Clozapine and Tardive Dyskinesia

TO THE EDITOR: Clozapine is associated with low rates of extrapyramidal side effects and is thought to have a minimal risk of tardive dyskinesia. Furthermore, clozapine has been shown to significantly diminish dyskinetic movements in patients with tardive dyskinesia and is considered an effective treatment for it (1). Despite these observations suggesting clozapine's benefits, there have been several case reports of tardive dyskinesia associated with clozapine. Several reports (2–4) have involved patients who received previous treatment with typical antipsychotics. The following report describes clozapine-related tardive dyskinesia appearing after 10½ years of treatment with clozapine in a woman who had had minimal exposure to typical antipsychotics.

Ms. A was a 33-year-old woman with a 16-year history of paranoid schizophrenia characterized by persistent auditory hallucinations, persecutory delusions, and negative symptoms. Initially, she was treated with haloperidol, 5 to 10 mg/day, for approximately 1 year and was then switched to fluphenazine decanoate, 37.5 mg intramuscularly every 2 weeks for 1 year; both treatments led to minimal response. She was subsequently given clozapine for her treatment-resistant schizophrenia. After an initial dose of 400 mg/day, her clozapine dose was gradually increased over a 1-year period to 875 mg/day. She eventually experienced remission of her auditory hallucinations and had significant improvement of her persecutory delusions and negative symptoms.

An assessment with the Abnormal Involuntary Movement Scale (5), performed before Ms. A started taking clozapine, revealed no evidence of dyskinetic movements. After 10½ years of treatment with clozapine, Ms. A was first noted to have mild repetitive involuntary jaw and tongue movements; she was given vitamin E, 800 IU b.i.d. The abnormal movements continued and gradually worsened. Her dose of clozapine was gradually reduced from 875 to 625 mg/day over 12 months. Ms. A's psychiatric status remained stable, and the abnormal involuntary movements persisted unchanged.

This case suggests that long-term treatment with clozapine may be associated with tardive dyskinesia in an individual with minimal exposure to conventional antipsychotics. Since the patient had approximately 2 years of exposure to typical antipsychotics before starting to take clozapine, their contribution cannot be discounted. Given that the patient had no evidence of involuntary movements before clozapine treatment and that she received clozapine for approximately 10½ years before the onset of tardive dyskinesia, the impact of typical antipsychotics is likely to be minimal at most. It is possible that the patient's dyskinesia would have occurred spontaneously in the absence of antipsychotic exposure, but this is unlikely. In conclusion, clozapine and the other atypical antipsychotic drugs appear to have greatly reduced the liability for tardive dyskinesia, but it appears that they have not totally eliminated the risk.

References

1. Bassitt DP, Louza Neto MR: Clozapine efficacy in tardive dyskinesia in schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 1998; 248:209–211
2. de Leon J, Moral L, Camunas C: Clozapine and jaw dyskinesia: a case report. J Clin Psychiatry 1991; 52:494–495
3. Dave M: Clozapine-related tardive dyskinesia. Biol Psychiatry 1994; 35:886–887
4. Kumet R, Freeman MP: Clozapine and tardive dyskinesia (letter). J Clin Psychiatry 2002; 63:167–168
5. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534–537

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Safety of Quetiapine During Pregnancy

TO THE EDITOR: Tamás Tényi, M.D., Ph.D., et al. (1) were the first, to our knowledge, to report pregnancy in a woman receiving quetiapine. There is little information as yet concerning the safety of atypical antipsychotic drugs used in pregnancy. We report the case of a woman who was treated with risperidone then quetiapine throughout pregnancy without complications.

Ms. A, a 33-year-old woman, experienced a first episode of psychosis that was initially treated with risperidone, 4 mg/day. After 2 weeks, her medication was switched to quetiapine because of a combination of higher prolactin levels (1997 mU/liter; <550 is the normal maximum) and poor clinical response. Pregnancy was diagnosed during week 4 of the 39-week gestation, after 2 weeks of quetiapine treatment. Conception took place despite hyperprolactinemia.

