

Letters to the Editor

Hypomanic Episodes After Receiving Ziprasidone: An Unintended "On-Off-On" Course of Treatment

Sir: Thus far, 2 case studies have reported on a total of 6 patients with hypomania possibly induced by the atypical antipsychotic ziprasidone,^{1,2} although it should be noted that none of these published cases can prove that hypomania was caused by ziprasidone. Here, I present a case that may be seen as supportive of such a causal relation.

Case report. Mr. A, a 40-year-old man, has suffered from bipolar schizoaffective disorder (ICD-10) since he was 18 years old. After 2 years of relative stability, he discontinued treatment with valproate and olanzapine in May 2002, against the advice of his psychiatrist, because he complained of sexual dysfunction. Shortly afterward, he developed a schizodepressive episode (ICD-10 F25.1) with mood-incongruent psychotic symptoms and a severe melancholic syndrome. After 2 months of hospital treatment, acute symptomatology had largely remitted. With combination treatment consisting of venlafaxine (150 mg/day), quetiapine (300 mg/day), and valproate (1200 mg/day), he was discharged to day-clinic treatment.

When Mr. A asked for a change of medication to help with erectile dysfunction, it was decided to treat him with ziprasidone instead of quetiapine, but all other medication was continued. His ziprasidone dose was increased to 100 mg/day, while quetiapine treatment was tapered off. Eight days after ziprasidone was started, he developed a hypomanic syndrome with a decreased need for sleep (3 hours per night), talkativeness, recklessness, high self-esteem, and racing thoughts. These symptoms worsened, and on day 10, ziprasidone was discontinued and quetiapine was restarted. The hypomanic syndrome remitted within 24 hours.

As the sexual dysfunction persisted and continued to be a major problem for Mr. A, he asked to be given ziprasidone again after 6 weeks because he hoped for fewer sexual side effects with ziprasidone. Ziprasidone (120 mg/day) was given for a second time, valproate and venlafaxine were continued, and quetiapine was slowly tapered off. After 8 days on ziprasidone, another hypomanic episode developed; this time, the patient's mood appeared to be dysphoric rather than euphoric. After 12 days, ziprasidone was discontinued for a second time and amisulpride was initiated. Again, the hypomanic syndrome remitted within 24 hours.

The temporal relationship with ziprasidone and the unintended "on-off-on" time course of this case support the idea that the 2 hypomanic episodes were induced by ziprasidone. However, one must be aware of the limitations of a single case report. In this case, ziprasidone may not have been effective enough to suppress underlying mania, which was better controlled by quetiapine and amisulpride. After the introduction of the atypical antipsychotics risperidone, olanzapine, and quetiapine,

there were several single case reports of exacerbation of maniclike symptoms during treatment with these medications, particularly in schizoaffective patients (for example, see Benazzi³). To date, large placebo-controlled trials have not indicated a causative relationship between most atypical antipsychotics and mania induction, especially in the case of olanzapine.⁴ Baldassano et al.¹ have suggested that the high serotonin and norepinephrine reuptake inhibition potencies of ziprasidone may be one potential and specific cause of mania induction. At the moment, it remains unresolved whether ziprasidone has such a potential side effect when given to bipolar affective patients. Further controlled data are needed.

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

REFERENCES

1. Baldassano CF, Ballas C, Datto SM, et al. Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disord* 2003;5:72-75
2. Davis R, Risch SC. Ziprasidone induction of hypomania in depression? [letter] *Am J Psychiatry* 2002;159:673-674
3. Benazzi F. Quetiapine-associated hypomania in a woman with schizoaffective disorder [letter]. *Can J Psychiatry* 2001;46:182-183
4. Baker RW, Milton DF, Stauffer VL, et al. Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord* 2003;73:147-153

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Worsened Agitation With Aripiprazole: Adverse Effect of Dopamine Partial Agonism?

Sir: Aripiprazole, a new antipsychotic, has a unique hypothesized mechanism of action: dopamine-2 partial agonism. It has been shown to improve symptoms of psychosis with a low risk for motor and metabolic side effects.¹ The present report describes 2 chronically ill patients with schizophrenia who experienced exacerbation of paranoia and anger when aripiprazole was added to stable doses of antipsychotic medication.

