Ziprasidone-Induced Angioedema: A Case Report

Sir: Ziprasidone is an antipsychotic agent that is generally well tolerated. Allergic responses to ziprasidone have been reported, including immunoglobulin E (IgE)–related pedal edema, life-threatening hypersensitivity syndrome, and angioedema. We present a report of a patient who developed angioedema upon starting ziprasidone treatment.

Case report. Mr A is a 30-year-old man who presented with psychotic symptoms characterized by persecutory delusions over a 6-week period. His diagnosis according to DSM-IV-TR was bipolar I disorder, most recent episode depressed, severe with psychotic features. He had had 2 previous episodes of mania with psychosis that were managed with short-term antipsychotic medication (olanzapine for the first episode and aripiprazole for the second) and maintenance mood stabilizers (lithium and sodium valproate for the second episode) without any adverse effects.

Mr A’s treating psychiatrist started him on ziprasidone therapy without any other concurrent medication. Prior to treatment with ziprasidone, Mr A had been free of all other prescription and nonprescription medication in the preceding 3 months. He commenced ziprasidone 20 mg twice daily on the first day and had a 40-mg tablet the next morning. Within 6 hours of taking the 40-mg dose, his tongue began to swell and he could not speak clearly. He experienced shortness of breath and was immediately transferred to the hospital by ambulance. Mr A had no past history of asthma, allergic rhinitis, urticaria, food allergies, eczematous dermatitis, or drug-related allergies.

On examination, his tongue and lips were swollen, extending up to the jaw line. There was partial obstruction to the airway, and the patient found it difficult to breathe through the mouth. There was no swelling noted of the genitalia, palms, soles, or eyelids. He had tachycardia, mildly elevated blood pressure, and an oxygen saturation of 97%. There was no lymphadenopathy or urticarial lesions, and the findings from systemic examination were normal.

The diagnostic impression was that Mr A’s presentation possibly represented an anaphylactic reaction to ziprasidone. He was immediately treated with nebulized and intramuscular epinephrine, intravenous hydrocortisone, and promethazine. He responded to these interventions, and within 10 minutes, he was discharged from a marginal increase in white cell count, the results of blood investigations were otherwise normal. Mr A was commenced on amisulpride treatment after a 5-day period. His diagnosis according to DSM-IV criteria was determined using the Mini-International Clinic of the Tartu University Hospital in Tartu, Estonia, between December 2006 and March 2008. Diagnosis according to DSM-IV criteria was determined using the Mini-International Neuropsychiatric Interview (MINI, version 5.0.0) and substantially

Effects of Bupropion Augmentation in Escitalopram-Resistant Patients With Major Depressive Disorder: An Open-Label, Naturalistic Study

Sir: There is a pressing need for improvement of treatment response to antidepressants in depression. Increasing evidence shows that bupropion, a norepinephrine and dopamine reuptake inhibitor, is one of the most widely chosen and effective augmenting agents for depressive patients with insufficient response to serotonin reuptake inhibitors. In this study, we evaluated the efficacy and tolerability of bupropion augmentation in nonresponders to escitalopram monotherapy in order to better understand this potential approach to improving treatment outcome in depression.

Method. The study sample consisted of 135 subjects with major depressive disorder (mean ± SD age = 31.1 ± 11.6 years, 66.1% female) recruited from outpatients admitted to the Psychiatry Clinic of the Tartu University Hospital in Tartu, Estonia, between December 2006 and March 2008. Diagnosis according to DSM-IV criteria was determined using the Mini-International Neuropsychiatric Interview (MINI, version 5.0.0) and substantially

References


Titus Mohan, MD
Tarun Bastiampillai, FRANZCP
Rohan Dhillon, FRANZCP

Author affiliations: The Queen Elizabeth Hospital, South Australia, Australia. Financial disclosure: None reported. Funding/support: None reported.

