

## Use of Olanzapine in Anorexia Nervosa

**Sir:** Barbarich et al.<sup>1</sup> report the potential benefits of olanzapine in treating anorexia nervosa. I disagree with their results and conclusions for the following reasons.

The study's small sample size of 17 patients, 12 of whom completed the study, could result in a type II error. That 71% of patients completed the study is not "noteworthy," as the authors claim. Powers and colleagues<sup>2</sup> published a 10-week trial of olanzapine treatment of anorexia nervosa with a 64% completion rate. Fassino and colleagues<sup>3</sup> reported a 75% completion rate in a randomized, placebo-controlled study of citalopram treatment of anorexia nervosa.

Curiously, for the 3 patients who terminated the study against medical advice, Barbarich et al. did not explain their reasons for doing so. It is reasonable to conclude that weight gain resulting from olanzapine treatment was a factor. By definition, patients with anorexia nervosa have a morbid fear of weight gain and obesity, and olanzapine-induced weight gain makes this medication a poor treatment option. Woodside and colleagues<sup>4</sup> found that concerns about weight gain among anorexia nervosa patients were a predictor in their premature termination from inpatient programs specializing in treating eating disorder.

Proposed mechanisms of olanzapine-induced weight gain include increased food intake, decreased motor activity, and increased ratio of weight gain:weight of food consumed.<sup>5</sup> In fact, olanzapine may not be a suitable medication for treating patients with anorexia nervosa due to its high incidence of weight gain.

Studies reporting weight gain during olanzapine use can be divided into short-term (less than 2 months) and long-term (3 months or more). Numerous short-term studies report significant weight gain during olanzapine treatment.<sup>2,6,7</sup> Patel and colleagues<sup>6</sup> found that patients treated with olanzapine gained an average of 3.8 kg. A 10-week, single-blind study of children aged 7 to 13 years with Tourette's syndrome found that olanzapine's most common side effect was weight gain (mean = 12.0 lb).<sup>7</sup> An open-label, 10-week study of olanzapine treatment of anorexia nervosa found an average 8.75-lb weight gain.<sup>2</sup>

Regarding long-term studies, Eli Lilly's package insert for Zyprexa<sup>8</sup> disclosed that, during treatment lasting a median of 238 days, 56% of patients gained more than 7% of their baseline weight, with an average weight gain of 5.4 kg. Haberfellner and Rittmannsberger<sup>9</sup> found that 67% of olanzapine-treated patients gained more than 7% of baseline initial body weight with a mean weight gain of 7.7 kg during the first year of treatment. In a 3-year, retrospective chart review, 86% of patients on olanzapine treatment gained an average of 3.65 kg.<sup>10</sup>

Four studies comparing olanzapine with other atypical antipsychotics found olanzapine was significantly associated with a greater weight gain.<sup>6,11-13</sup> A retrospective analysis of children and adolescents receiving olanzapine or quetiapine found that patients taking olanzapine had significantly increased weight and body mass index (BMI) compared with other patients taking quetiapine.<sup>6</sup> A long-term study<sup>11</sup> comparing olanzapine and risperidone found a statistically significant ( $p < .005$ ) difference in weight gain between these atypical antipsychotics (8.34 vs. 2.74 kg). A 6-month, open, observational study<sup>12</sup> comparing olanzapine and risperidone found significant weight gains in both groups, with 11.3 kg of weight gain in the olanzapine-treated group ( $p = .001$ ) and 5.9 kg in the risperidone group ( $p = .023$ ). Another long-term study<sup>13</sup> of risperidone and olanza-

pine found a greater rate of weight gain in olanzapine-treated patients (57%) than risperidone-treated patients (13%).

In another study,<sup>14</sup> olanzapine-treated patients who had gained more than 20% in weight lost an average of 2.25 kg ( $p = .03$ ) 10 weeks after being switched to quetiapine. However, merely discontinuing olanzapine may counteract any weight gain; an animal study found that body weight returned to baseline levels once olanzapine was discontinued.<sup>5</sup> This study also compared olanzapine with haloperidol and found that haloperidol was not associated with increased weight or food consumption.

Another reason olanzapine may not be a preferred treatment for anorexia nervosa is that patients with anorexia nervosa are especially vulnerable to weight gain from olanzapine. Two studies found that having a lower BMI is associated with very significant weight gain.<sup>9,11</sup>

In their discussion, Barbarich and colleagues<sup>1</sup> de-emphasized their small sample size and the high dropout rate in their study. Readers could therefore misconstrue the validity of the results. Moreover, the "major limitation" of the study should be its brief duration of 6 weeks. Anorexia nervosa is a chronic disease that requires long-term treatment. However, long-term use of olanzapine is associated with increasing risk of patient weight gain.<sup>8-12</sup> Because patients with anorexia nervosa have a morbid fear of weight gain and obesity, long-term compliance with olanzapine treatment would be problematic for them.

