A Discussion of 2 Double-Blind Studies Comparing Risperidone and Quetiapine in Patients With Schizophrenia

See Editorial on p. 185.

Sir: We read with great interest the recent article by Zhong and colleagues[1] reporting results of a trial comparing quetiapine and risperidone for the treatment of schizophrenia. In that double-blind, 8-week study, there was a statistically significant difference favoring risperidone on the change at endpoint on the Positive and Negative Syndrome Scale (PANSS) positive symptoms subscale (an a priori secondary efficacy measure). In the same month, we[2] published similar findings from a double-blind, placebo-controlled trial comparing these 2 atypical antipsychotics in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization (least squares mean ± SE change from baseline to endpoint of the monotherapy phase for PANSS positive symptoms: –8.7 ± 0.5 with risperidone and –5.9 ± 0.5 with quetiapine; $p < .01$).

The complementary results from these 2 independent studies[1,2] using comparable dosing regimens support an efficacy benefit with risperidone compared with quetiapine for positive symptoms. Results from the primary efficacy measure (change in PANSS total score) are also consistent between the 2 studies, demonstrating greater improvement with risperidone. While the difference was statistically significant in our report[2] and not statistically significant in that of Zhong et al.,[1] methodological differences as described later may underlie this seeming discrepancy. Another important clinical between-treatment difference observed by Zhong et al.[1] was the proportion of patients withdrawing from the study due to lack of efficacy (24.3% for quetiapine vs. 13.7% for risperidone). Although the authors reported that "the proportion of patients withdrawing due to lack of efficacy was higher with quetiapine than with risperidone,"[1(p1096)] our χ^2 analysis of these data found the difference to be significant ($p < .001$). This difference between treatment groups was consistent with the PANSS last-observation-carried-forward (LOCF) results.

The tolerability results reported by Zhong et al.[1] suggested no unexpected adverse events, with profiles as expected with these agents, and were also similar to those that we reported.[2] While the incidence of spontaneously reported extrapyramidal symptoms (EPS) was significantly higher in the risperidone group as compared with the quetiapine group, the p.r.n. use of anticholinergic agents for these symptoms was low (6.9% and 5.6%, respectively), with no significant difference between groups. In contradiction to reports of EPS, improvements in mean Abnormal Involuntary Movement Scale and Simpson-Angus Scale total scores (standardized measures of EPS) were observed in both groups. A between-group difference of ≈0.1 was reported for change from baseline to endpoint in Barnes Akathisia Rating Scale score. While this met the level of statistical significance, the clinical relevance of this small score change is questionable.

There are several methodological issues worthy of comment. The first is the lack of a placebo arm, which is acknowledged by Zhong and colleagues.[1] As observed in other reports,[2,3] placebo response can be dramatic in an acutely ill patient population, and inclusion of a placebo comparator is critical to the interpretation of findings. Without a placebo comparator, one might draw erroneous conclusions on the magnitude of the effect of an active treatment, particularly in an acute study of hospitalized patients in which they are receiving extensive clinical care in addition to medication treatment. A second key issue not sufficiently addressed by the authors is the choice of the 1-tailed test of noninferiority with an equivalence margin of 6 points (with < 25 points in standard deviation) on the change in PANSS total score. Clinical evidence to support this equivalence margin was not provided, as is recommended by CONSORT standards for reporting non-inferiority studies.[4] Our study[2] used a 2-tailed superiority test to compare the differences between treatment arms on PANSS measures, a distinction that may have contributed to the different conclusions reached regarding between-group comparisons on PANSS total score. A third methodological issue to consider is the proportion of patients receiving risperidone or quetiapine prior to study enrollment; approximately double the number of patients had received risperidone (27.5%) compared to quetiapine (13.3%). In our study,[2] patients who received adequate doses of either drug for more than 1 week prior to study entry were excluded. This prior exposure in the population enrolled by Zhong et al.,[1] and apparent treatment failure, could have contributed to a bias in the study results in favor of quetiapine.

