

### Clozapine-Induced Pericarditis, Pericardial Tamponade, Polyserositis, and Rash

**Sir:** Clozapine is an antipsychotic medication introduced to the United States in 1989. It is a tricyclic dibenzodiazepine derivative chemically related to the traditional antipsychotic medication loxapine.<sup>1</sup> Side effects pose a significant problem during clozapine therapy. Adverse reactions occur most frequently during the initiation of clozapine treatment and during the acute treatment and dose titration phase.<sup>2</sup> Clozapine's adverse effects, including agranulocytosis, seizures, hypersalivation, orthostasis, tachycardia, constipation, and drowsiness, are well described.<sup>3</sup>

Reports in the literature of uncommon and rare side effects of clozapine include cutaneous reactions with urticaria or eczematous exanthema with pruritus,<sup>4</sup> allergic asthmatic reaction,<sup>5</sup> polyserositis,<sup>6,7</sup> a syndrome resembling systemic lupus erythematosus (SLE),<sup>8</sup> papular rash and bilateral pleural effusion,<sup>9</sup> pericarditis and elevated troponin I,<sup>10</sup> pericarditis with pericardial effusion,<sup>11</sup> myocarditis,<sup>12</sup> Sweet syndrome with polyserositis,<sup>13</sup> and sudden death.<sup>14</sup> We report a case of pericarditis, polyserositis, and rash that developed after the initiation of clozapine therapy and that subsequently resolved after discontinuation of clozapine.

**Case report.** Ms. A, a 36-year-old woman, has had a diagnosis of schizophrenia (DSM-IV criteria) since the age of 20 years and a remote medical history of seizure disorder. On arrival in 2003 to the emergency department of an urban general hospital with her case manager, Ms. A was delusional and paranoid. She was making racial slurs and vague threats and was religiously preoccupied. She thought Jesus was on the walls and in her apartment, was talking to angels, and believed the Lord had been sitting on her shoulders for 17 years. She thought that people were trying to break in to her apartment and rape her and that she was controlled via implanted devices.

At the time of her presentation Ms. A's medications included quetiapine, 400 mg q.h.s.; paroxetine, 20 mg q.h.s.; aripiprazole, 15 mg b.i.d.; olanzapine, 20 mg q.h.s.; and ziprasidone, 80 mg b.i.d. She had no significant past medical history except for a distant history of a seizure disorder. Specifically, she had no history of heart disease, rheumatologic conditions, intravenous (IV) drug use, chest surgery or injury, or hypersensitivities to any medications or drugs. She also had no family history of relevant medical conditions. She was placed on a 72-hour hold and admitted to an inpatient psychiatry unit.

Once Ms. A was hospitalized, divalproex sodium was started for her manic symptoms and all other medications except aripiprazole were discontinued. While receiving the combination of aripiprazole and divalproex sodium, Ms. A improved behaviorally but continued to manifest prominent delusions. Because of the ongoing delusions, aripiprazole was discontinued and a trial of clozapine was initiated on the third day of hospitalization. Clozapine was started at 25 mg/day and was titrated to 300 mg/day over the course of 10 days. Orthostatic blood pressure changes occurred but did not result in complaints of dizziness. On clozapine treatment, Ms. A seemed more organized. Her delusions lessened but never went completely away. Her sleep and appetite were good. Ms. A was discharged to home while receiving clozapine, 300 mg p.o. q.h.s., and divalproex sodium, 1500 mg p.o. q.h.s., after being in the inpatient psychiatry unit for 2 weeks. At the time of her discharge, both her mother and her case manager believed that she had returned to her baseline

level of functioning. She was scheduled to follow up with an outpatient psychiatry clinic in 2 weeks.

Ms. A presented to the emergency department again 6 days after her hospital discharge, this time with complaints of shortness of breath, rash, and paranoid thinking. The emergency department physician noted that Ms. A was persistently tachypneic, tachycardic, and hypoxic. Her physical examination revealed a diffuse erythematous macular rash around her neck and chest. Vital signs showed pulse rate in the range of 110 to 120 b.p.m., respiratory rate of 22 to 26 breaths per minute, blood pressure of 129/58 mm Hg, and oxygen saturation of 85% on room air.

A chest roentgenogram gave evidence of possible consolidation in the lower lobes posteriorly and bilateral pulmonary effusions. Chest computed tomography angiogram did not show thromboembolism. Ms. A was started on rocephin, 1 g IV, and zithromax, 500 mg IV, for presumable pneumonitis and was admitted to the medical intensive care unit.