The authors also asserted, "Currently, there are no other effective pharmacotherapies that significantly improve behavior in ill patients with anorexia nervosa."<sup>1(p1482)</sup> The literature and one of the authors himself do not support this statement. Kaye and colleagues<sup>15</sup> found that approximately two thirds of individuals with eating disorders had at least 1 anxiety disorder during their lifetimes, with obsessive-compulsive disorder and social phobia being most common. Moreover, patients with eating disorders in remission without prior anxiety disorders had tendencies toward anxiety, perfectionism, and harm avoidance. Anxiety disorders and tendencies toward anxiety disorders make the selective serotonin reuptake inhibitors reasonable candidates for patients with anorexia nervosa.

Indeed, a MEDLINE literature search<sup>16</sup> from 1966 through 2003 found that fluoxetine helped reduce symptoms of obsessive-compulsive disorder and depression in patients with anorexia nervosa; the author of the review recommended that fluoxetine be used for relapse prevention or to treat anorexia nervosa symptoms after weight restoration.

One of this study's authors (Kaye) has previously published 2 articles about the efficacy of fluoxetine in treating anorexia nervosa. Kaye and colleagues<sup>17</sup> reported a long-term, open trial in which fluoxetine helped 29 of 31 anorexia nervosa patients maintain their body weight at or above 85% average body weight. Kaye and colleagues<sup>18</sup> also reported a double-blind, placebo-controlled study of fluoxetine treatment of 35 patients with the restricting type of anorexia nervosa. Sixty-three percent of these patients remained on fluoxetine treatment for 1 year and had reduced relapse rates. Another study<sup>19</sup> reported improved symptoms of depression and weight gain in anorexia nervosa patients treated with fluoxetine. Yet another study<sup>20</sup> found that monotherapy with venlafaxine or fluoxetine increased BMI and reduced scores on the Eating Disorder Examination. Moreover, only venlafaxine reduced State-Trait Anxiety Inventory scores.

Three studies support the efficacy of citalopram in treating anorexia. Fassino and colleagues<sup>3</sup> performed a 3-month, randomized, placebo-controlled study with citalopram. Citalopram-

treated patients had significant decreases in their scores on the Beck Depression Inventory and Symptom Checklist-90 depression subscale and obsessive-compulsive symptoms, Eating Disorder Inventory-2 impulsiveness, and State-Trait Anger Expression Inventory trait anger. Weight gain on citalopram treatment was similar to that with placebo. Calandra and colleagues<sup>21</sup> found that an 8-week open trial of 20 mg daily of citalopram effectively, safely, and significantly reduced Eating Disorder Inventory and Binge Scale body dissatisfaction subscale scores in patients with anorexia nervosa. A 6-month, open trial with citalopram showed a 46.9% satisfactory response rate in weight improvement, improved menses, and decreased Symptom Checklist-90 and Eating Disorder Inventory-2 scores.<sup>22</sup>

Finally, a 6-month, open trial of low-dose haloperidol found it effective as an adjunctive treatment in reducing Eating Disorder Inventory score, Clinical Global Impressions-Improvement scale score, Eating Disorder Inventory total score, and the Eating Disorder Inventory subscales of drive for thinness, bulimia, and interoceptive awareness scores.<sup>23</sup>

In conclusion, the potential benefits of olanzapine use in anorexia nervosa must be weighed with its limitations (especially weight gain) and alternative medications that show efficacy.