doi:10.4088/JCP.08l04657

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by psychiatric history and medical records. A depression severity of at least “moderate” was required for inclusion as indicated by a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 22 or higher. Only secondary current comorbid anxiety disorders, including generalized anxiety disorder and social phobia, but not other psychiatric or somatic diseases were allowed. None of the patients had psychotic features during their depressive episodes or met criteria for psychotic depression. Patients were treated with escitalopram 10–20 mg/day for 12 weeks in an open-label naturalistic design. No other medications, except zolpidem or zopiclone for insomnia, were allowed during the study. After 12 weeks, the nonresponders to 20 mg of escitalopram monotherapy were given a combination of 20 mg of escitalopram and 150–300 mg/day of bupropion for an additional 6 weeks. Clinical severity and treatment response were assessed biweekly using the MADRS and Clinical Global Impressions (CGI) scale. The 17-item Hamilton Rating Scale for Depression (HAM-D-17) and the Beck Depression Inventory (BDI) were also used as secondary assessments of depressive symptoms, and adverse effects were reported on the Toronto Side Effect Scale (TSES) at each visit. There were high correlations between assessments on the clinical scales MADRS or HAM-D-17 and the BDI self-evaluations.

At week 4 of the initial 12-week study, the dose of escitalopram was increased and kept at 20 mg/day until the end of the study in patients who demonstrated less than a 50% decrease in MADRS total score. Patients showing at least 50% decline in the MADRS total score at week 4 continued on the 10-mg dose. However, later the dose was increased and kept at 20 mg in 2 patients who showed exacerbation of depressive symptoms in follow-up visits, one at week 5 and one at 6.

Bupropion was started at 150 mg/day in the morning and was allowed to increase up to 300 mg/day, given as 150 mg twice daily, after week 2 or later if patients still demonstrated insufficient response according to clinical assessments. The patients were defined as responders if the decrease in both MADRS and HAM-D-17 total scores was at least 50% and the score on the CGI-Improvement scale was 2 or less. The remitters were defined as those whose scores were less than 12 on the MADRS and less than 8 on the HAM-D-17. The Human Studies Ethics Committee of the University of Tartu approved the study protocol, and all patients provided written informed consent.

Results. At the end of week 12 of treatment with escitalopram, 82 patients (60.7%) were defined as responders (Figure 1) and 79 of them (58.5%) achieved remission. Forty-four patients (32.6%) showed insufficient or partial response to treatment, and 9 patients (6.7%) discontinued escitalopram treatment due to lack of efficacy or adverse effects. The daily dose of escitalopram was increased and kept at 20 mg in 85 patients, 41 of whom were responders. The nonresponders to escitalopram monotherapy had significantly higher prevalence of melancholic type of depression than did responders (86.4% vs. 63.4%, respectively, p = .007) and experienced more adverse events, including weakness and fatigue, during the escitalopram stage of the trial according to TSES assessments (p < .05).

In total, 41 patients showing nonresponse to 8 weeks of monotherapy with 20 mg of escitalopram received bupropion augmentation, whereas 3 patients declined to continue participation in the study due to personal reasons. At week 6 of augmentation, 25 (61.0%) were defined as responders and 22 of them (53.7%) achieved remission, whereas 13 patients (31.7%) showed insufficient or partial response and 3 patients (7.3%) discontinued due to adverse effects or lack of efficacy. Bupropion dose was increased to 300 mg in 24 patients, of whom 14 were responders. Only muscle twitching was reported more often or more severely on the TSES and the BDI self-evaluations. The mean ± SD daily dose of bupropion did not significantly differ between the 2 groups (265 ± 66 mg vs. 234 ± 76 mg, respectively, p = .30), demonstrating also that frequency or severity of adverse effects was not related to administered dose of medication. None of the following characteristics differed significantly between responders and nonresponders to bupropion augmentation: age, sex, onset of disease, melancholic features, number of previous depressive episodes, and duration of current depressive episode.