Despite methodological distinctions, results from these 2 independent comparative studies are actually complementary for some efficacy (positive symptoms) as well as tolerability (adverse event profiles) findings. This suggests that they represent important clinical information to guide clinicians in the appropriate use of these medications.

At the time of submission, Dr. Gharabawi was an employee of Janssen Pharmaceutica, Inc., and he is currently an employee of Hoffman-La Roche, Nutley, N.J. Drs. Bossie, Pandina, and Kujawa are employees of Janssen Pharmaceutica, Inc. Dr. Greenspan is an employee of Johnson & Johnson Pharmaceutical Research and Development. Dr. Zhu is an employee of Ortho-McNeil Janssen Scientific Affairs. Drs. Bossie, Pandina, Kujaum, Greenspan and Zhu are stock shareholders in Johnson & Johnson.

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Dr. Sweitzer and Colleagues Reply

Sir: Dr. Gharabawi's recent letter regarding the trials conducted by Potkin et al.[1] and Zhong et al.[2] highlights several salient points on the interpretation of data from comparative studies. Questions were raised about the trial designs that merit a response in the wider context of ongoing research on atypical antipsychotic efficacy and safety.

Gharabawi and colleagues comment on several aspects of the methodology of the trial by Zhong et al.,[2] primarily in an attempt to account for the nonsignificant difference between quetiapine and risperidone for the primary endpoint (PANSS total score). These were as follows: lack of placebo arm, use of a 1-tailed test of non-inferiority, lack of justification for the equivalence margin, and exclusion of patients with known lack of response to study medication.

The lack of placebo arm in the study by Zhong et al.[2] was acknowledged as a limitation by the authors; however, the trial design was based on CONSORT guidelines, which state that in non-inferiority trials in which the efficacy of the reference treatment (risperidone) is established and in widespread use, a placebo or untreated group may be deemed unethical.[3]

A 1-tailed test was used only for the primary analysis of non-inferiority of quetiapine relative to risperidone; all secondary analyses were conducted using 2-tailed superiority tests ($\alpha = .05$). A 2-tailed superiority test of change from baseline in PANSS total scores failed to reach statistical significance (–15.1 for quetiapine vs. –18.1 for risperidone; $p = .052$), and the 95% confidence interval (–0.02 to 5.87) fell entirely within the 6-point equivalence margin.

The selection of an equivalence margin of 6 points was based on a review of published trials of atypical antipsychotics available at the time of trial design (2000), in which differences of ≥ 6 points on the PANSS scale were considered clinically significant and differences ≤ 5.8 were considered not clinically significant.[4–7] A standard deviation of 25 points for PANSS total scores (also based on data from these studies[4–7]) corresponds to an effect size ≈0.24; this contrasts with the study design by Potkin et al.,[1] which assumed an effect size of 0.5.

Finally, Gharabawi and colleagues suggest that the study by Zhong et al.[2] may have been biased in favor of quetiapine because a higher proportion of patients had previously received risperidone versus quetiapine. However, this argument is only valid if nonresponders to these medications are included in the study population; in fact, in the trial by Zhong et al.,[2] nonresponders were specifically excluded.

Although Gharabawi and colleagues concluded that these studies were "complementary for some efficacy (positive symptoms) as well as tolerability (adverse event profiles) findings," the literature as a whole indicates that when quetiapine and risperidone are used at appropriate doses, the efficacy of the two agents is comparable, and these agents may, in fact, be differentiated by their tolerability profiles.[8–12]

All authors have received support from and are employees of AstraZeneca. Drs. Sweitzer and Brecher are stock shareholders in, have stock options in, and have stock in 401k plans for AstraZeneca. Dr. Lazarus is a stock shareholder in AstraZeneca.