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

## REFERENCES

- Barbarich NC, McConaha CW, Gaskill J, et al. An open trial of olanzapine in anorexia nervosa. *J Clin Psychiatry* 2004;65:1480–1482
- Powers PS, Santana CA, Bannon YS. Olanzapine in the treatment of anorexia nervosa: an open label trial. *Int J Eat Disord* 2002;32:146–154
- Fassino S, Leombruni P, Daga G, et al. Efficacy of citalopram in anorexia nervosa: a pilot study. *Eur Neuropsychopharmacol* 2002;12:453–459
- Woodside DB, Carter JC, Blackmore E. Predictors of premature termination of inpatient treatment for anorexia nervosa. *Am J Psychiatry* 2004;161:2277–2281
- Arjona AA, Zhang SX, Adamson B, et al. An animal model of anti-psychotic-induced weight gain. *Behav Brain Res* 2004;152:121–127
- Patel NC, Kistler JS, James EB, et al. A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. *Pharmacotherapy* 2004;24:824–830
- Stephens RJ, Bassel C, Sandor P. Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome: a pilot study. *J Child Adolesc Psychopharmacol* 2004;14:255–266
- Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2004. Available at: <http://pi.lilly.com/us/zyprexa-pi.pdf>. Accessed November 30, 2003
- Haberfellner EM, Rittmannsberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004;19:251–253
- Jackson WC, Manning JS, Connor PD, et al. Retrospective study of olanzapine in depressive and anxious states in primary care. *Prim Care Companion J Clin Psychiatry* 2004;6:199–202
- Lee E, Leung C-M, Wong E. Atypical antipsychotics and weight gain in Chinese patients: a comparison of olanzapine and risperidone. *J Clin Psychiatry* 2004;65:864–866
- McIntyre RS, Mancini DA, Srinivasan J, et al. The antidepressant effects of risperidone and olanzapine in bipolar disorder. *Can J Clin Pharmacol* 2004;11:e218–e226
- Ghaemi SN, Hsu DJ, Rosenquist KJ, et al. Long-term observation comparison of risperidone and olanzapine in bipolar disorder. *Ann Clin Psychiatry* 2004;16:69–73
- Gupta S, Masand PS, Virk S, et al. Weight decline in patients switching from olanzapine to quetiapine. *Schizophr Res* 2004;70:57–62
- Kaye WH, Bulik CM, Thornton L, et al. Comorbidity of anxiety disorders with anorexia and bulimia nervosa. *Am J Psychiatry* 2004;161:2215–2221
- Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003;37:890–892
- Kaye WH, Weltzin TE, Hsu LK, et al. An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry* 1991;52:464–471
- Kaye WH, Nagata T, Weltzin TE, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001;49:644–652
- Gwirtsman HE, Guze BH, Yager J, et al. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *J Clin Psychiatry* 1990;51:378–382
- Ricca V, Mannucci E, Paionni A, et al. Venlafaxine versus fluoxetine in the treatment of anorectic outpatients: a preliminary study. *Eat Weight Disord* 1999;4:10–14
- Calandra C, Gulino V, Insera L, et al. The use of citalopram in an integrated approach to the treatment of eating disorders: an open study. *Eat Weight Disord* 1999;4:207–210
- Pallanti S, Quercioli L, Ramacciotti A. Citalopram in anorexia nervosa. *Eat Weight Disord* 1997;2:216–221
- Cassano GB, Miniati M, Pini S, et al. Six-month open trial of haloperidol as an adjunctive treatment for anorexia nervosa: a preliminary report. *Int J Eat Disord* 2003;33:172–177

**Michael Menaster, M.D.**  
Private Practice  
San Francisco, California

## Ms. Barbarich-Marsteller and Dr. Kaye Reply

**Sir:** In response to the letter to the editor “Use of Olanzapine in Anorexia Nervosa,” we would like to address the author’s criticisms. We appreciate the author’s concerns and interest in improving treatment for anorexia nervosa.

It is well known that individuals with anorexia nervosa are inherently difficult to treat, even in an inpatient setting. Moreover, it has been argued<sup>1</sup> that inpatients with anorexia nervosa are more than twice as likely (33.3%)<sup>1</sup> to drop out of an inpatient treatment program than individuals in a general psychiatric ward (16%).<sup>2</sup> In our study, there were 3 subjects who left the treatment program against medical advice. The author of the letter states, “It is reasonable to conclude that weight gain resulting from olanzapine treatment was a factor.” However, there were no significant differences in mean weight gain between the 12 subjects who completed the full 6 weeks of the study (7.0 ± 2.0 kg) and either the 3 subjects who left against medical advice (7.4 ± 1.2 kg, *p* = .74) or the 5 subjects who completed less than 5 weeks of the study (5.6 ± 3.0 kg, *p* = .29). Therefore, the evidence does not support the author’s conclusion that weight gain resulting from olanzapine use was a factor in terminating treatment. Moreover, one rationale for using an atypical antipsychotic such as olanzapine in the treatment of anorexia nervosa is to promote weight gain in order to attain the stable weight and nutritional status needed for psychological treatments to be effective.

In our article, we argued that “currently, there are no other effective pharmacotherapies that significantly improve behavior in ill patients with anorexia nervosa.” Dr. Menaster’s response that “the literature and one of the authors himself do not support this statement” is unfounded. While we acknowledge the author’s citation of citalopram in treating anorexia nervosa during the acute phase, in both the open trial<sup>3</sup> and the double-blind, placebo-controlled trial<sup>4</sup> of fluoxetine published by our group, fluoxetine was administered only after acute weight restoration. Therefore, these studies did not assess fluoxetine as a treatment during the ill state when individuals were less than 85% of their ideal body weight. In a recent study by our group,<sup>5</sup>

we also reported that administration of nutritional supplements did not increase the efficacy of fluoxetine in underweight individuals with anorexia nervosa. Moreover, in the articles cited by the author of the letter, Kim<sup>6</sup> argued that fluoxetine was not effective as a primary or acute therapy, and although Gwirtsman et al.<sup>7</sup> reported an improvement in depressive symptoms, their study consisted of only 6 subjects with no control group. Taken together, these studies suggest that fluoxetine is effective in preventing relapse only when administered after weight restoration, and not during the acute, underweight phase of the illness.