Because a consolidation could not be ruled out, Ms. A underwent further work-up for pneumonia including white blood cell count, sputum cultures, and bronchoalveolar lavages. These tests ruled out the diagnosis of pneumonia. A rheumatologic work-up for SLE and other autoimmune disease was negative. Repeated chest roentgenograms; computerized tomography of chest, abdomen, and pelvis; and repeated echocardiograms showed that Ms. A had bilateral pleural effusions, a pericardial effusion, and a small amount of ascites. An echocardiogram showed moderate-sized pericardial effusion and normal ejection fraction. Subsequent serial echocardiograms revealed an increasing amount of pericardial fluid with some hemodynamic changes suggestive of tamponade. A Swan-Ganz catheter was placed to monitor hemodynamics more closely, and intravenous diuretics, indomethacin, and steroids were initiated.

Clozapine and divalproex sodium were discontinued after the diagnosis of pericarditis. Pericardiocentesis with pericardial window was electively performed on the fourth day of hospitalization with no complication. Cytology and gram and fungal stains and cultures of the pericardial fluid were negative. Coxsackie virus titers were negative. Pericardial biopsy showed chronic inflammatory changes. Dermatology consultation was obtained, and a skin biopsy showed pathologic changes consistent with leukoclastic dermatomyositis.

By week 2 of the second hospitalization, Ms. A showed improvement. Repeat roentgenograms and echocardiograms revealed gradual resolution of the pericardial and pleural effusions and ascites. The skin rash had also subsided dramatically. Risperidone was started and titrated to 4 mg b.i.d. Ms. A tolerated risperidone well, and her behavioral and psychotic symptoms returned to their baseline levels. She was discharged on risperidone, 4 mg p.o. b.i.d.; furosemide, 20 mg p.o. q.d.; and a steroid taper.

In summary, Ms. A developed severe cardiopulmonary and moderate dermatologic symptoms in a very short period after initiation of clozapine therapy. She became symptom free and showed marked improvement in rash, pericardial and pleural effusions, and ascites once clozapine was discontinued.

There are many causes of pericarditis, including infectious and noninfectious etiologies.<sup>15</sup> In our patient, rash and cardiopulmonary symptoms began soon after starting clozapine, and marked improvement was promptly noted after discontinuation of the medication. The temporal relationship between the onset of symptoms and the onset of clozapine strongly suggests

clozapine as the likely etiology of the patient's difficulties. Although divalproex sodium was started and stopped at the same time as clozapine, it has not been implicated in the literature as causing polyserositis and pericarditis either alone or in combination with other drugs. The sequence of events and clinical presentation in this case are consistent with previous reports of clozapine-induced polyserositis.<sup>6,7</sup> However, the severity of pericarditis and cardiac tamponade, pleural effusion, and ascites with subsequent rash makes this case unique. This patient presented with no clinical history to suggest any risk for the development of these complications, and there is no literature that identifies patients that may be at risk based on medical history, sex, age, or other factors. In conclusion, although clozapine-induced polyserositis is infrequently reported in the literature, clinicians should be aware of this uncommon but potentially life-threatening condition.

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## REFERENCES

1. Buch DL. Clozapine: a novel antipsychotic. *Am Fam Physician* 1992;45:795-799
2. Lieberman JA, Safferman AZ. Clinical profile of clozapine: adverse reactions and agranulocytosis. *Psychiatr Q* 1992;63:51-70
3. Baldessarini RJ, Frankenburg FR. Clozapine: a novel antipsychotic agent. *N Engl J Med* 1991;324:746-754
4. Burki HB. Neuroleptics: Foundations and Therapy. In: Langer G, Heimann H, eds. *Psychopharmacology: Foundations and Therapy* [in German]. Vienna, Austria: Springer-Verlag; 1983:205-300
5. Stoppe G, Muller P, Fuchs T, et al. Life-threatening allergic reaction to clozapine. *Br J Psychiatry* 1992;161:259-261
6. Daly JM, Goldberg RJ, Braman SS. Polyserositis associated with clozapine treatment [letter]. *Am J Psychiatry* 1992;149:1274-1275
7. Catalano G, Catalano MC, Frankel Wetter RL. Clozapine induced polyserositis. *Clin Neuropharmacol* 1997;20:352-356
8. Wickert WA, Campbell NR, Martin L. Acute severe adverse clozapine reaction resembling systemic lupus erythematosus [letter]. *Postgrad Med J* 1994;70:940-941
9. Stanislav SW, Gonzalez-Blanco M. Papular rash and bilateral pleural effusion associated with clozapine [letter]. *Ann Pharmacother* 1999;33:1008-1009
10. Kay SE, Doery J, Sholl D. Clozapine associated pericarditis and elevated troponin I [letter]. *Aust N Z J Psychiatry* 2002;36:143-144
11. Murko A, Clarke S, Black DW. Clozapine and pericarditis with pericardial effusion [letter]. *Am J Psychiatry* 2002;59:494
12. Killian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999;354:1841-1845
13. Schonfeldt-Lecuona C, Connemann BJ. Sweet's syndrome and polyserositis with clozapine [letter] [Erratum in *Am J Psychiatry* 2003;160:204]. *Am J Psychiatry* 2002;159:1947
14. Kang UG, Kwon JS, Ahn YM, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry* 2000;61:441-446
15. Braunwald E. Pericardial disease. In: *Harrison's Principles of Internal Medicine*. 15th ed. New York, NY: McGraw-Hill; 2001:1365-1366