Case 1. Mr. A, a 54-year-old man with a 25+ year history of DSM-IV schizophrenia, had been placed in a forensic hospital after being found not guilty by reason of insanity related to a violent felony. He manifested chronic paranoid delusions that intensified during acute illness exacerbations and were accompanied by markedly increased anger and, frequently, threats of violence and assault requiring treatment in high-security wards. Mr. A had no insight into his illness, resulting in nonadherence, symptom exacerbation, and assaultiveness and mandating in-

voluntary treatment with haloperidol decanoate to control psychosis. Haloperidol decanoate 200 mg IM every 4 weeks was moderately effective in diminishing paranoid delusions and anger, allowing Mr. A to progress from maximum to medium security in December 2002. Haloperidol treatment was complicated by marked extrapyramidal symptoms (EPS) that were only partially controlled by benztrapine.

In an effort to improve residual paranoid ideation and severe EPS, aripiprazole was added as an augmenting agent at 15 mg p.o. every morning. Over the following 4 weeks, Mr. A experienced modest improvement in tremor. After 28 days of aripiprazole augmentation, Mr. A became acutely angry/irritable and intensely paranoid over a 48-hour period, culminating in assault on staff and regression to maximum security. Aripiprazole was subsequently discontinued, and over the ensuing 4 weeks his level of anger and paranoia returned to baseline; he was progressed to medium security after 44 days. Mr. A was very apologetic toward staff on his return. He described feeling very angry around the time of the assault, but could not describe why; there were no identifiable acute stressors. Twenty weeks after stopping aripiprazole, Mr. A's illness status remains at baseline, with no recurrence of acute anger or paranoia.

Case 2. Mr. B, a 51-year-old man with a 30+ year history of DSM-IV schizophrenia, had been treated in a forensic hospital for 15 years. His illness manifested with prominent auditory hallucinations; paranoid, grandiose, and bizarre delusions; inappropriate affect; and thought disorder. He was often angry/irritable and threatening in response to his symptoms, and he had a history of repeated assaults. He remained psychotic despite adequate trials of several typical antipsychotics, risperidone (up to 7 mg/day), quetiapine (up to 1000 mg/day), and, most recently, olanzapine (up to 60 mg/day); he developed agranulocytosis on clozapine treatment. In March 2003, while Mr. B was being treated with court-ordered olanzapine 60 mg/day, aripiprazole 10 mg/day p.o. was added in an effort to improve ongoing psychosis. After 9 days of combined therapy, Mr. B was noted to be responding openly to auditory hallucinations, was overtly paranoid, and became threatening toward other patients. There were no significant stressors associated with his symptomatic worsening. As a result of the emergence of clearly worsened paranoia and anger, aripiprazole was discontinued. Over the following weeks, Mr. B's psychotic symptoms and mood disturbance returned to baseline levels, where they remain 12 weeks later.

This report describes the apparent emergence of intense paranoid ideation and acute anger in the context of aripiprazole augmentation of a stable antipsychotic regimen. It is possible that the episodes described represent the natural course of schizophrenia, as the symptoms observed were not new to these patients. However, the temporal relationship between starting aripiprazole, the emergence of symptomatic worsening, and improvement with withdrawal of aripiprazole argues against this. The only published efficacy trial involving aripiprazole documented anxiety and psychotic exacerbation as potential side effects.¹

It is possible that in the context of postsynaptic dopamine receptor up-regulation (in response to chronic dopamine blockade), aripiprazole's agonist effects may enhance dopamine neurotransmission in limbic areas, resulting in intensification of psychosis. The difference in time course of the emergence of symptomatic worsening in the cases described may be due to differences in the tenacity of dopamine binding between haloperidol and olanzapine,² with haloperidol better able than olanzapine to compete with aripiprazole at the receptor site.

A third possible explanation is a metabolic interaction between aripiprazole and haloperidol or olanzapine. Aripiprazole is metabolized via 3A4 and 2D6 enzyme subsystems,³ but it does not up-regulate or block the activity of either. Haloperidol is metabolized, in large part, via the 2D6 subsystem. In this setting, competition between drugs would tend to raise serum levels of both agents, which would most likely not diminish the efficacy of haloperidol. Olanzapine is metabolized predominantly via the 1A2 subsystem, making metabolic interaction between it and aripiprazole unlikely.