In response to the author's criticism of our small sample size (N = 17), our original report acknowledged that "these findings must be considered with extreme caution." Moreover, we recognize the author's argument that "anorexia nervosa is a chronic disease that requires long-term treatment" beyond the 6-week period of the study. Nevertheless, this study was designed as an open trial to obtain preliminary data to assess the efficacy of olanzapine in the treatment of anorexia nervosa and to determine the need for a double-blind, placebo-controlled trial. Therefore, the relatively small sample size and short duration of treatment are appropriate. Overall, our results support the need for a controlled study of olanzapine in the acute treatment of anorexia nervosa.

*The research reported in Barbarich-Marsteller and colleagues' original article was supported in part by Eli Lilly and Company.*

#### REFERENCES

1. Kahn C, Pike K. In search of predictors of dropout from inpatient treatment for anorexia nervosa. *Int J Eat Disord* 2001;30:237-244
2. Miles J, Adlersberg M, Reith G, et al. Discharges against medical advice from voluntary psychiatric units. *Hosp Community Psychiatry* 1976;27:859-864
3. Kaye WH, Weltzin TE, Hsu LK, et al. An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry* 1991;52:464-471
4. Kaye WH, Nagata T, Weltzin TE, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001;49:644-652
5. Barbarich NC, McConaha CW, Halmi KA, et al. Use of nutritional supplements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *Int J Eat Disord* 2004;35:10-15
6. Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003;37:890-892
7. Gwirtsman HE, Guze BH, Yager J, et al. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *J Clin Psychiatry* 1990;51:378-382

**Nicole C. Barbarich-Marsteller, B.S.**

Department of Neurobiology and Behavior  
State University of New York at Stony Brook  
Stony Brook, New York

**Walter H. Kaye, M.D.**

Department of Psychiatry  
University of Pittsburgh Medical School  
Pittsburgh, Pennsylvania

### Injection Site Pain With Long-Acting Risperidone

**Sir:** In a recent report in the *Journal*,<sup>1</sup> only 1 of 141 patients in a 12-week multicenter trial of injectable long-acting risperidone complained of pain at the site of injection, which was mild. Pain at the injection site has been noted to be a problem with first-generation antipsychotics.<sup>2,3</sup> The authors speculated that the water-based formulation of risperidone might account for the low frequency of injection site pain. In a previous study,<sup>4</sup>

patient ratings of pain on a visual analogue scale after injections of long-acting risperidone were similar to ratings of pain after injections of placebo after the first and sixth injections. Pain after the sixth injection was rated by the investigators as present in 16% to 20% of cases in the 3 dose groups. In another study,<sup>5</sup> injection site pain was found in 32% of patients after the first injection and 20% after the 25th injection. Patients rated the pain as mild, with a median rating of 10 on a 100-mm visual analogue scale after the first injection and 5 after the 25th injection.

In clinical practice as well, pain at the injection site is common. In our experience, 4 of 11 patients who received long-acting risperidone in the last 6 months at one of our facilities complained of pain at the injection site. The first injection caused the pain in 2 cases, and in 2 other cases it was caused by subsequent injections. None of these 4 patients refused long-acting risperidone, but 1 of them needed encouragement to continue it. Complaints of injection site pain are also reported by a number of prescribers who subscribe to a popular psychopharmacology list serve (list can be accessed by contacting Ivan Goldberg at psydoc@psyc.com.net).

Risperidone is the only second-generation antipsychotic currently available as a long-acting preparation. This preparation is generally well tolerated and effective and may be less likely than oral risperidone to cause tardive dyskinesia.<sup>6</sup> One of the main reasons for using it is to try to improve compliance. Pain at the injection site is known to be related to compliance with long-acting antipsychotics both in clinical experience and in at least one clinical study<sup>3</sup>; hence, it is important to be aware of this potential side effect and make all attempts to minimize it.

First, the possibility of pain at the injection site should be discussed with the patient in advance. In particular, the patient should be told that the pain is likely to diminish with subsequent injections. Second, the needle used for risperidone injections is 20 gauge (relatively thick). Also, it is about 2 inches long, which makes it probable that the needle can hit the bone in thin individuals, causing pain. While it is important to inject the drug deep intramuscularly, in patients with minimal fat and low muscle mass, the needle should not be injected so deep as to hit the bone. Third, when cold fluid is injected, it can cause cryogenic pain at the injection site. Therefore, the manufacturer's recommendation that the drug should be allowed to come to room temperature before being injected should be scrupulously followed.<sup>7</sup> Fourth, the recommendation to use the buttocks alternately should be followed.<sup>7</sup> Last, administration of an analgesic shortly prior to or at the time of the injection should be strongly considered for cases with persistent pain.<sup>8</sup>