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## Applying Parsimony to "An African Patient With Ziprasidone Intolerance"

**Sir:** Awareness of and sensitivity to ethno-pharmacologic issues are vital when treating a person of a particular cultural/racial background, but it seems equally important to apply the principle of parsimony to cases like the one described in a recent (June 2005) letter by Hein and colleagues ("An African Patient with Ziprasidone Intolerance").<sup>1</sup> The authors suggest that their patient, who was of Nubian, Arabic, and Irish background, was particularly sensitive to a typical 40 mg b.i.d. dose of ziprasidone because of his "African ethnicity." They bolstered their claim by citing this case as the second report of a person of African background who experienced severe side effects from a "commonly recommended dose of ziprasidone."

The most appropriate explanation for apparent ziprasidone toxicity in this patient seems to be the most simple. Genetic polymorphism is not an exceedingly rare occurrence in any population. Although this patient was one half Nubian, this does not mean that his sensitivity to ziprasidone should automatically be attributed to this aspect of his genetic-neurophysiologic milieu.

I recently treated a graduate student of Middle-Eastern background who had received previous counseling at an Ivy League university. She presented with anxiety and depression symptoms that affected her ability to initiate and engage herself in writing her dissertation. She commented that her previous therapist had "overemphasized cultural differences" in therapy, which, in her case, had not allowed her to make progress.

This is not to suggest that a patient's cultural background should be de-emphasized or ignored in any way. Understanding our patients commonly requires a balanced application of ethno-cultural sensitivity leavened by the principles of Occam's razor. In general we should refrain from jumping to complicated assumptions when attempting to make sense of unexpected clinical outcomes.

*Dr. Anders reports no financial or other relationship relevant to the subject of this letter.*

## REFERENCE

1. Hein J, Gregor A, Bartholomä A, et al. An African patient with ziprasidone intolerance [letter]. *J Clin Psychiatry* 2005;66:800

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## Dr. Hein Replies

**Sir:** Our letter is the first report of a dramatically increased serum concentration of ziprasidone and the second report of the occurrence of severe side effects with that same medication, both effects occurring despite a demonstrably normal dose of the drug. As it happens, both patients in question had an African ethnic background.

The great William of Occam suggested that "entities are not to be multiplied beyond necessity,"<sup>1</sup> the principle that has become known as "Occam's razor." Dr. Anders agrees with our proposal that a genetic polymorphism is the likely cause for the increased serum concentration in our patient. But to ignore the

ethnicity of these patients when genetic issues are at hand could mean to ignore an important piece of a possibly new "entity" in Occam's sense. In the empirical science of medicine, applying parsimony should not mean forgoing inquisitiveness.

*Dr. Hein reports no financial or other relationship relevant to the subject of this letter.*

#### REFERENCE

1. Hirsch ED Jr, Kett JF, Trefil J, eds. *The New Dictionary of Cultural Literacy*. Boston, Mass: Houghton Mifflin Co; 2002

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### Initial Evidence of the Beneficial Effects of Glutamate-Modulating Agents in the Treatment of Self-Injurious Behavior Associated With Borderline Personality Disorder

**Sir:** Self-injurious behavior (SIB) in patients with borderline personality disorder (BPD), especially cutting, represents a serious and often intractable clinical problem.<sup>1</sup> There are few validated pharmacologic strategies for managing SIB.<sup>1-3</sup> We describe our initial experience using glutamate-modulating agents in 2 patients with BPD and prominent SIBs. In both cases, the first 2 in which we have tried this approach, cutting behavior dramatically decreased after initiating treatment with the glutamate-modulating agent riluzole. In 1 case, the reduction in SIB persisted when treatment was switched from riluzole to *N*-acetylcysteine (NAC), an amino acid agent that also modulates glutamate activity.