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Indexing of Reports on Aripiprazole Augmentation of Clozapine

Sir: I read with interest 2 letters published in the April 2006 issue, "High-Dose Aripiprazole in Treatment-Resistant Schizophrenia"[1] and "Clozapine Augmentation With Aripiprazole for Negative Symptoms."[2] The first letter states, "Comparatively little information is available regarding the use of aripiprazole at doses higher than 30 mg/day."[1(p675)] The authors of the second letter state, "We found no published reports on the use of aripiprazole as an augmentation agent to clozapine."[2(p675)]

I authored the first such article to describe aripiprazole in this fashion, and it was published in *Psychiatry 2005*.[3] This report described 2 patients with treatment-resistant schizophrenia who had successfully used aripiprazole augmentation of clozapine to enhance efficacy and minimize side effects in a way similar to that described by Clarke and colleagues.[2] One of the patients described in my article used high-dose aripiprazole up to 90 mg/day in combination with 700 mg/day of clozapine. Aripiprazole augmentation enhanced antipsychotic benefit while also helping this patient to lose 40 of the 45 pounds she had gained on treatment with clozapine alone. The other patient had used 15 mg/day of aripiprazole to reduce his dose of clozapine to 150 mg/day, which then helped reduce sedation and sialorrhea.

I applaud your publishing of these reports, as they add to a growing body of evidence that high-dose antipsychotics and combining of antipsychotics may be useful strategies to treat schizophrenia in some individuals. Unfortunately, it appears that the *Psychiatry 2005* article was not found in a literature search by these authors. Information from Elizabeth Klumpp, executive editor of *Psychiatry 2005*, revealed that this article is available on CINAHL Indexing Service and that application for MEDLINE is anticipated by the end of 2006.

Lack of a uniform medical literature search service may lead researchers to believe data are missing when in fact reports may be available. Many authors may not even be aware that different search services exist to provide this kind of information. Reports such as these in different journals may broaden the availability of this information to those who do not have access to a wide variety of research journals. I encourage more reporting of patients such as those described in *The Journal of Clinical Psychiatry*.

This letter was shown to Dr. Clarke, who declined to reply.—Editor
Dr. Ashton reports no financial or other relationship relevant to the subject of this letter.

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Drs. Duggal and Mendhekar Reply

Sir: We thank Dr. Ashton for his interest in our letter. It is encouraging to see that other psychiatrists have tried aripiprazole at higher doses and also in combination with other atypical antipsychotics in treatment-resistant schizophrenia.

While the issue of using high doses of antipsychotics and combining 2 atypicals is still debatable, we agree with Dr. Ashton that more reporting of such cases would enhance understanding of and also stimulate research in this area. With regards to database search, PubMed/MEDLINE offer a larger database for literature search than Cumulative Index to Nursing and Allied Health Literature (CINAHL) and are universally accepted search tools in psychiatry research. Unfortunately, the article authored by Dr. Ashton was not listed in the PubMed search done by us.

Drs. Duggal and Mendhekar report no financial or other relationship relevant to the subject of this letter.

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Successful Use of Phenelzine in Treatment-Resistant Panic Disorder

Sir: Paroxetine, fluoxetine, sertraline, venlafaxine, clonazepam, and alprazolam are currently the only medications approved by the U.S. Food and Drug Administration for the treatment of panic disorder. In practice, first-line treatment usually involves selective serotonin reuptake inhibitors (SSRIs). Other treatment options might include tricyclic antidepressants (most commonly clomipramine and imipramine), venlafaxine, buspirone, nefazodone, β-blockers, and monoamine oxidase inhibitors (MAOIs). Reversible inhibitors of monoamine oxidase type A (RIMAs) are a popular treatment option in Europe, but they are not approved in the United States for panic disorder. Although some textbooks state that MAOIs are effective for treatment-resistant panic disorder[1] (this question has even appeared in the Psychiatry Resident In-Training Examination[2]), there is little documented evidence to support this conclusion.