*Dr. Piminti is on the speakers bureaus of AstraZeneca and Eli Lilly, has been on the speakers bureau of Janssen, and has received funding from AstraZeneca. Dr. Mago has been on the speakers bureaus of Bristol-Myers Squibb and Pfizer.*

#### REFERENCES

1. Lindenmayer J-P, Eerdekens E, Berry SA, et al. Safety and efficacy of long-acting risperidone in schizophrenia: a 12-week, multicenter, open-label study in stable patients switched from typical and atypical oral antipsychotics. *J Clin Psychiatry* 2004;65:1084-1089
2. Hay J. Complications at site of injection of depot neuroleptics. *BMJ* 1995;311:421
3. Bloch Y, Mendlovic S, Strupinsky S, et al. Injections of depot antipsychotic medications in patients suffering from schizophrenia: do they hurt? *J Clin Psychiatry* 2001;62:855-859
4. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003;160:1125-1132



5. Fleischhacker WW, Eerdeken M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry* 2003;64:1250–1257
6. Keith SJ, Pani L, Nick B, et al. Practical application of pharmacotherapy with long-acting risperidone for patients with schizophrenia. *Psychiatr Serv* 2004;55:997–1005
7. Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceutica Products LP; 2003
8. Bloch Y, Levkovitz Y, Atshuler A, et al. Use of topical application of lidocaine-prilocaine cream to reduce injection-site pain of depot antipsychotics. *Psychiatr Serv* 2004;55:940–941

**Narsimha R. Pinninti, M.B.B.S., M.D., D.P.M.**

Department of Psychiatry  
School of Osteopathic Medicine  
University of Medicine and Dentistry of New Jersey  
Cherry Hill, New Jersey  
**Rajnish Mago, M.D.**  
Department of Psychiatry  
Thomas Jefferson University  
Philadelphia, Pennsylvania

**Dr. Lindenmayer and Colleagues Reply**

**Sir:** We thank Drs. Pinninti and Mago for making the important point that pain at the injection site might hamper compliance with long-acting antipsychotics. Although they report that pain at the injection site after administration of long-acting risperidone is common in their patients, this observation does not match the reports of pain assessments in published trials or in our clinical experience.

In the assessment of the impact of repeated injections with long-acting risperidone reported by Kane et al.,<sup>1</sup> investigators rated pain at the injection site immediately after the sixth injection as absent in 90% of patients in the placebo group and absent in 80%, 81%, and 84% of patients in the 25-, 50-, and 75-mg risperidone groups, respectively. In the same study, mean patient pain ratings were low at all assessments, with comparable scores among patients receiving placebo and long-acting risperidone. Mean  $\pm$  SD visual analogue scale (VAS) scores were higher at the first injection compared with the final injection: placebo, 15.6  $\pm$  20.7 (first), 12.5  $\pm$  18.3 (final); 25 mg, 11.8  $\pm$  14.4 (first), 10.0  $\pm$  12.4 (final); 50 mg, 16.3  $\pm$  21.9 (first) 13.6  $\pm$  21.7 (final); and 75 mg, 16.0  $\pm$  17.9 (first), 9.6  $\pm$  16.0 (final,  $p < .01$ ).

Mean patient VAS ratings were also low at all assessments in the 50-week study reported by Fleischhacker et al.<sup>2</sup> In neither of the studies did patients stop treatment because of injection site pain. According to a recent survey at our own 340-bed inpatient and 450-outpatient psychiatric center, there are currently 87 patients treated with long-acting risperidone. Of these patients, 2 have reported to their psychiatrist any experience of pain at the injection site, and none have refused treatment because of pain experiences.

In conclusion, few patients complain of injection site pain with long-acting risperidone; furthermore, as the authors suggest, reports of injection site pain do not have an impact on the willingness of the patients to continue medication. The authors make a number of very useful recommendations, most of which are currently included in the package insert of the medication.<sup>3</sup> An alternative to their recommendation for the administration of an analgesic prior to or at the time of injection in cases of persistent pain is to choose a different medication administration route.

*Dr. Lindenmayer has been a consultant for Bristol-Myers Squibb, Novartis, Eli Lilly, and Janssen; has received grant/research support from Eli Lilly, AstraZeneca, and Pfizer; and has been on the speakers/advisory boards of Janssen, Bristol-Myers Squibb, and Novartis. Drs. E. Eerdeken and M. Eerdeken are employees of Johnson & Johnson.*

**REFERENCES**

1. Kane J, Eerdeken M, Lindenmayer J-P, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003;160:1125–1132
2. Fleischhacker WW, Eerdeken M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry* 2003;64:1250–1257
3. Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceutica Products LP; 2003