Riluzole is indicated for the treatment of amyotrophic lateral sclerosis and is a potent antiglutamatergic agent. It is thought to work by reducing synaptic release of glutamate, inactivating voltage-gated sodium channels in cortical neurons, and reducing the excitatory-inhibitory balance in the brain by inhibiting  $\gamma$ -aminobutyric acid reuptake.<sup>4,5</sup> Altered glutamatergic neurotransmission has recently been implicated in the pathophysiology of mood and anxiety disorders.<sup>6,7</sup> Recent studies suggest that riluzole is efficacious in the treatment of psychiatric disorders such as depression and obsessive-compulsive disorder.<sup>8-12</sup> *N*-acetylcysteine is a readily available amino acid that is often used for its antioxidant properties. However, it is also thought to modulate glutamate by stimulating the cysteine-glutamate antiporter located on glia, increasing extrasynaptic glutamate levels and thereby stimulating the feedback inhibition of synaptic glutamate release.<sup>13</sup>

**Case 1.** Ms. A, a 25-year-old woman, has had a history of posttraumatic stress disorder (PTSD) and BPD (DSM-IV). She was referred for psychiatric treatment in 2003 by her primary care provider after several office visits for suturing of self-inflicted abdominal lacerations. Her primary care physician noted refractory symptoms of depression and anxiety and her inability to stop cutting. Ms. A had begun repeatedly cutting herself approximately 4 months prior to her referral secondary to poor stress coping mechanisms, feelings of guilt, depression, and anxiety from trauma-related memories.

Despite intensive outpatient psychiatric treatment (including individual psychotherapy, cognitive-behavioral therapy, and

pharmacotherapy), Ms. A's symptoms persisted for approximately 1 year with minimal improvement. Medication management included trials of citalopram, fluoxetine, mirtazapine, venlafaxine, olanzapine, bupropion, risperidone, aripiprazole, clonazepam, alprazolam, lorazepam, and lamotrigine. Medications provided little symptomatic relief, and her SIB continued. Riluzole was added to her medication regimen of escitalopram, 20 mg/day, and clonazepam, 1 mg/day, to target symptoms of treatment-resistant depression, after informed consent was obtained from the patient for this off-label use. After 6 weeks of treatment with riluzole, dosed at 50 mg twice a day, there was little improvement in mood or anxiety. However, she reported a significant attenuation in her previously intense cravings to cut between week 2 and 3 of riluzole treatment. By week 4 of treatment, she was able to stop all SIB and reported no cravings to cut. She remained on riluzole treatment for approximately 8 weeks, which represented the longest period that she did not engage in SIB since first being referred for psychiatric treatment.

Unfortunately, Ms. A experienced significant sedation on riluzole treatment and requested to stop the medication despite its beneficial effects. Within 1 week of riluzole cessation, her desire to cut herself returned. She was then treated with NAC, 600 mg b.i.d. Within 2 weeks of starting treatment with NAC, her desire to cut again decreased. Ms. A's self-report was that treatment with NAC significantly attenuated the self-injurious cravings but was not as effective as riluzole in eradicating those desires. In any event, she has continued not to engage in any SIBs for more than 6 months while being treated with either riluzole or NAC.

**Case 2.** Ms. B, a 45-year-old woman, has had a long history of BPD, major depressive disorder, obsessive-compulsive disorder, and generalized anxiety disorder (DSM-IV). She had a several-year history of engaging in SIB such as hitting herself until she bruised, banging her head, and repeatedly cutting herself with a razor. These self-injurious behaviors and her desires to cut worsened during times of stress. She was treated with individual psychotherapy, cognitive-behavioral therapy, and pharmacotherapy. Medication management included treatment trials, alone or in combination, of venlafaxine, sertraline, topiramate, gabapentin, lorazepam, trazodone, aripiprazole, and risperidone.