The possible emergence of intense paranoid ideation and marked anger with aripiprazole demands caution in using this agent in chronically ill, tenuously controlled psychotic patients. In this setting, starting at low doses (e.g., 5 mg/day) and titrating slowly, while observing for intensification of symptoms, is warranted.

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

REFERENCES

1. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002;63:763-771
2. Kapur S, Seeman P. Does fast dissociation from the dopamine D₂ receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry* 2001;158:360-369
3. Abilify [package insert]. Rockville, Md: Otsuka Pharmaceutical Co Ltd; 2002

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Possible Role of Divalproex Sodium in Sedation Induced by Antipsychotic Medications

Sir: Makela et al.¹ recently reported 3 successful cases of modafinil use in patients experiencing sedation secondary to antipsychotic medication treatment. The cases were well described and informative. In 2 of the cases, the patients were concomitantly taking divalproex sodium; however, no serum drug levels are reported. Divalproex sodium may have contributed to the patients' sedation, especially in combination with the antipsychotic agents. Interestingly, 2 of the 3 cases described improved motivation, which raises the possibility that modafinil could possibly benefit patients experiencing amotivation. I agree with the authors on the need for further investigation in a more controlled manner to assess the efficacy and safety parameters of modafinil use in patients experiencing sedation secondary to antipsychotic treatment.

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

REFERENCE

1. Makela EH, Miller K, Cutlip WD. Three case reports of modafinil use in treating sedation induced by antipsychotic medications [letter]. *J Clin Psychiatry* 2003;64:485-486

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Valproate for Hostility in Schizophrenia Patients

Sir: Agitation, aggression, and hostility are frequent manifestations of psychiatric illnesses, with symptoms ranging from mild irritability to marked physical violence. "The Expert Consensus Guidelines: Treatment of Schizophrenia"¹ recommends valproate as a first-line adjunctive therapy for hostility/aggression, indicating that there is a subgroup of schizophrenia patients whose hostility and aggression persist despite adequate antipsychotic therapy. Research suggests that valproate demonstrates efficacy in the treatment of agitation and impulsive aggression in psychiatric patients.^{2,3} The current study was designed to evaluate the efficacy of adjunctive valproate in schizophrenia outpatients who exhibit persistent hostility despite prolonged olanzapine therapy.

Method. Ten patients who met DSM-IV criteria for schizophrenia, paranoid type, with at least mild hostility, provided written informed consent and were enrolled in a 1-year, open-label, prospective trial. Patient demographics were as follows: 50% male (N = 5), 90% white (N = 9), mean \pm SD age = 37 \pm 5.8 years, age at onset = 20.5 \pm 3.3 years, and number of previous antipsychotics = 3.8 \pm 2.3. All participants had been receiving a stable dose of olanzapine for 3 months prior to study enrollment.

Valproate therapy was initiated at 250 mg t.i.d. and adjusted within a projected dose range of 750 to 2000 mg/day to achieve serum valproic acid levels between 50 and 100 μ g/mL. All patients were prescribed olanzapine and valproate. No other concomitant medications were allowed in the study. Patients were evaluated with the Positive and Negative Syndrome Scale (PANSS) for schizophrenia⁴ at baseline, 6 months, and 12 months.

Results. Analysis of variance results indicate a statistically significant difference in PANSS item P-7 (hostility) scores between baseline and endpoint (F = 18.55, df = 2,27; p < .0001). Further analysis of P-7 using Scheffé tests revealed a statistically significant difference in scores between baseline and 6 months (F = 10.40, df = 2,27; p < .001) and between baseline and 12 months (F = 16.68, df = 2,27; p < .001). The difference between 6 and 12 months was not significant (F = 0.74, df = 2,27; p > .05). Descriptive statistics of the sample at endpoint revealed the following data (shown as mean \pm SD): (1) olanzapine dose = 19 \pm 6.6 mg/day, (2) valproate dose = 1425 \pm 373.6 mg/day, and (3) serum valproate level = 76.8 \pm 15.7 μ g/mL. Weight gain (9.2 \pm 3.0 lb [4.2 \pm 1.4 kg]) was the most commonly reported side effect.