While numerous trials have shown efficacy of RIMAs in the treatment of panic disorder,[3–7] and limited data exist showing efficacy of phenelzine for panic disorder[8] and phobic anxiety,[9] a literature search using Evidence Based Medicine Reviews-Cochrane Central Register of Controlled Trials with the search terms *treatment resistant panic disorder*, *panic disorder* and *monoamine oxidase inhibitors*, and *panic disorder* and *drug resistance* and using an Ovid Medline search with the terms *panic disorder* and *drug resistance* showed no clinical trials or case reports supporting MAOIs or RIMAs for treatment-resistant or treatment-refractory panic disorder. This case report demonstrates successful phenelzine treatment of severe, treatment-resistant panic disorder with agoraphobia.

Case report. Mr. A, a 45-year-old computer engineer with poorly controlled DSM-IV panic disorder, was seen in an outpatient clinic. When he presented in 2005, he was having about 2 panic attacks per day, characterized by the sudden onset of extreme anxiety, diaphoresis, derealization, abdominal distress, and fear of losing control. These symptoms peaked about 15 minutes after onset and lasted about 1 hour, with residual anxiety lasting most of the day. He was agoraphobic. His panic attacks had started 5 years earlier and had been at the presenting severity level for 2 years. He denied use of alcohol, tobacco, and illegal drugs as well as coffee and any other anxiogenic herbal or over-the-counter products. At the time of presentation, his medications included paroxetine 20 mg q.a.m., mirtazapine 30 mg q.h.s., clonazepam 1 mg b.i.d., alprazolam 1 mg q.i.d., and metoprolol XL 200 mg q.d., which was prescribed for hypertension. In the past, he had failed adequate trials of escitalopram, sertraline, venlafaxine, and quetiapine.

After the initial evaluation, mirtazapine treatment was discontinued, and the dose of paroxetine was increased to 60 mg q.d. for the next 6 weeks. He was taught deep-breathing exercises. The rather short-acting benzodiazepine alprazolam was immediately replaced with an equivalent dose of the longer acting clonazepam 1 mg q.i.d. Despite these interventions, the patient's panic and general anxiety symptoms significantly worsened, and eventually he was placed on alprazolam 1 mg q.i.d., clonazepam 1 mg t.i.d., and gabapentin 1200 mg t.i.d., which brought him back to a relative baseline of minimal functioning. His paroxetine dose was then tapered to 40 mg q.d. for 7 days followed by 20 mg q.d. for 7 days, then discontinued. Two weeks after his last dose of paroxetine, he was started on phenelzine 15 mg q.d., which was increased to the target dose of 15 mg q.i.d. in 9 days.

After 4 days of treatment with phenelzine 15 mg q.i.d., Mr. A's panic attack frequency decreased to 1 panic attack every other day, which was the lowest rate experienced in the last 2 years. His panic attacks continued to diminish, and, currently, he has not had a panic attack in 8 weeks, which is by far his longest period free of panic attacks since they began. He currently has no agoraphobia. He remains on clonazepam 0.5 mg q.a.m., alprazolam 0.25 mg q.h.s., and gabapentin 1200 mg t.i.d.

This case report demonstrates a successful treatment of a patient meeting DSM-IV criteria for panic disorder with agoraphobia who was treatment resistant to numerous trials of SSRIs and behavioral therapy but responded extremely well to the addition of phenelzine. This report gives some support to the efficacy of MAOIs in treatment-resistant panic disorder.

Drs. Buch and Wagner report no financial or other affiliation relevant to the subject of this letter.

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Azithromycin and Catatonic Symptoms

Sir: The interesting case report by Plana et al.[1] highlights the importance of identifying catatonic symptomatology in our clinical day-to-day practice. Although it is feasible that azithromycin can cause depression with psychotic and catatonic symptoms, it is important to think of other possible mechanisms before considering an idiosyncratic reaction.