After Ms. B gave informed consent for off-label use, riluzole, 50 mg twice a day, was added to her medication regimen of sertraline, 200 mg/day; risperidone, 2 mg each evening; modafinil, 200 mg/day; and clonazepam, 1 mg 3 times per day. Ms. B reported a marked attenuation and, ultimately, complete cessation of the desire to engage in SIB after treatment with riluzole. As with Ms. A, the attenuation in SIB occurred between week 2 and 3 of treatment with riluzole. By week 4, Ms. B had experienced a complete cessation of her desire to cut and has not engaged in any self-injurious behaviors in more than 6 months. This represents the longest period of time that she has not engaged in SIB over the last several years.

The neural circuitry and neurotransmitter systems contributing to SIB in BPD are poorly understood. The clinical literature on pharmacotherapy for SIB is sparse, although the use of opiate antagonists and clonidine in BPD has received support from small uncontrolled studies.<sup>2,3</sup> Antiglutamatergic agents have been shown to reduce SIB in some animal models,<sup>14,15</sup> although the direct applicability of such models to BPD is unclear. A number of case reports and open-label studies have suggested that the anticonvulsants lamotrigine and topiramate may be beneficial in the treatment of SIB in various forms of mental retardation<sup>16-18</sup> and possibly in BPD.<sup>19</sup> Interestingly, both lamotrigine and topiramate modulate glutamate neurotransmission,

albeit not as potently as riluzole. Taken together, preclinical studies implicating glutamatergic neurotransmission in the pathophysiology of SIB and our clinical observations regarding the beneficial effects of riluzole and NAC suggest that glutamate-modulating agents may prove to be important new tools in the treatment of this difficult constellation of behaviors.

Our clinical experience with Ms. A suggests functional overlap between riluzole and NAC in this case. This finding is of potential importance to this patient population, because of the low cost, ready availability, and attractive safety profile of NAC. More research will be needed to determine precisely how the efficacy of NAC compares to that of riluzole.

Common adverse effects associated with riluzole treatment include asthenia, nausea, sedation, and increased liver function tests (LFTs). Regular LFT monitoring is suggested by the manufacturer.<sup>20</sup> Our first patient, Ms. A, experienced significant sedation, which is perhaps the most common side effect with this medication. The riluzole used in these cases was purchased; there was no support from the manufacturer.

While lessons from case reports are limited in their generalizability, the efficacy of riluzole and NAC in these treatment-resistant patients is consistent with mechanistic hypotheses related to SIB. Further examination of the role of glutamate-modulating agents in the treatment of SIB appears warranted.

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## REFERENCES

- Lieb K, Zanarini MC, Schmahl C, et al. Borderline personality disorder. *Lancet* 2004;364:453–461
- Roth AS, Ostroff RB, Hoffman RE. Naltrexone as a treatment for repetitive self-injurious behavior: an open label trial. *J Clin Psychiatry* 1996;57:233–237
- Philipsen A, Richter H, Schmahl C, et al. Clonidine in acute aversive inner tension and self-injurious behavior in female patients with borderline personality disorder. *J Clin Psychiatry* 2004;65:1414–1419
- Urbani A, Belluzzi O. Riluzole inhibits the persistent sodium current in mammalian CNS neurons. *Eur J Neurosci* 2000;12:3567–3574
- Jehle T, Bauer J, Blauth E, et al. Effects of riluzole on electrically evoked neurotransmitter release. *Br J Pharmacol* 2000;130:1227–1234
- Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47:351–354
- Rosenberg DR, MacMaster FP, Keshavan MS, et al. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. *J Am Acad Child Adolesc Psychiatry* 2000;39:1096–1103
- Coric V, Milanovic S, Wasylink S, et al. Beneficial effects of the anti-glutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder [letter]. *Psychopharmacology (Berl)* 2003;167:219–220
- Zarate CA, Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 2004;161:171–174
- Sanacora G, Kendell SF, Fenton L, et al. Riluzole augmentation for treatment-resistant depression [letter]. *Am J Psychiatry* 2004;161:2132
- Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry* 2005;57:430–432
- Coric V, Taskiran S, Pittenger C, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry* 2005;58:424–428
- Baker DA, McFarland K, Lake RW, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003;6:743–749
- King BH, Cromwell HC, Lee HT, et al. Dopaminergic and glutamatergic interactions in the expression of self-injurious behavior. *Dev Neurosci* 1998;20:180–187
- Shishido T, Watanabe Y, Kato K, et al. Effects of dopamine, NMDA, opiate, and serotonin-related agents on acute methamphetamine-induced self-injurious behavior in mice. *Pharmacol Biochem Behav* 2000;66:579–583
- Uvebrant P, Bauziene R. Intractable epilepsy in children: the efficacy of lamotrigine treatment, including non-seizure-related benefits. *Neuropediatrics* 1994;25:284–289
- Davanzo PA, King BH. Open trial lamotrigine in the treatment of self-injurious behavior in an adolescent with profound mental retardation. *J Child Adolesc Psychopharmacol* 1996;6:273–279
- Shapira NA, Lessig MC, Murphy TK, et al. Topiramate attenuates the self-injurious behavior in Prader-Willi syndrome. *Int J Neuropsychopharmacol* 2002;5:141–145
- Preston GA, Marchant BK, Reimherr FW, et al. Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. *J Affect Disord* 2004;79:297–303
- Rilutek (riluzole). Physician's Desk Reference. Montvale, NJ: Thompson Healthcare; 2004