Discussion. Results of this study suggest that adjunctive valproate may be helpful in reducing hostility in patients with schizophrenia. Winterer and Hermann⁵ note that valproate affects serotonin, γ -aminobutyric acid, glutamate, sodium ion channels, membrane fluidity, and RNA expression. Additionally, it may have an effect on temporal lobe pathology, thought to be involved in the etiology of schizophrenia, which may account for the clinical effect of valproate in the reduction of psychomotor agitation, hostility, and aggression.

Limitations of this study include small sample size, lack of comparator group, open-label design, and observer bias. Further investigation with larger, controlled samples is warranted to better determine efficacy and safety of this treatment.

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honoraria from Eli Lilly and AstraZeneca. Ms. Kirshner has served as a consultant to and on the speakers or advisory boards for Eli Lilly. Dr. Johnson has served as a consultant to Eli Lilly; received grant/research support from Eli Lilly, Abbott, Bristol-Myers Squibb, and Janssen; and received honoraria from Eli Lilly and AstraZeneca.

REFERENCES

1. The Expert Consensus Guidelines: Treatment of Schizophrenia. *J Clin Psychiatry* 1999;60(suppl 11):1-80
2. Davis LL, Ryan W, Adinoff B, et al. Comprehensive review of the psychiatric uses of valproate. *J Clin Psychopharmacol* 2000;20(suppl 1):1-17
3. Lindenmayer JP, Kotsaftis A. Use of sodium valproate in violent and aggressive behaviors: a critical review. *J Clin Psychiatry* 2000; 61:123-128
4. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-276
5. Winterer G, Hermann WM. Valproate and the symptomatic treatment of schizophrenia spectrum patients. *Pharmacopsychiatry* 2000;33:182-188

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Use of Propofol for Alcohol Withdrawal Delirium: A Case Report

Sir: Alcohol withdrawal delirium is a serious medical complication of alcohol dependence. Treatment typically involves the aggressive use of benzodiazepines.¹ I report a case of alcohol withdrawal delirium not responsive to benzodiazepines alone but successfully treated with a combination of propofol and benzodiazepines.

Case report. Mr. A, a 31-year-old white man, was admitted to the medical intensive care unit for alcohol withdrawal delirium (DSM-IV). He was continuously agitated and confused for approximately 48 hours despite administration of increasing amounts of intravenous lorazepam, up to 15 mg every hour with 4-mg boluses every 4 hours. Intravenous haloperidol, 5 mg every 4 hours, was added with no behavioral improvement.

On the third day, the patient was intubated, haloperidol was discontinued, and propofol, up to 110 mg/kg/min, was added, while the high doses of lorazepam were continued. Mr. A was unresponsive to painful stimuli during the propofol and lorazepam infusion. Efforts to discontinue propofol after 2 days resulted in reemergence of behavioral problems. On day 6, propofol, up to 40 mg/kg/min, was restarted, along with continued doses of lorazepam, 8.5 mg every hour. On day 8, propofol was discontinued for the second time without adverse effect. Lorazepam was gradually tapered off without incident. The patient was discharged in a stable condition after 15 days of hospitalization.

Propofol is a lipophilic agent typically used for anesthesia. Few studies have described the use of propofol for alcohol withdrawal.^{2,3} Propofol is believed to affect the glutamate and γ -aminobutyric acid (GABA) receptors and may be useful as an adjunctive medication in refractory alcohol withdrawal com-

pared with benzodiazepines, which only potentiate the GABA receptors.

Psychiatrists are often consulted for the management of alcohol withdrawal delirium. Use of the combination of propofol and benzodiazepines, which has been reported only in emergency medicine and critical care journals, can decrease severe agitation during delirium tremens by acting as a sedative. The effect of propofol on morbidity, mortality, or course of illness is unclear. Although psychiatrists may be unfamiliar with propofol since it is an anesthetic agent, propofol may be useful in addition to benzodiazepines for treating refractory alcohol withdrawal.