A collaborative decision was reached to have Ms. A continue taking quetiapine throughout pregnancy because of the level of risk and family history of psychosis. We found no reports of complications during pregnancy or teratogenicity in the medical literature or manufacturer's database regarding quetiapine. Clinical improvement was monitored by using various clinical rating scales at baseline and at the 6-week, 3-month, and 9-month time points. Ms. A's scores on the Brief Psychiatric Rating Scale were 21, 0, 4, 0, and 1; her Global Assessment Scale (2) scores were 35, 84, 81, 91, and 89. Her side effects were negligible. Her initial maintenance dose of 300 mg/day was reduced to 200 mg/day at week 21. This dose remained stable until 4 weeks before Ms. A's estimated due date, when her quetiapine dose was reduced by 50 mg/day each week to enable breast-feeding after birth. Ms. A remained in remission throughout pregnancy and at week 39 gave birth to a healthy girl. The baby weighed 3.61 kg. Her Apgar score in the first minute was 8, and after 5 minutes, it was 9. No problems developed in the first month postpartum. There was no exacerbation of psychosis, and successful breast-feeding was initiated.

This case adds to the small database on the safety of administering atypical antipsychotic drugs at conception and throughout pregnancy. Given the low risk of extrapyramidal and sexual side effects with these drugs, it is likely that they will be used in younger, sexually active patient groups. This report and that of Dr. Tényi et al. on the safety of quetiapine during pregnancy are encouraging. More information is required regarding the long-term effects on children exposed to these drugs in utero. We concur with Dr. Tényi et al. (1) that a

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cautious clinical approach should be adopted that weighs benefits and risks on a case-by-case basis.

References

1. Tényi T, Trixler M, Keresztes Z: Quetiapine and pregnancy (letter). Am J Psychiatry 2002; 159:674
2. Endicott J, Spitzer RL, Fleiss JL, Cohen J: The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33:766–771

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Quetiapine and Falsely Elevated Nortriptyline Level

TO THE EDITOR: Drug interference in laboratory assays is becoming more complicated as newer drugs are introduced. This is the first report, to our knowledge, of the atypical antipsychotic quetiapine causing falsely elevated serum levels of nortriptyline by standard immunoassay.

Ms. A was a 42-year-old woman with diagnoses of schizoaffective disorder and borderline personality disorder. She was hospitalized for acute exacerbation of schizoaffective disorder with psychosis, depression, and suicidal ideation. Quetiapine was added to her medication regimen (nortriptyline, 25 mg q.i.d.; levothyroxine, 0.1 mg/day; and lithium, 300 mg t.i.d.) and titrated up to 200 mg t.i.d. over several weeks.

Her serum nortriptyline level, measured at admission, was noted to be 34 ng/ml. Several weeks later, a repeat serum level was noted to be 487 ng/ml. Ms. A, however, exhibited no signs of acute toxicity. Discussion with the reference laboratory revealed that the supratherapeutic level had been ascertained by using standard immunoassay. Repeat analysis of her blood with high-performance liquid chromatography demonstrated a blood level of nortriptyline of 216 ng/ml. Although high, this level was more consistent with her drug dose and clinical picture.

Ms. A's original serum drug level was assessed by using the Tricyclic Antidepressants Assay (Abbott Laboratories, Abbott Park, Ill.), a fluorescence polarization immunoassay run on the TDx/TDxFlx analyzer (Abbott Laboratories). Based on the competitive binding principle, this assay uses antibodies that detect a wide variety of tricyclic compounds in serum and plasma. Quetiapine, structurally similar to the tricyclic antidepressants, has been noted to interfere with immunoassays for tricyclic antidepressants (1, 2). Repeat analysis of Ms. A's serum by using high-performance liquid chromatography demonstrated the presence of quetiapine and its metabolites. These were identified and differentiated from Ms. A's serum levels of nortriptyline and nortriptyline metabolites.

In summary, quetiapine can interfere with standard immunoassays for tricyclic compounds and indicate falsely elevated levels. It is advisable to alert the laboratories of patients taking quetiapine when serum tricyclic assays are performed. In these circumstances, high-performance liquid chromatography, rather than an immunoassay, is the test of choice.