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### Orally Disintegrating Antipsychotics May Promote Compliance and Adherence in Patients With Schizophrenia

**Sir:** Kane et al., in their recent (January 2005) CME activity “Optimizing Pharmacotherapy to Maximize Outcome in Schizophrenia,”<sup>1</sup> recommend using a long-acting depot injection in patients who fail to adhere to antipsychotic treatment. While depot medications ensure compliance, they may not foster certain aspects of the doctor-patient relationship, and even with depot medication, about 25% of patients stop keeping scheduled appointments and no longer receive depot injections within 1 year after starting treatment.<sup>2</sup> Furthermore, depot medications may be associated with an increased risk for prolonged side effects.<sup>3</sup> Thus, before opting for depot medication, the clinician may first consider orally disintegrating tablets (ODTs) for facilitating compliance and adherence in this patient population.

There are several antipsychotics recently developed and currently available as ODTs, including clozapine, risperidone, and olanzapine. All of the above-mentioned ODTs rapidly disintegrate on contact with saliva without the need for water,<sup>4</sup> effectively mask the taste of the medication,<sup>5</sup> and are bioequivalent to comparable dosages of the oral tablet.<sup>6–8</sup>

Orally disintegrating tablets may become a valuable alternative method for treating noncompliant or nonadherent patients, as the ease of administration of an ODT may encourage patients to comply with their daily medication regimen.<sup>4</sup> It has been suggested that olanzapine ODTs may facilitate a successful therapeutic outcome in psychotic symptoms, compliance attitude, and health-seeking behaviors during acute treatment,<sup>6</sup> and a small group of patients switched from risperidone oral tablets to ODTs rated the ODTs as very acceptable.<sup>9</sup> However, ODTs may not benefit all patients with compliance or adherence issues, as evidenced by 1 recent report in the literature of a patient who was able to “cheek” her olanzapine ODTs.<sup>10</sup> The clozapine ODT

and risperidone ODT<sup>10</sup> are larger in size than the olanzapine ODT, and therefore concealment of the tablets in the mouth would be more difficult.

In conclusion, the atypical antipsychotics available as ODTs may promote adherence and compliance and may particularly benefit those patients who (1) seek convenience because they are active, working, or going to school; (2) are concerned about calling attention to their medication; or (3) have no access to water at the time of dosing. Because the use of ODTs may offer a practical potential for fostering adherence and patient responsibility in patients with schizophrenia, their use should be considered before resorting to the more invasive depot medications. Alternatively, when treatment with an ODT fails to lead to improved adherence and compliance, the clinician should consider a depot formulation.

