

An African Patient With Ziprasidone Intolerance

Sir: The issue of ethnopsychopharmacology has been receiving increased attention lately. One study showed significant differences in treatment response in schizophrenia between various populations,¹ but data on the subject are sparse, particularly for newer antipsychotic drugs. We report on a patient of African descent who developed intolerable side effects in response to ziprasidone, a recently approved atypical antipsychotic medication. The patient's plasma ziprasidone level was subsequently shown to be drastically increased despite low dosage. This case seems especially noteworthy in light of the recent report of a female African American patient who developed an acute dystonic reaction in response to ziprasidone at the recommended dosage of 40 mg b.i.d.² No plasma levels were reported for that case.

Case report. A 45-year-old male patient was admitted to our hospital in February 2004 with a recurrence of chronic schizophrenia (DSM-IV criteria). The patient had no other significant medical history or condition. Laboratory results, including liver and kidney function tests, were all within normal limits. Treatment with 40 mg of ziprasidone daily led to a reduction of psychotic symptoms, but also to an intolerable sedation, markedly increased motor drive, and sialorrhea, while orientation remained fully intact. The patient was treated on an inpatient basis with full monitoring of drug administration; thus, an accidental overdose can be ruled out. No concomitant medication was given. The patient held a normal diet and took no other drugs. A routine screening for illegal drugs proved negative. The serum ziprasidone concentration was subsequently shown to be 619 ng/mL, 15 times above the therapeutic range. This result was confirmed with a second test, and medication with ziprasidone was discontinued.

After the discontinuation of ziprasidone, we initiated treatment with aripiprazole. A dose of 15 mg/day led to a significant improvement but also to the temporary reappearance of psychotic symptoms under severe stress. With 30 mg/day of aripiprazole, we saw a complete remission of productive psychotic symptoms with only mild negative symptomatology and no side effects.

The patient's father is Nubian, and his mother's ethnic background is Arabic and Irish. Two siblings from a previous marriage of the patient's father, a paternal uncle, and a female maternal cousin were also diagnosed with schizophrenia. The patient was first diagnosed with paranoid schizophrenia in 1992 and had numerous subsequent hospitalizations. His treatment was repeatedly complicated by insufficient therapeutic effects or severe adverse reactions to neuroleptic medication as follows: no significant reduction of psychotic symptoms with flupenthixol, amisulpride, or quetiapine administered sequentially; severe extrapyramidal motoric symptoms with haloperidol, zuclopenthixol, and risperidone; and a drastic reduction of leukocytes with both clozapine and olanzapine. These complications always led to a reduction of the neuroleptic medication to subtherapeutic doses and consecutive psychotic recurrences in reaction to stressful life events.

Ziprasidone is an atypical antipsychotic with a high 5-HT_{2D} receptor affinity ratio, which inhibits dopamine and serotonin reuptake. It is thought to be metabolized predominantly by aldehyde oxidase. Cytochrome P450 3A4 (CYP3A4) is the drug's other metabolic pathway, mediating approximately one third of the metabolism.³ While studies could show a 35% to 40% in-

crease of ziprasidone levels when the drug is given in combination with a CYP3A4 inhibitor, no drug interactions affecting the activity of aldehyde oxidase are currently known.

A review of the available data for African populations concluded that certain ethnicities have CYP2D6 and CYP2C19 polymorphisms that lead to a slower metabolizing of neuroleptic drugs.⁴ Although our patient was of African descent and had a history of severe side effects in response to neuroleptic medication, both of these CYP enzymes were shown to be normal in a genotype analysis (CYP2D6: fast metabolizer; CYP2C19: intermediate type). Neither of these enzymes, however, is thought to be directly involved in ziprasidone metabolism. Phenotype analyses of CYP enzymes were not obtained. The latter method is currently discussed for an improved prediction of interindividual variations of psychopharmacologic treatment regimens.⁵

Our case is the second report of a patient of African ethnicity who responded with severe side effects to a commonly recommended dose of ziprasidone. Currently, no genetic polymorphisms of either of the 2 enzymes involved in the metabolizing of ziprasidone are known to cause an altered drug metabolism. It might be speculated that in certain African ethnicities such polymorphisms occur.

Drs. Hein, Gregor, Bartholomä, Heinz, and Juckel report no financial or other relationship relevant to the subject of this letter.

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Monosymptomatic Hypochondriacal Psychosis: Atypical Presentation and Response to Olanzapine

Sir: Monosymptomatic hypochondriacal psychosis (MHP) is an illness characterized by a single delusion of somatic type that can present at any age from late adolescence onward, equally affecting both sexes and having a poor prognosis without treatment.¹ Infestation with parasites, body dysmorphic phobia, and halitosis are the most commonly reported somatic delusions.¹ Pimozide has been frequently used and reported to be effective in the treatment of MHP, but has the potential for

undesirable side effects including tardive dyskinesia and cardiac conduction defects.¹ Several recent reports suggest the successful treatment of MHP, in particular delusional parasitosis, with atypical antipsychotics, i.e., risperidone²⁻⁶ and olanzapine.^{7,8} There are very few reports of efficacy of these drugs in uncommon forms of MHP.^{5,9,10} In the present report, we describe a case of MHP with an uncommon presentation and response to olanzapine.