**Jean-Pierre Lindenmayer, M.D.**

Psychopharmacology Research Unit  
Nathan Kline Institute for Psychiatric Research  
and New York University  
Manhattan Psychiatric Center  
Wards Island, New York  
**Els Eerdeken, Ph.D.**  
**Mariëlle Eerdeken, M.D., M.B.A.**  
Johnson & Johnson Pharmaceutical  
Research and Development  
Beerse, Belgium

**Do Antihypertensives Make Tranylcypromine Safer?  
Three Case Reports**

**Sir:** Monoamine oxidase inhibitors (MAOIs) have never been widely prescribed because of the risk of hypertension when combined with tyramine-containing foods or sympathomimetic amine drugs.<sup>1</sup> Hypertensive reactions have also been reported, albeit less frequently, in patients who adhere to MAOI dietary restrictions. While some of these so-called spontaneous hypertensive reactions have been reported to occur shortly after MAOI ingestion, others appear unrelated to the time of drug intake.

We report on 3 physically healthy treatment-refractory depressed patients taking the MAOI tranylcypromine who had hypertensive symptoms shortly after medication intake that were independent of dietary violations. Each patient's blood pressure was systematically observed (1) within 1 week of hypertensive symptoms before and 30 and 60 minutes after tranylcypromine ingestion and (2) after concomitant treatment with the calcium channel blocker amlodipine before and 30 and 60 minutes after tranylcypromine ingestion. The use of a calcium channel blocker to treat MAOI-induced hypertensive crises has been suggested previously.<sup>2,3</sup>

**Case 1.** Mr. A, a 54-year-old man, reported headaches, palpitations, chest pain, and sweating associated with the intake of 60 mg/day of tranylcypromine. In the clinic, his blood pressure was 108/72 mm Hg (heart rate [HR] was not noted). However, 30 minutes after the patient received 30 mg of tranylcypromine, his blood pressure rose to 150/84 mm Hg (associated with a throbbing headache). After 90 minutes, it remitted to 120/66 mm Hg. Concomitant amlodipine was prescribed. Eleven days later, with doses of 80 mg/day of tranylcypromine and 10 mg/day of amlodipine, Mr. A's baseline blood pressure was 108/70 mm Hg (HR = 94) and remained stable 30 and 60 minutes after inges-

tion of 60 mg of tranylcypromine (108/72 mm Hg [HR = 76] and 112/70 mm Hg [HR = 128], respectively). Seven weeks later, with doses of 120 mg/day of tranylcypromine and 10 mg/day of amlodipine, his blood pressure did not exceed 110/80 mm Hg after tranylcypromine challenge.

**Case 2.** Ms. B, a 57-year-old woman, described acute onset of palpitations approximately 30 minutes after ingestion of 80 mg/day of tranylcypromine. In the clinic, 30 minutes after the patient took 40 mg of tranylcypromine, her blood pressure rose from 128/80 mm Hg (HR = 80) to 150/84 mm Hg (HR = 76) and then fell to 130/80 mm Hg (HR = 80) after 60 minutes. Amlodipine was prescribed. Two months later, when Ms. B was maintained on tranylcypromine (80 mg/day) and amlodipine (5 mg/day), her blood pressure was 110/80 mm Hg (HR = 76) and remained stable 30 and 60 minutes after ingestion of 40 mg of tranylcypromine (106/80 mm Hg [HR = 84] and 110/78 mm Hg [HR = 80], respectively).

**Case 3.** On treatment with 40 mg/day of tranylcypromine, Mr. C, a 55-year-old man, complained of headaches, diarrhea, dry mouth, and fatigue. In the clinic, 30 minutes after the patient took 30 mg of tranylcypromine, his blood pressure rose from 108/70 mm Hg (HR = 76) to 150/80 mm Hg (HR = 72). Sixty minutes after intake, it fell to 122/76 mm Hg (HR = 100). With tranylcypromine (70 mg/day) and amlodipine (5 mg/day), Mr. C's blood pressure was 110/70 mm Hg (HR = 68) and did not rise after he took 40 mg of tranylcypromine (110/66 mm Hg [HR = 60] at 30 minutes and 112/64 mm Hg [HR = 60] at 60 minutes).

A total of 5 patients in our clinic have been treated with tranylcypromine since we began prescribing amlodipine for associated increases in blood pressure. One patient exhibited no hypertensive symptoms during treatment, and another patient, upon beginning tranylcypromine treatment, was already being treated with the antihypertensive enalapril. These 2 patients, therefore, did not receive amlodipine. The remaining 3 patients, as reported above, experienced spontaneous hypertensive symptoms shortly after taking tranylcypromine. In each case, prior to treatment with amlodipine, the patient's blood pressure significantly increased 30 to 60 minutes following ingestion of tranylcypromine, with spontaneous remission 30 to 60 minutes later. Each patient denied dietary indiscretion. Whether the rise in blood pressure after MAOI intake explains "spontaneous" hypertensive crises or represents another phenomenon is unclear. It would be worthwhile to report the timing of the last dose of drug and the timing of "spontaneous" hypertensive crises. If hypertension occurs shortly after drug ingestion, it should not be considered spontaneous.