In agreement with previous studies, we found that bupropion augmentation successfully facilitated treatment response in nonresponders to monotherapy with an SSRI. However, our remission rate with bupropion augmentation was higher than those demonstrated by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, probably due to lower dropout and discontinuation rates and to methodological differences. We found that the melancholic features of depression were associated with insufficient or partial response to escitalopram and that these could effectively be resolved by bupropion augmentation. Our results may give additional support to the importance of focusing treatment on the predominant or driving symptomatology of depression in order to maximize the chances of response and remission among patients and suggest that the use of bupropion is an appropriate treatment for patients with melancholic type of depression. Importantly, there were similarly low proportions of patients who discontinued either monotherapy with escitalopram or combined treatment with bupropion due to adverse events, indicating that both medications were generally well tolerated. Although our response and remission rates with escitalopram monotherapy were comparable to those reported by previous randomized and controlled clinical trials with escitalopram, we showed that almost all responders fulfilled the criteria for remission. We suggest that a longer treatment period and relatively earlier increasing of dose up to 20 mg/day (from week 4) might significantly reduce the difference between the response and remission rates, due to cumulative treatment efficacy in some patients. In addition, a consistent
increase in response rates was also demonstrated in another study using long-term treatment with escitalopram, suggesting that responders are more likely to achieve remission during longer treatment periods. Although severity of depressive symptoms and treatment response were carefully rated at each visit and were supported by patients’ self-evaluation, placebo responses cannot be excluded in our study due to the naturalistic, open-label design. Further randomized clinical trials with longer follow-up periods and larger sample sizes would be necessary to evaluate the efficacy of bupropion augmentation in resistant depression and particularly with melancholic features.

This investigation was supported by Estonian Science Foundation grant 7034 (Dr. Maron) and target grant SF0180125s08 (Dr. Vasar) from the Ministry of Education of Estonia.

Drs. Maron and Nutt have served as consultants for and have received grants and honoraria from Lundbeck and GlaxoSmithKline. Drs. Eller and Vasar report no additional financial or other relationships relevant to the subject of this letter.

Trial Registration: www.anzctr.org.au Identifier ACTRN12609000295246.

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Eduard Maron, M.D., Ph.D.
Research Department of Mental Health
North Estonia Medical Centre Foundation
Psychiatry Clinic
Tartu, Estonia

Triin Eller, M.D.
Veiko Vasaar, M.D.
Department of Psychiatry
University of Tartu
Tartu, Estonia

Department of Community Based Medicine
Psychopharmacology Unit
University of Bristol
Bristol, United Kingdom

Pseudohallucinations Versus True Hallucinations in Prodromal Psychosis: Does It Really Matter?

Sir: According to the traditional accounts of European psychiatry, true hallucinations are apparent perceptions of an external object in the absence of adequate sensory stimuli. Conversely, Sims’ states that Kandinsky and Jaspers described pseudohallucinations as a separate form of perception from true hallucination. Pseudohallucination is a perceptual experience that is figurative, not concrete or “real,” is located in inner subjective space, and is perceived with the “inner” ear (or eye) (Table 1). In other characteristics, pseudohallucinations are more like true hallucinations than fantasy. Thus, pseudohallucination may have definite outline and vivid detail, it may be retained for some time, and it is not deliberately evoked.3 Jaspers’ stressed that there is a gradation from the more fully formed pseudohallucination to vivid imagery but that there is an absolute distinction between hallucination and pseudohallucination because of the inner location of the latter. As a consequence of these original speculations, it is a common belief that pseudohallucinations do not have the same psychiatric significance as true hallucinations, and thus clinicians expend some clinical effort to distinguish the two. True hallucinations are thought to be both indicative of a morbid mental state such as psychosis, while pseudohallucinations are thought to be of less diagnostic significance and not necessarily psychopathological. However, pseudohallucinations may be an attenuated and subtle expression of an evolving psychosis. There have been no previous studies of the degree to which pseudohallucinations are predictive of the subsequent development of psychosis. Here we report 5 cases of young (age range, 18–26 years), drug-naive subjects presenting at a clinical service for prodromal signs of psychosis4 because they were hearing internal voices (pseudohallucinations). At the time of the first assessment (2005 through 2008), these symptoms did not meet DSM-IV threshold for a psychotic episode but met the inclusion clinical criteria for an “at-risk mental state” (ARMs), which is associated with an elevated clinical risk of psychosis.5 The diagnosis was based on assessment by 2 experienced clinicians using the Comprehensive Assessment for the ARMS (CAARMS).43
The authors report no financial or other relationships relevant to the subject of this letter.