One of these possible mechanisms could involve hyponatremia. Cadle and colleagues[2] reported syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with azithromycin, and the onset of psychiatric symptoms in their case was linked with severe hyponatremia. Both hyponatremia[3–5] and rapid correction of hyponatremia[6,7] have been shown to be associated with catatonic symptoms. In the present case,[1] there are several candidates for causation of hyponatremia, including refusal of food and water by the patient. It is well known that the elderly are usually more prone to electrolyte disturbances, including hyponatremia,[8] and are at high risk of developing hyponatremia when treated with most drugs, including thiazides. The risk appears to be even higher in the presence of malignancy. Both spironolactone and chlorthalidone can cause hyponatremia.

The report[1] mentions the creatine kinase (CK) level as 250 IU/L, which is higher than normal (though creatine phosphokinase level is reported as 15 IU/L). Markedly raised CK level with clarithromycin (in conjunction with theophylline in an elderly patient with dehydration) has been reported.[9] In another case with raised CK level, a causality assessment revealed a probable association with atorvastatin and a possible association with esomeprazole and clarithromycin.[10]

Although there appears to be a temporal relationship between azithromycin administration and the onset of catatonic symptoms, the flu-like illness presenting with myalgia, cough, and fever could itself also contribute to catatonic symptoms. A study from Spain[11] of 33 patients diagnosed with legionellosis (mean age = 61 years) reports elevation of CK in 79% and hyponatremia in 12% of cases.

If the patient reported by Plana et al.[1] suffered from legionellosis, that could have contributed to a raised CK level and hyponatremia, which could have contributed to catatonic symptoms.[10] Underdiagnosis and underreporting of legionellosis are high, and possibly only 2% to 10% of estimated cases are reported.[12] One study[13] found that psychiatric symptoms present commonly in legionella infection and the common signs included hallucinations (8.4%), agitation/stupor (4.1%), and affective disorders (3.1%). Hyponatremia and CK level elevation were present in up to 89% and 50% of patients, respectively. In another study,[14] the common signs included stupor (27%), hyponatremia (53%), and increased levels of CK (37%).

Lastly, clarithromycin figures in several case reports[15,16] of mania and acute psychosis, including 1 patient presenting with delusions, paranoia, and hallucinations, when clarithromycin was co-administered with amoxicillin.[15] The phenomenon has been labeled as "Hoigne's syndrome" or "antibiomania."[15] This report[15] also cites 18 known cases of anxiety, mania, hallucinations, and psychosis associated with clarithromycin and 1 associated with amoxicillin. The Medicines and Healthcare products Regulatory Agency Web site[17] mentions 14 reports of psychiatric symptoms associated with azithromycin (387 with clarithromycin), including psychosis, irritability, and hallucinations.

The report by Plana et al.[1] rightly underlies that catatonic disorder due to general medical condition (or organic catatonic disorder) must be first considered in every patient with catatonic signs, particularly in a patient with new-onset catatonia.

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

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Drs. Plana and Blanch Reply

Sir: Dr. Ahuja points out the importance of considering organic catatonic disorder in a patient with new-onset catatonia and expresses concern that we did not focus on that issue in our case report.[1]

First, our case report was based on a patient who was admitted to the medical emergency room with a diagnosis of catatonic syndrome. Past history of psychiatric disorders and current organic causes of the flu syndrome were absolutely excluded. No relevant alterations in laboratory (blood and urine) results, thyroid levels, toxicology, computed tomography scan of the brain, and lumbar puncture were found. Catatonia could not be due to hyponatremia, because sodium levels were between physiologic levels (144 mEq/L).

Against the hypothesis that the flu syndrome was the cause of the catatonia, we emphasize chronology of the facts. First, the patient developed flu syndrome with myalgia, cough, and fever. She became better when she finished amoxicillin treatment; all symptoms disappeared except for tracheobronchitis. For this reason, azithromycin therapy was started. Then, the psychiatric symptoms appeared.