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#### REFERENCES

1. Kane JM, ed. Optimizing Pharmacotherapy to Maximize Outcome in Schizophrenia [ACADEMIC HIGHLIGHTS]. *J Clin Psychiatry* 2005; 66:122–133
2. Young JL, Zonana HV, Shepler L. Medication noncompliance in schizophrenia: codification and update. *Bull Am Acad Psychiatry Law* 1986;14:105–122
3. Chong SA, Mythily, Lum A, et al. Prolonged QTc intervals in medicated patients with schizophrenia. *Hum Psychopharmacol* 2003;18:647–649
4. Bogner RH, Wilkosz MF. Fast-Dissolving Tablets. *USPharmacist*. Available at: [http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/FastDissolving.htm&pub\\_id=8&article\\_id=842](http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/FastDissolving.htm&pub_id=8&article_id=842). Accessed Jan 5, 2005
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth Dissolving Tablets: A Novel Drug Delivery System. *Pharma Times* 2003;35. Available at <http://www.indianpharma.org/pt/index.php/2003/6June/mouth.htm>. Accessed Oct 19, 2004
6. Kinon BJ, Hill AL, Liu H, et al. Olanzapine orally disintegrating tablets in the treatment of acutely ill non-compliant patients with schizophrenia. *Int J Neuropsychopharmacol* 2003;6:97–102
7. Risperdal, Risperdal M-Tab, product monograph. Toronto, Ontario, Canada: Janssen-Ortho Inc; March 2, 2004
8. FazaClo Orally Disintegrating Tablets [package insert]. Parsippany, NJ: Alamo Pharmaceuticals; May 2004
9. Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorder. *Can J Psychiatry* 2004;49:701–703
10. Freudenreich O. Treatment noncompliance with orally disintegrating tablets [letter]. *Can J Psychiatry* 2003;48:353–354

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#### Dr. Kane Replies

**Sir:** My colleagues and I appreciate Dr. Tornatore's comments. The availability of orally disintegrating antipsychotics is certainly a welcome addition to our psychopharmacologic treatment options. They allow easier assurance by an observer that medication has indeed been taken. However, we are unaware of any data from controlled trials demonstrating actual advantages over usual oral formulations in terms of long-term adherence, relapse rates, and other variables. In contrast, there are a num-

ber of double-blind, controlled trials demonstrating superiority of long-acting injectable medication over oral medication.<sup>1</sup>

When one considers the variety of reasons why nonadherence occurs, particularly in patients with schizophrenia, it is not realistic to assume that orally disintegrating tablets would have any long-term impact on this problem. When patients are at risk for relapse due to nonadherence, that risk should not be allowed to continue with unproven alternatives prior to initiating a proven safe and effective approach. In terms of safety, there are no systematic data suggesting that antipsychotic medication administered via long-acting injection is associated with any greater safety concerns than oral medication taken for the same period of time.

It is also unfounded to suggest that long-acting injectable medication "may not foster certain aspects of the doctor-patient relationship." This assertion is often raised as a challenge to the use of long-acting medications, without any data to support such an assertion and without any consideration of the overall risks and benefits of such treatment decisions.

We certainly would welcome controlled trials assessing the potential of orally disintegrating tablets to reduce the very high rates of poor and partial adherence in patients with schizophrenia. Long-acting injectable medication would make an ideal comparator along with usual oral formulations.

*Dr. Kane has been a consultant for Abbott, Janssen, Pfizer, Eli Lilly, and Bristol-Myers Squibb and has received honoraria from Abbott, Bristol-Myers Squibb, and Janssen.*

#### REFERENCE

1. Davis J, Barter J, Kane JM. Antipsychotic Drugs. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*, vol. 2. 5th ed. Baltimore, Md: Williams & Wilkins; 1989:1591–1626

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#### Reexamining Paroxetine and Cognitive-Behavioral Therapy in Postpartum Depression and Anxiety

**Sir:** The recent (September 2004) study by Misri et al.<sup>1</sup> evaluating the use of paroxetine and cognitive-behavioral therapy (CBT) to treat postpartum depression and anxiety is timely and informative; however, I have several concerns.

The results of the study are not generalizable to the majority of women with postpartum depression and anxiety. At best, the sample is representative only of the very small subset of women with severe comorbid anxiety and depression who are diagnosed by their primary care physician and referred for specialty care. We know that only 1 in 3 women with postpartum psychiatric disorders receives a diagnosis from any doctor,<sup>2</sup> and we know that many women with depressive and anxious disorders are treated by primary care physicians without further referral. The diagnosis and referral of the women in this sample may indicate the severity of their symptoms, but may also differentiate them from the majority of women suffering from postpartum depression and anxiety in ways not explored by the authors of this study. Although random assignment to treatment group can alleviate the need for random sampling, complete exclusion of certain women from the sample must be addressed as a limitation in generalizability.

Another concern is the lack of information about the CBT treatment. The authors make no mention of fidelity checks to make sure that the intervention was the same for all participants in the CBT treatment group. Although the intervention was manual based, the manuals were adapted for use with postpartum women. The effectiveness of using materials and interventions not specifically designed for the target population is questionable.