### Table 1. Psychopathological Features of Hallucination, Pseudohallucination, and Imagery

<table>
<thead>
<tr>
<th>Domain</th>
<th>Hallucination</th>
<th>Pseudohallucination</th>
<th>Imagery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Experience</td>
<td>Concrete, tangible, objective, real</td>
<td>Pictorial subjective</td>
<td>Pictorial subjective</td>
</tr>
<tr>
<td>2. Location</td>
<td>Outer objective space</td>
<td>Inner subjective space</td>
<td>Inner subjective space</td>
</tr>
<tr>
<td>3. Definition</td>
<td>Definite outlines, complete sound</td>
<td>Definite outlines, complete sound</td>
<td>Indefinite, incomplete, only individual details</td>
</tr>
<tr>
<td>4. Vividness</td>
<td>Full, fresh, bright</td>
<td>Full, fresh, bright</td>
<td>Most elements are dim or neutral</td>
</tr>
<tr>
<td>5. Constancy</td>
<td>Retained</td>
<td>Retained</td>
<td>Evanescent</td>
</tr>
<tr>
<td>6. Independence</td>
<td>Cannot be dismissed, recalled, or changed at will</td>
<td>Cannot be dismissed, recalled, or changed at will</td>
<td>Requires voluntary creation</td>
</tr>
</tbody>
</table>

Partly derived from information in Jaspers.2

### References


**A 5-Year Follow-Up of Diabetes Knowledge in Persons With Serious Mental Illness and Type 2 Diabetes**

Sir: Despite the high prevalence of type 2 diabetes in persons with serious mental illness, there has been only limited study of diabetes knowledge in this group. In a previous report, we found that among 201 persons with serious mental illness and type 2 diabetes, the mean score on a diabetes knowledge test was only 54%.1 We reassessed the diabetes knowledge of persons in our sample 5 years later, in a period of heightened focus on diabetes among persons with serious mental illness.

**Method.** We recruited psychiatric outpatients with type 2 diabetes and either schizophrenia or major mood disorder as previously described.1 Participants were evaluated initially between September 1, 1999, and September 30, 2002, and reevaluated again approximately 5 years later between December 8, 2004, and July 12, 2007. Disease-specific diabetes knowledge was assessed at baseline and at follow-up by the general subscale of the Diabetes Knowledge Test (DKT),1 which was administered in a 1-to-1 interview by research personnel.

The test items are designed to be representative of the larger domain of illness-specific diabetes knowledge appropriate for individuals with type 2 diabetes. The score is calculated as the percentage of correct answers out of 14 multiple choice test items that assess diabetes-related issues including dietary choices, blood glucose testing, and medical problems that are associated with diabetes. We compared the percentage correct for the total score and
specific knowledge of participants did not improve during this time period is concerning. Our data suggest that there is a gap between the current focus on diabetes management of persons with serious mental illness in the medical literature and the level of information about diabetes that is acquired by patients with co-occurring serious mental illness and diabetes in routine clinical settings. Increased education and discussion about diabetes by psychiatric clinicians with their patients who have diabetes are called for.

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Faith B. Dickerson, PhD
Julie Kreyenbuhl, PharmD, PhD
Richard W. Goldberg, PhD
LiJuan Fang, MS
Deborah Medoff, PhD
Clayton H. Brown, PhD
Lisa Dixon, MD

Author affiliations: Sheppard Pratt Health System (Dr Dickerson); the VA Capitol Hill Healthcare Network Mental Illness Research, Education, and Clinical Center (Drs Kreyenbuhl, Goldberg, Brown, and Dixon); and the Departments of Psychiatry (Drs Kreyenbuhl, Goldberg, Medoff, Brown, and Dixon and Ms Fang) and Epidemiology (Dr Brown), University of Maryland School of Medicine, Baltimore, Maryland.