The letter reported numerous psychiatric symptoms secondary to macrolide treatment, including 14 reports with azithromycin in the Medicines and Healthcare products Regulatory Agency Web site. For this reason, the option of azithromycin as a cause of the catatonic syndrome should be taken into consideration.

In conclusion, we agree with Dr. Ahuja about the importance of considering organic causes for catatonic symptoms, but when a remarkable organic alteration is not found, we have to look for other causes.

The authors report no financial or other relationship relevant to the subject of this letter.

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Delayed Sleep Phase Syndrome, ADHD, and Bright Light Therapy

Sir: Accumulating evidence suggests that many children with attention-deficit/hyperactivity disorder (ADHD) have a primary sleep disorder that accounts for some of their behavioral dysregulation.[1,2] Most previous reports have focused on the association between ADHD and sleep in children with sleep-disordered breathing or restless legs syndrome.[3–8] Here, we present a case in which ADHD symptoms and delayed sleep phase syndrome (DSPS) were rapidly relieved with bright light therapy.

Individuals with DSPS have difficulty falling asleep and waking up at their desired time.[9] They suffer from long sleep latencies and late sleep-onset times on account of a delay, in clock time, of their major sleep period,[10] which arises from a delayed endogenous circadian rhythm.[11] DSPS in children is often wrongly diagnosed as psychological insomnia or is attributed to inappropriate behaviors. Treatments that change the circadian rhythm phase or timing have been shown to be effective in the treatment of DSPS.

Case report. An 11-year-old boy was treated in the community since 2003 for ADHD. He was previously treated with methylphenidate 15 mg in the morning, 10 mg at noon, and 10 mg in the evening with limited improvement. He was then tried on dextroamphetamine 7.5 mg at 10:00 a.m. and at noon and 5 mg at 3:00 p.m. with some improvement. In March 2005, he was assessed in our sleep clinic following his mother's complaint that he had sleep difficulties. He met the criteria for ADHD, combined type (DSM-IV[12]), and his sleep was assessed off medication by an Actiwatch (AW64 series; Mini Mitter, Bend, Ore.) coupled with a sleep diary for 1 week. These data confirmed his delayed bedtime (later than 1:00 a.m. 80% of the time), and parents' and teachers' reports indicated that he was sleepy during the day.

In April 2005, the patient was taken off medication and bright light therapy was administered using a SADelite portable light (Northern Light Technologies, Montreal, Quebec, Canada)

that emitted full-spectrum visible light (10,000 lux at a distance of 60 cm). On the morning before starting the intervention, his functioning was measured using the Continuous Performance Test (CPT)[13] and the Conners' Teacher Global Index (CGIS-T).[14] His CPT scores were in the clinical range (i.e., > 60), and his CGIS-T score was 64. The patient was advised to perform half an hour of bright light therapy daily for 1 week between 6:00 a.m. and 7:00 a.m. He was instructed to wear the Actiwatch on his nondominant wrist. By the end of the 1-week intervention, his sleep onset had advanced by 2 hours, his CPT performance had improved to average, and his CGIS-T score was 45. Follow-up 3 months after the intervention indicated that he had maintained the improvement.

This case study shows that DSPS may be associated with ADHD symptoms and may manifest as difficulties in falling asleep and in waking up. In this case, the patient's ADHD symptoms were significantly improved following 1 week of bright light therapy. If this disorder had not been detected, he most likely would have suffered from multiple behavioral and attentional problems. We recommend actigraphic sleep monitoring during the initial period of ADHD diagnosis in children with reported sleep difficulties or daytime sleepiness.

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Correction

In the article "Omega-3 Fatty Acids: Evidence Basis for Treatment and Future Research in Psychiatry" by Marlene P. Freeman, M.D., et al. (December 2006 issue, pp. 1954–1967), a statement acknowledging administrative support from the American Psychiatric Association should have been included. The online version of the article has been corrected.