References

1. Sloan KL, Haver VM, Saxon AJ: Quetiapine and false-positive urine drug testing for tricyclic antidepressants (letter). Am J Psychiatry 2000; 157:148–149
2. Al-Mateen CS, Wolf CE II: Falsely elevated imipramine levels in a patient taking quetiapine (letter). J Am Acad Child Adolesc Psychiatry 2002; 41:5–6

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Comparative Effectiveness of Antipsychotic Drugs

TO THE EDITOR: Regarding the study by Jan Volavka, M.D., Ph.D., et al. (1), the authors should be commended for attempting to differentiate four different antipsychotics in a single trial. However, I believe that the conclusions reached in this study cannot be supported by the data. During the last 6 weeks of the trial, the dose was increased in all four treatment groups. Only the olanzapine group had greater efficacy as a result. Why was the dose increased in the other treatment groups if there was no further improvement? In the case of risperidone, this increase resulted in a mean dose of 11.6 mg/day. It has been well established that risperidone doses above 10 mg/day are less effective than lower doses (2). Thus, this study demonstrated that investigators are unable to optimize patient response using dose titration. An alternative design (e.g., with a fixed dose) should have been employed.

The authors made little justification for the choice of olanzapine dose. The current labeling for olanzapine states that its antipsychotic efficacy occurs between 10 and 15 mg/day and that doses above 10 mg/day are not more efficacious. Despite this, the labeling was ignored, and the authors chose a target dose of 20 mg/day. Why did the authors design a trial in which patients were targeted with olanzapine at twice the recommended dose? Furthermore, why were the patients allowed to have their doses titrated up to 40 mg/day of olanzapine—more than twice the known safety limit? Fortunately, there were no serious adverse events during the trial. Further studies are needed to demonstrate that higher doses of olanzapine may be warranted and are safe. This should have been stated in the text.

In addition to problems with efficacy, there is also the issue of potential unblinding of the trial due to lack of tolerability. The authors attempted to mask the expected extrapyramidal symptoms of haloperidol by giving their patients prophylactic benztropine. A benztropine placebo was given for the other antipsychotics, and actual benztropine was blindly used only if needed. The labeling for risperidone indicates there is a dose-related increase in extrapyramidal symptoms. This becomes significantly higher than with placebo in doses of more than 10 mg/day. In the present trial, 32% of the patients taking risperidone required benztropine, compared to 13% for both the olanzapine and clozapine patients. For a rater observing extrapyramidal symptoms, the a priori likelihood that the patient was taking risperidone was significantly higher; as a result, it is conceivable that the blinding may have been compromised and the scoring biased.

In summary, by arbitrarily picking doses outside currently approved drug labeling, using a dose titration scheme that

was unable to detect the maximally effective dose, and failing to adequately mask extrapyramidal symptoms, the authors designed a study that could not possibly have reached a conclusion as to which antipsychotic drug was superior to haloperidol. It is unfortunate that this trial belongs to the growing category of studies in which a flawed design yields uninterpretable results.

References

1. Volavka J, Czobor P, Sheitman B, Lindenmayer J-P, Citrome L, McEvoy JP, Cooper TB, Chakos M, Lieberman JA: Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 2002; 159:255–262; erratum, 159:2132
2. Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151:825–835

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TO THE EDITOR: We read with interest the study by Dr. Volavka and colleagues comparing three second-generation antipsychotics and haloperidol in patients with chronic schizophrenia. In this study, olanzapine was randomly assigned to a second cohort of patients after the study had been in progress for 15 months. The result of the combined cohorts was that olanzapine had the largest effect size for total scores on the Positive and Negative Syndrome Scale.