In the 3 patients who experienced hypertensive symptoms, the rise in blood pressure following MAOI intake was prevented when tranylcypromine was combined with the calcium channel blocker amlodipine. There were no patients who did not benefit from the addition of amlodipine. The possibility of medication-induced hypertensive crisis needs to be monitored in any patient taking tranylcypromine. Whether this concern applies to other MAOIs is unknown. Our data do not clarify the role of maintenance calcium channel blocker therapy in preventing a hypertensive reaction to accidental ingestion of tyramine-containing foods.

*Supported by grant 1002073 from the National Alliance for Research on Schizophrenia and Depression, Great Neck, N.Y.*

*Dr. Quitkin has been a consultant for Organon, has received honoraria from Pfizer, has served on the speakers/advisory board for Eli Lilly, and is a major stock shareholder in Cyberonics. Dr. Stewart has*

*received grant/research support from Eli Lilly, Pfizer, Organon, and Glaxo; has received honoraria from Eli Lilly, Organon, Pfizer, Forest, Shire, and Somerset; and has served on the speakers/advisory board for Organon and Shire.*

#### REFERENCES

1. Klein DF, Gittelman R, Quitkin F, et al. *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*. 2nd ed. Baltimore, Md: Williams and Wilkins Company; 1980
2. McGrath PJ, Harrison W. Cardiovascular effects of monoamine oxidase inhibitor antidepressants and lithium. In: Kane JM, Lieberman JA, eds. *Adverse Effects of Psychotropic Drugs*. New York, NY: The Guilford Press; 1992:298-317
3. Clary C, Schweizer E. Treatment of MAOI hypertensive crisis with sublingual nifedipine. *J Clin Psychiatry* 1987;48:249-250

**Bonnie P. Taylor, Ph.D.**

**Frederic M. Quitkin, M.D.**

**Patrick J. McGrath, M.D.**

**Jonathan W. Stewart, M.D.**

Department of Therapeutics  
College of Physicians and Surgeons  
Columbia University  
New York, New York

#### Development of Subtle Psychotic Symptoms With Memantine: A Case Report

**Sir:** Memantine is a medication that has been recently approved in the United States for the treatment of moderate-to-severe Alzheimer's disease. It is a low-to-moderate affinity, noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist.<sup>1</sup> The use of other noncompetitive NMDA antagonists such as ketamine and phencyclidine is known to produce psychotic symptoms.<sup>2,3</sup> In the clinical trials used for the U.S. Food and Drug Administration registration of memantine, the reported rates of hallucinations were comparable to those with placebo (3% for memantine, 2% for placebo).<sup>1</sup> For memantine's therapeutic usefulness with Alzheimer's disease, it has been hypothesized that memantine protects against glutamatergic excitotoxicity while sparing the synaptic responses required for normal cognitive function, thus avoiding the adverse effects observed with medications such as ketamine.<sup>4</sup> We recently observed a patient with Alzheimer's disease who experienced possible psychotic symptoms while taking memantine.

**Case report.** Ms. A, a 69-year-old woman, was being followed by the Geriatric Psychiatry Branch of the National Institute of Mental Health, Bethesda, Md., as part of a follow-up research study. She was one of 8 patients in our research clinic who were being treated with memantine by their local doctors. In December 2002, she had been diagnosed with early Alzheimer's disease (DSM-IV-TR criteria). Following this diagnosis, she was started on donepezil treatment. She tolerated the medication well and was increased to her current dose of 15 mg daily by her primary care doctor. Her disease remained in the mild range with a Folstein Mini-Mental State Examination<sup>5</sup> score of 27/30 in August 2004.

Ms. A had comorbid diagnoses of major depressive disorder, anemia of chronic disease, asthma, hypertension, arthritis, and hypercholesterolemia. Her major depressive disorder was in partial remission with citalopram treatment (her Hamilton Rating Scale for Depression [HAM-D]<sup>6</sup> score in August 2004 was 13). Ms. A's last visit to our program prior to her visit in August

2004 was in December 2003. The HAM-D was not performed at that time, but her mood was noted as “upbeat—smiling and talkative,” and the absence of delusions or hallucinations was noted. She had no prior history of psychotic symptoms with her major depressive disorder, and she had never experienced especially vivid or intense dreaming or difficulty distinguishing dreams from reality.

Her primary care doctor started her on treatment with memantine after it became available in the United States in January 2004. She initiated therapy at 5 mg twice each day from January 13, 2004, to February 13, 2004. Her dose was then increased to 10 mg twice each day. She had no other medication or medical changes at that time.