Case report. Mr. A, a 26-year-old man, had a 5-year illness characterized by the belief that he had cancer of the esophagus. He had been to multiple physicians and undergone endoscopy, laryngoscopy, chest x-ray, and barium swallow in addition to other investigations, which revealed no abnormalities. He had a firm belief that because of the cancer he was unable to swallow either liquid or solid food. On being forced to eat, he complained of food sticking at the same place in his esophagus where he believed the tumor to be located. He would vomit out food material. At the time of presentation in January 2004, Mr. A had stopped taking food for 1 month and was receiving nasogastric feeding. His body mass index was 11, in contrast to 16 before the onset of illness. He attributed his emaciation to the tumor. He avoided going outside, saying that people might make fun of him, and hid his thin body in loose clothes. His sleep and personal care were normal.

He had no depressive, schizophrenic, or anxiety symptoms. He did not report any other problems in other parts of the body. There was neither a family history of any mental illness nor a history of any similar symptoms in family members or friends. In the past, he had been treated with selective serotonin reuptake inhibitors (SSRIs) and typical neuroleptics, singly as well as in combination, with no significant benefit.

Mr. A was started on treatment with olanzapine 5 mg/day, which was gradually increased to 10 mg/day. He started drinking liquids by the end of the second week, and the delusion became fleeting. After 3 weeks, on further incremental increase to 15 mg/day, the patient gave no spontaneous report of psychopathology, but he reported the symptoms on direct questioning. Upon increase of the medication dose to 20 mg/day, he started taking solid and liquid food by mouth with no complaint of cancer or a sticking sensation in his esophagus. His body weight increased from 35 to 45 kg over the next 2 months. He maintained steady improvement for the next 6 months but discontinued medication on his own; 2 months later, his symptoms recurred. The symptoms decreased with restarting of olanzapine treatment at the previous dose.

The index patient presented with a well-systematized, nonbizarre delusion of having a disease, i.e., cancer of the esophagus, in the absence of schizophrenic or depressive symptoms and substance use. He had no comorbid medical condition. He fulfilled the DSM-IV criteria for delusional disorder of somatic type, also known as MHP. In contrast to the typically reported cases of MHP, the index patient had an unusual somatic delusion of having cancer of the esophagus.

Trials of multiple SSRIs with or without typical neuroleptics including pimozide had not helped this patient, whereas addition of olanzapine resulted in significant improvement in his state. Therefore, olanzapine appears to have been effective for treating his delusional state. There are a few recent reports showing beneficial effects of olanzapine in MHP, particularly delusional parasitosis. A 69-year-old female patient responded to 5 mg/day of olanzapine,⁸ a 51-year-old female patient responded to 5 mg/day of olanzapine,⁷ and another 66-year-old male patient responded to 10 mg/day of olanzapine.⁷ Regarding other types of MHP, there is only 1 report of a 62-year-old man

presenting with a delusion of hardening of saliva causing obstruction in swallowing that responded to olanzapine 5 mg/day, following a failed trial of paroxetine.¹⁰

In the earlier case reports mentioned, the patients were of an older age group, with similar symptomatology except in the last case,¹⁰ and responded to lower doses of olanzapine, in contrast to our patient, who was younger, had an atypical presentation, and required a higher dose, i.e., 20 mg/day. These reports suggest the probable effectiveness of olanzapine in MHP irrespective of age and sex of patient, clinical presentation, and dose of the drug. With regard to side effect profile, there were no side effects in this case. However, careful attention is warranted because of reports of metabolic disturbances associated with the use of atypical antipsychotics.

On the basis of limited observation, olanzapine therapy can be considered as an alternative in the treatment of MHP.

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A Case of Delirium and Subsequent Pancytopenia Associated With the Oral Loading of Valproic Acid

Sir: Some studies have shown that the oral loading of valproic acid or divalproex sodium is most likely safe and leads to more rapid antimanic effects than standard titration of these agents.¹⁻⁴ Although there are some case reports of delirium^{5,6} or pancytopenia⁷⁻¹² associated with valproic acid, as far as we know, serial acute adverse effects such as delirium and pancytopenia resulting from the oral loading of valproic acid have not

yet been reported. We present a case in which manic symptoms were relieved rapidly with the oral loading of valproic acid, but delirium and subsequent pancytopenia developed as acute, severe adverse effects.

Case report. Mr. A, a 49-year-old man with DSM-IV schizoaffective disorder, bipolar type, was admitted in July 2004 for worsening psychotic symptoms. The results of his initial blood chemistry workup were normal, and his body weight was 80 kg. We started treatment with the oral loading of valproic acid, 2000 mg/day, and risperidone, 2 mg/day. Risperidone was titrated by 2 mg every 2 days to 8 mg/day, and valproic acid was maintained at a dose of 2000 mg/day.

On the third day after valproic acid loading, the patient's serum valproic acid level was 125 µg/mL, and he began to develop delirium. On the sixth day, his valproic acid level was 126 µg/mL. Therefore, on the seventh day, the valproic acid dose was tapered to 1500 mg/day.