The authors found no cohort effect. For their statistical analysis, they assumed that if a cohort effect were present, the three first-cohort medications (i.e., haloperidol, risperidone, and clozapine) should have all fared better in the second cohort. We question this assumption. If the second cohort consisted of patients with a better prognosis for second-generation antipsychotics, we would have expected the following: haloperidol should not have been effective in either cohort because both cohorts were selected to be resistant to neuroleptics, clozapine should have performed well in both cohorts, and risperidone should have been inferior to clozapine in the first cohort (1) and comparable in the second cohort (2, 3). The reported results fit these assumptions fairly well. Haloperidol was indeed ineffective in both cohorts. Clozapine did moderately well in both cohorts, with scores on the Positive and Negative Syndrome Scale increasing only a small amount in the second cohort (6.48 versus 7.05, respectively). The risperidone group's improvement scores increased from −0.03 in the first cohort (N=25) to 7.93 in the second cohort (N=16). The latter appears comparable to the improvement with olanzapine (9.1, N=39). In summary, the cohort results appear too different to be validly combined.

Other analyses in this article seem to favor olanzapine. The authors reported that two patients had seizures while taking risperidone, but none had seizures while taking olanzapine. However, the authors did not note the discordance of the results for their small group of patients with seizure rates in the premarketing trials of these antipsychotics. According to the package inserts, there was a higher rate of seizures with olanzapine than with risperidone (0.9% and 0.3%, respectively). Two patients developed neutropenia with risperidone, and the authors cited a published report of another instance. They did not mention that olanzapine is associated with at least 10 cases, which we found in a PUBMED search.

Finally, the article's abstract stated—without qualification—that improvements in negative symptom scores "were superior" with clozapine and olanzapine. The supporting evidence seems weak at best. Negative symptom scores on the Positive and Negative Syndrome Scale decreased from 21.7 at baseline to 20.1 after 14 weeks of olanzapine, including 6 weeks at the top dose of 30 mg/day. The risperidone patients' negative symptoms did not improve at 8 mg/day nor at the 11.6-mg/day dose taken between weeks 8 and 14. But risperidone might have equaled or exceeded the tiny improvement produced by olanzapine had the dose been kept at 8 mg/day or reduced during weeks 8–14. Notwithstanding the authors' two citations (one unpublished), suggesting that 8 mg/day of risperidone may be better than 4 mg/day, most data and expert opinions indicate better results with risperidone doses below 8 mg/day (4–8; Marder and Meibach, 1994). For a more balanced and appropriately cautious interpretation of the data in this study, this deserved acknowledgment.

References

1. Azorin JM, Spiegel R, Remington G, Vanelle JM, Pere JJ, Giguere M, Bourdeix I: A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. Am J Psychiatry 2001; 158:1305–1313
2. Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, Baumann P (The Risperidone Study Group): Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. Am J Psychiatry 1998; 155:499–504
3. Wahlbeck K, Cheine M, Tuisku K, Ahokas A, Joffe G, Rimon R: Risperidone versus clozapine in treatment-resistant schizophrenia: a randomized pilot study. Prog Neuropsychopharmacol Biol Psychiatry 2000; 24:911–922
4. Ho BC, Miller D, Nopoulos P, Andreasen NC: A comparative effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. J Clin Psychiatry 1999; 60:658–663
5. Lane HY, Chiu WC, Chou JC, Wu ST, Su MH, Chang WH: Risperidone in acutely exacerbated schizophrenia: dosing strategies and plasma levels. J Clin Psychiatry 2000; 61:209–214
6. Love RC, Conley RR, Kelly DL, Bartko JJ: A dose-outcome analysis of risperidone. J Clin Psychiatry 1999; 60:771–775
7. Williams R: Optimal dosing strategies with risperidone: updated recommendations. J Clin Psychiatry 2001; 62:282–289
8. Conley RR, Mahmoud R: A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001; 158:765–774; erratum, 158:1759

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TO THE EDITOR: Caution is needed when interpreting the results of the study by Dr. Volavka et al. The article and the accompanying editorial (1) acknowledged that the cohort effect cannot be ruled out, the dose of risperidone was too high, and 18% of the funding was obtained from Eli Lilly and Company. The olanzapine arm of the study was included 15 months after the study had started; there was no quetiapine arm, although both drugs became available around the same time. Use of haloperidol in comparison with either loxapine or molindone as a comparator first-generation antipsychotic drug is questionable. Both offer certain advantages over other first-generation antipsychotics.