Six weeks after being placed on treatment with the higher dose, Ms. A reported that she had been feeling more “confused” during the day and had been having intense, vivid dreams and nightmares. She had trouble distinguishing the dreams from reality. In July 2004, she became convinced that an event she had dreamed, the illness of a family member, was real. She called local area hospitals to find her relative. At this point, her primary care doctor discontinued memantine treatment, and the patient’s confusion and intense dreaming resolved quickly. This symptom has not recurred since the discontinuation of memantine.

Vivid and intense dreams or nightmares can be a symptom of psychosis. This symptom can be an adverse effect of dopaminergic therapy for Parkinson’s disease,<sup>7,8</sup> a symptom of schizophrenia,<sup>9</sup> and an adverse effect of other medications that act on the central nervous system.<sup>10,11</sup> Case studies of psychotic symptoms with memantine treatment of Parkinson’s disease have been reported,<sup>12</sup> but not, to our knowledge, with memantine use in Alzheimer’s disease. In this case report, we describe a woman with mild Alzheimer’s disease who experienced vivid, intense dreams and nightmares and difficulty distinguishing dreams from reality after being started on memantine treatment. The dreams stopped after discontinuation of memantine. This patient suffers from major depressive disorder, which can also be a cause of psychotic symptoms. However, to the best of our knowledge, her depressive disorder was stably in partial remission and has never been associated with psychotic symptoms.

Memantine shares a mechanism with medications known to cause psychotic adverse effects. However, memantine shows strong voltage dependency and rapid blocking/unblocking kinetics, which may explain the low rates of psychiatric adverse effects reported with its use in controlled clinical trials.<sup>13</sup> Of note, the reported potential psychiatric adverse effects in the package insert<sup>1</sup> include confusion, hallucinations, agitation, insomnia, depression, anxiety, and somnolence. Subtle psychotic adverse effects may not have been specifically detected as a potential adverse effect. In a recent study of patients with moderate-to-severe Alzheimer’s disease, “agitation” was listed as the most common reason for discontinuation of memantine.<sup>14</sup> Psychotic adverse effects such as those experienced by our patient may contribute to agitation, and these symptoms can be difficult to detect, especially in a moderately to severely demented population. We recommend that clinicians prescribing memantine evaluate patients carefully for subtle psychotic symptoms.

*Dr. Sunderland has been a consultant for or participated in the speakers/advisory boards of Pfizer, AstraZeneca, Lundbeck, and Bristol-Myers Squibb. The other authors report no financial affiliation or other relationship relevant to the subject matter of this letter.*

#### REFERENCES

- Namenda [package insert]. St Louis, Mo: Forest Pharmaceuticals; 2003
- Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 2001;158:1367–1377
- Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 1991;148:1301–1308
- Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer’s disease. *CNS Drug* 2003;9:275–308
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62
- Arnulf I, Bonnet AM, Damier P, et al. Hallucinations, REM sleep, and Parkinson’s disease: a medical hypothesis. *Neurology* 2000;55:281–288
- Sharf B, Moskovitz C, Lupton MD, et al. Dream phenomena induced by chronic levodopa therapy. *J Neural Transm* 1978;43:143–151
- Levin R, Daly RS. Nightmares and psychotic decompensation: a case study. *Psychiatry* 1998;61:217–222
- Thompson DF, Pierce DR. Drug-induced nightmares. *Ann Pharmacother* 1999;33:93–98
- Lepkifker E, Dannon PN, Iancu I, et al. Nightmares related to fluoxetine treatment. *Clin Neuropharmacol* 1995;18:90–94
- Riederer P, Lange KW, Kornhuber J, et al. Pharmacotoxic psychosis after memantine in Parkinson’s disease [letter]. *Lancet* 1991;338:1022–1023
- Parsons CG, Gruner R, Rozental J, et al. Patch clamp studies on the kinetics and selectivity of *N*-methyl-D-aspartate receptor antagonism by memantine (1-amino-3,5-dimethyladamantan). *Neuropharmacology* 1993;32:1337–1350
- Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer’s disease. *N Engl J Med* 2003;348:1333–1341

**Edward D. Huey, M.D.**  
**Irene H. Dustin, M.S.N., C.R.N.P.**  
**Gerald P. Overman, Pharm.D.**  
**Nadeem Mirza, M.D.**  
**Trey Sunderland, M.D.**  
 Geriatric Psychiatry Branch  
 National Institute of Mental Health  
 Bethesda, Maryland

#### Correction

In the article “Extended-Release Carbamazepine Capsules as Monotherapy for Acute Mania in Bipolar Disorder: A Multi-center, Randomized, Double-Blind, Placebo-Controlled Trial” by Richard H. Weisler, M.D., et al. (March 2005 issue, pp. 323–330), the percentages shown in the Abstract results and Table 4 should be as follows: dizziness, 39.3%; somnolence, 30.3%; and nausea, 23.8%. The online version of the article has been corrected. The staff regrets the error.