On the 11th day after loading therapy, Mr. A's valproic acid level was 115 µg/mL, and valproic acid treatment was stopped due to a continuous state of delirium. Throughout the monitoring, his liver function test results were normal. Four days after valproic acid treatment was stopped, the patient's delirium ceased, but manic symptoms persisted. Thereafter, we restarted the oral loading of valproic acid, 1500 mg/day, and amisulpride, 400 mg b.i.d., instead of risperidone, and his manic symptoms soon disappeared.

Twenty days after valproic acid treatment (1500 mg/day) was restarted, pancytopenia was detected during routine laboratory testing. Mr. A was found to have a white blood cell count of $2.9 \times 10^3/\mu\text{L}$, a red blood cell count of $2.8 \times 10^6/\mu\text{L}$, a hemoglobin level of 10.1 g/dL, a platelet count of $58 \times 10^3/\mu\text{L}$, 33.9% neutrophils, and an absolute neutrophil count of 983.1/ μL . At that time, his valproic acid level was 94 µg/mL. Valproic acid therapy was then discontinued again, and complete blood counts (CBCs) were monitored daily. The patient's concurrent medications included amisulpride, 400 mg b.i.d.; thioridazine, 100 mg, and zolpidem, 10 mg, at bedtime; and benzotropine, 1 mg, in the morning. There was no detection of fever or bleeding tendency. Four days after valproic acid treatment was stopped, pancytopenia resolved spontaneously with no sequelae.

Our case shows that the abrupt increase of blood concentration of valproic acid may cause acute adverse effects such as delirium and pancytopenia. In this case, pancytopenia resolved spontaneously after discontinuation of valproic acid. Other medical problems were not observed. If these adverse reactions had not been detected by routine blood monitoring, however, more severe consequences would have developed.

We recommend intensive CBC and valproic acid level monitoring, especially during the initial period of the oral loading of valproic acid therapy.

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Issues to Consider in the Assessment and Treatment of Paraphilic Patients

Sir: I read with interest the letter to the editor authored by Briken and colleagues.¹ Although I certainly appreciate the points raised in their case report, it is important to consider the following issues when evaluating and treating patients afflicted with paraphilic disorders. (1) As documented in the orchietomy and pharmacotherapy literature, paraphilic patients remain at risk for sexual offense recidivism irrespective of the biological treatment they are receiving. In other words, a patient's risk is decreased, but not necessarily abolished, with treatment.²⁻⁷ (2) Testosterone levels are not directly correlated to sexual reoffending.⁸ Although a patient may have suppressed testosterone levels following luteinizing hormone-releasing hormone agonist therapy, he or she may still be symptomatic and therefore may need to be assessed for concurrent treatments (e.g., augmentation with medroxyprogesterone acetate).⁹ (3) If the ultimate goal of treatment is minimization of a patient's risk for sexual recidivism, comorbid psychiatric disorders need to be treated with the same vigor as the underlying paraphilia.^{10,11} (4) Finally, as is true for many patients, paraphiliacs may engage in suicidal behaviors independent of their psychiatric disorder(s) and treatment status.¹ Therefore, treatment providers need to monitor for depressive symptoms and suicidality while providing sex offender-specific therapy.

In conclusion, because paraphilic patients represent a quite complex and sometimes difficult to treat patient population, ongoing assessment of a patient's treatment needs is critical.

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

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Dr. Briken and Colleagues Reply

Sir: The 4 issues Dr. Saleh mentioned in his letter are important and well known in the scientific debate about treatment of paraphilic patients. In our first study of the treatment of paraphilias with luteinizing hormone–releasing hormone (LHRH) agonists, we showed that the effect of these agents, especially on paraphilic fantasies, remains questionable.¹ Nobody who is working in the field would say that the risk of recidivism in sexual offenders is abolished with medication. In our systematic

review of the treatment of paraphilia with LHRH agonists,² we proposed a treatment algorithm that includes the issues Dr. Saleh mentioned. This algorithm also describes the augmentation of leuprolide with other agents and the treatment of comorbid disorders. Medroxyprogesterone acetate is not available in Germany, and we did not administer cyproterone acetate in the reported case since the patient suffered from a hepatitis C infection. The patient's comorbid drug and alcohol abuse was treated intensively. The patient reported that he attempted suicide because he was frightened of being incarcerated.

Although treatment recommendations were followed in the case reported, recommendations sometimes remain theoretical and do not represent clinical practice. We published the case report mainly for 2 reasons: (1) In the literature on pharmacologic treatment of paraphilic sex offenders, relapses are reported very rarely, maybe more rarely than they are observed in routine clinical practice. Until 2003, there was no report of reoffending during treatment with LHRH agonists.² (2) The patient we described was not mandated for treatment under court order. Treatment of this group of patients can have several dilemmas, e.g., that individuals refuse interventions even though treatment providers think they might be helpful or necessary. Ongoing assessment is necessary and helps to decrease the risk for reoffending but cannot abolish relapses if compliance is a problem. Minimization of the problem of noncompliance will not help in its prevention.

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