The authors note that further research with a larger sample is needed to determine whether the shorter time to remission for the group receiving CBT with medication is statistically significant. In the meantime, they suggest that the results of their research argue for the economic benefits of eschewing CBT treatment. I would argue that, with such a small sample, a statistical trend toward faster remission times—even if only 2 weeks out of 12—is critical, and we should continue to support the combination of CBT and medication therapy. Research demonstrates that maternal psychological disorders can have critical long-term effects on child development.<sup>3</sup> Two weeks in the life of an infant may have more significance than we can gauge at this time, and given the fragile nature of mother-child attachment, caution should be employed when examining the statistical versus clinical significance of the findings. A power analysis would have clarified the ability of the data to answer this question.

One final caution involves the role of the principal investigator. The article implies that the principal investigator in this study had the authority to include and/or exclude participants on the basis of DSM-IV diagnoses, was not blind to condition, and assessed the participants each week using standardized assessments (the authors note that a psychiatrist blind to condition conducted the first week assessments only). Both DSM-IV diagnoses and the Hamilton rating scales (used in the study by Misri and colleagues to assess levels of depression and anxiety) are subject to rater bias. These concerns are magnified given the appearance of a possible financial conflict of interest due to funding from GlaxoSmithKline Canada.

*Ms. McClendon reports no financial or other relationship relevant to the subject of this letter.*

#### REFERENCES

1. Misri S, Reebye PR, Corral M, et al. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004;65:1236–1241
2. Heneghan AM, Silver EJ, Bauman LJ, et al. Do pediatricians recognize mothers with depressive symptoms? *Pediatrics* 2000;106:1367–1373
3. Cohn JF, Tronick EZ. Three-month-old infants' reaction to simulated maternal depression. *Child Dev* 1983;54:185–193

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#### Dr. Misri and Colleagues Reply

**Sir:** We appreciate the response of Ms. McClendon to our article on paroxetine and cognitive-behavioral therapy (CBT) in the treatment of comorbid postpartum depression and anxiety. We agree that our findings are from women with severe comorbid depression and anxiety, as indicated by their Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety scores at baseline, and are therefore representative of only this select population. Due to the relative lack of research on the

clinical effectiveness of combined pharmacologic and psychological interventions for postpartum depression and anxiety, the primary aim of the study was to provide readers with preliminary information on this subject taken from a select sample treated at a tertiary hospital outpatient clinic. Consequently, the sample size utilized in our study was small. Clearly, further research into the efficacy of combination therapy in a larger population is recommended, and additional investigation into the efficacy of these treatments in postpartum women with less severe symptomatology is required.

Of note, another study of women with postpartum depression who were recruited from a largely unselected systematic sample of newly delivered mothers produced similar results.<sup>1</sup> We do not eschew CBT treatment altogether, but recommend that, on the basis of the findings of our study, it may not be warranted in the acute phase of treatment. In fact, we recommend that patients with mild-to-moderate illnesses be referred for psychotherapy.<sup>2</sup>

Ms. McClendon voiced concern regarding the lack of information available about the CBT treatment utilized in our study. The treatment was administered to all participants by the same registered Ph.D.-level psychologist who adhered to a manual that was developed specifically for the treatment of women with postpartum depression and anxiety. The purpose of the manual was to ensure that the treatment was standardized and replicable.

Ms. McClendon expressed concerns regarding the role of the principal investigator. The principal investigator did have the authority to include and/or exclude participants on the basis of DSM-IV-TR diagnoses. However, it is important to note that diagnostic clarifications were made prior to randomly assigning participants to treatment groups, and, as a result, rater bias was not a concern at that time. Further, the principal investigator was, in fact, blind to treatment condition. The original article does indicate that the psychiatrist prescribed paroxetine to the participants and monitored their progress on a weekly basis with standardized assessments; notably, however, all participants, regardless of treatment group, were prescribed paroxetine as part of the study. The psychiatrist was unaware of which participants were receiving CBT in conjunction with the medication treatment, and we therefore do not feel that any bias in rating affected our comparisons of the 2 groups. Further, the Edinburgh Postnatal Depression Scale, a self-report measure, was administered to bolster the clinician ratings that were utilized.

Finally, although GlaxoSmithKline Canada did contribute funding for our study in the form of an unrestricted grant, they had no input into the experimental design, data acquisition, statistical analyses, or interpretation of the results.

#### REFERENCES

1. Appleby L, Warner R, Whitton A, et al. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. *BMJ* 1997;314:932–936
2. Ryan D, Milis L, Misri N. Depression during pregnancy. *Can Fam Physician* 2005;51:1087–1093

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