of atypical drugs, these newer agents are not entirely free of risk. As a result, clinicians should remain aware of the signs of NMS and be prepared to diagnose it early and discontinue triggering antipsychotic drugs.

There is fairly consistent and convincing evidence that the atypical antipsychotics have a significantly reduced liability for TD and are also effective in suppressing dyskinesias in patients with preexisting TD. In some studies of atypicals, the incidence of TD is no greater than the rate of spontaneous dyskinesias among untreated schizophrenic patients.

The question of reversibility of TD in relation to treatment with atypicals is incompletely addressed. Studies with clozapine and olanzapine are encouraging in suggesting that apart from suppression, TD may be reversible during treatment with these drugs, with recovery enduring beyond drug discontinuation in some patients. However, case reports of dyskinesias worsening after withdrawal from atypicals and prior reports of resolution of TD even during treatment with typical antipsychotics temper any conclusions on the specific therapeutic effects of atypicals on TD.

Additional data are required for more recently marketed atypicals (quetiapine and ziprasidone) in relation to Parkinson's disease, NMS, catatonia, and TD.

The new generation of atypical antipsychotics offers a choice of agents that may be more broadly effective but are clearly better tolerated from a neurologic point of view. They represent an unequivocal advance in reducing the problems associated with acute and long-term, drug-induced movement disorders. As a result, the risk of movement disorders has become just one of a number of considerations in the choice among antipsychotics for treatment of patients with schizophrenia.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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