Financial disclosure: None reported. Funding/support: The work described in this letter was supported in part by an unrestricted grant from Bristol-Meyers Squibb and by National Institutes of Health grant RO1MH058717. doi:10.4088/JCP08I0602

Aripiprazole Treatment of Risperidone-Induced Hyperprolactinemia

Sir: Hyperprolactinemia is a well-recognized complication of some antipsychotic agents that results from the blocking of dopamine-2 (D2) receptors in the anterior pituitary.1 Aripiprazole, a potent partial agonist of the D2 receptors,2 inhibits spontaneous prolactin release from isolated anterior pituitary slices.3 Clinically, switching to aripiprazole monotherapy resolves antipsychotic-induced hyperprolactinemia.4,5 A double-blind, placebo-controlled trial and a few single case reports demonstrated that the addition of aripiprazole reversed haloperidol-induced hyperprolactinemia and associated symptoms.6,8 We conducted an 8-week, prospective, open-label study to assess whether adjunctive treatment with aripiprazole would improve risperidone-induced hyperprolactinemia.

Method. Twenty-one male Chinese outpatients and inpatients meeting DSM-IV criteria for schizophrenia were recruited after they gave informed consent and institutional review board approval was obtained. Data were collected from December 2007 to June 2008.

Nineteen subjects completed the trial, receiving a fixed dose of 10 mg/d of aripiprazole at 7:00 AM for 8 weeks. The doses of...
risperidone and concomitant medications remained fixed throughout the study. Serum prolactin levels were measured at baseline and 2, 4, and 8 weeks using standard radioimmunoassay. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions scale (CGI). Tolerability was evaluated with the Barnes Akathisia Scale (BAS) and the Simpson Angus Scale (SAS). The same investigator rated patients with these scales at baseline and at 8 weeks.

**Results.** Mean ± SD prolactin levels at baseline and 2, 4, and 8 weeks were 62.4 ± 22.1 ng/mL, 26.1 ± 11.2 ng/mL, 18.9 ± 8.1 ng/mL, and 18.1 ± 7.7 ng/mL, respectively ($F = 41.68$, $df = 5$, $P < .0001$). Pairwise comparisons showed that prolactin levels significantly decreased between baseline and 2, 4, and 8 weeks, and between 2 and 4 weeks ($P < .0001$), with no significant difference between 4 and 8 weeks. At the completion of the study, all patients demonstrated significantly reduced serum prolactin levels, and 6 of 19 (32%) patients had clinically normal prolactin levels.

The patients showed no significant changes in PANSS or CGI scores or in SAS or BAS scores between baseline and week 8. Only a few side effects were noted, including tachycardia (n = 2) and anorexia and headache (n = 1; both side effects were in the same patient).

To our knowledge, this is the first open-label prospective trial of aripiprazole to treat risperidone-induced hyperprolactinemia. Our study found that 8 weeks of adjunctive aripiprazole treatment was effective, safe, and well tolerated in reducing elevated prolactin levels. The mechanism for the resolution of hyperprolactinemia using aripiprazole is likely due to its unique partial agonist activity at D₂ receptors and relatively high D₂ receptor affinity. The partial agonist property means that, in the presence of dopamine (DA) hypoactivity, as induced by risperidone, aripiprazole will function as a DA agonist, restoring tonic inhibition to anterior pituitary gland.

Limitations of the present study include the relatively small sample size, the short duration of the trial, and the use of the fixed dose of aripiprazole. Therefore, larger, double-blind, placebo-controlled studies of longer duration with different doses of aripiprazole (especially higher doses, such as 20 or even 30 mg) might further investigate efficacy, safety, tolerability, and a dose-dependent effect of adjunctive aripiprazole.

**References**


**Author affiliations:** Beijing Hui-Long Guan Hospital (Drs Chen, S. L. Wang, Bian, Liu, N. Wang, Yang, and Zhang) and Institute of Mental Health, Peking University (Dr Su), Beijing, China; and Department of Psychiatry, Baylor College of Medicine, Houston, Texas (Drs Haile, Kosten, and Zhang). **Authorship note:** Drs Chen and Su contributed equally to this work. **Financial disclosure:** None reported. **Funding support:** This study was funded by the Stanley Medical Institute Foundation (05T-459, 05T-726) (Dr Zhang) and the Department of Veterans Affairs, VISN 1, Mental Illness Research, Education and Clinical Center (MIRECC) and National Institute on Drug Abuse K05-DA0454 and P50-DA18827 (Dr Kosten).

J Clin Psychiatry 70:7, July 2009

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