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

REFERENCES

1. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse: withdrawal and treatment. *Med Clin North Am* 1997;81:881-907
2. McCowan C, Marik P. Refractory delirium tremens treated with propofol: a case series. *Crit Care Med* 2000;28:1781-1784
3. Coomes TR, Smith SW. Successful use of propofol in refractory delirium tremens. *Ann Emerg Med* 1997;30:825-828

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Two Cases of Perospirone-Induced Mania in Schizophrenia

Sir: Perospirone, a benzisothiazole derivative, is a new atypical antipsychotic recently marketed for the treatment of schizophrenia in Japan. Like other atypical antipsychotics, perospirone is characterized by a high binding affinity for both 5-HT_{2A} and D₂ dopamine receptors and has been documented to have antipsychotic efficacy similar to that of conventional antipsychotics, but with fewer extrapyramidal side effects.¹ All of the atypical antipsychotics but clozapine have been reported to occasionally precipitate mania or hypomania.²⁻⁴ Here, we report the occurrence of perospirone-induced mania/hypomania in 2 schizophrenia patients.

Case 1. Mr. A was a 16-year-old male with DSM-IV paranoid-type schizophrenia and no prior episodes of clear affective symptoms. He experienced his first psychotic symptoms at 15 years of age. He had taken risperidone, zotepine, and haloperidol with no improvement in his symptoms. At the age of 16, Mr. A was admitted to the hospital in November 2001 and started on olanzapine treatment. Although olanzapine was continued for 6 weeks and increased to 30 mg/day, his symptoms did not improve. His olanzapine regimen was then tapered off, and perospirone was initiated and titrated up to 36 mg/day. After administration of perospirone, the patient's psychotic symptoms gradually ameliorated. However, after 1 week of receiving 36 mg/day of perospirone, he developed hypomanic symptoms, including euphoric mood, pressured speech, and an elevated sex drive. We therefore decreased his perospirone dose to 24 mg/day, and the patient's hypomanic episode resolved over the next 2 weeks. Six months after his admission, Mr. A was discharged without recurrence of either psychotic features or hypomanic symptoms at a perospirone dose of 24 mg/day.

Case 2. Ms. B, a 31-year-old woman, had an 11-year history of chronic paranoid schizophrenia (DSM-IV) and had previously experienced no marked affective symptoms. She was admitted in January 2002 after a failure to respond to sequential trials of haloperidol, risperidone, and olanzapine. Ms. B was started on clozapine treatment to control treatment-unresponsive auditory hallucinations and thought broadcasting. After clozapine treatment, her psychotic symptoms gradually subsided. However, in the 15th week of treatment, clozapine was discontinued due to agranulocytosis. One week after cessation of clozapine treatment, the patient's agranulocytosis normalized, but her psychotic symptoms returned; perospirone treatment was therefore begun at 12 mg/day. The following day, Ms. B became euphoric, with frequent laughter. The content of her auditory hallucinations was sexual. To treat her psychotic symptoms, the dose of perospirone was rapidly increased to 36 mg/day. While her psychotic symptoms remained unchanged, her manic symptoms, such as continuous laughing, psychomotor agitation, and decreased need for sleep, worsened further. Perospirone was thus discontinued and replaced with olanzapine. One week after cessation of perospirone treatment, the patient's manic symptoms resolved fully; however, her psychotic symptoms persisted.

As noted above, we have encountered 2 schizophrenic patients who developed clear manic/hypomanic features after administration of perospirone, an antipsychotic compound that is on the market only in Japan. In line with these observations, other types of atypical antipsychotics have also been reported to induce mania or hypomania. For example, both risperidone and olanzapine are documented to precipitate mania in patients with schizophrenia, schizoaffective disorder, and bipolar disorder,² and quetiapine and ziprasidone have been reported to induce hypomania in patients with schizoaffective disorder and major depression.^{3,4} However, to our knowledge, clozapine and conventional antipsychotics do not induce mania or hypomania. It follows, therefore, that a tendency to precipitate mania or hypomania may be a common characteristic of atypical antipsychotics, although clozapine may be an exception. Although the mechanism by which atypical antipsychotics, including perospirone, precipitate mania is unclear, 5-HT_{2A} receptor blockades may be involved in the effect of atypical antipsychotics on mood swings. Clinicians need to be alert to the possibility of a switch to mania during atypical antipsychotic treatment.

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REFERENCES

1. Onrust SV, McClellan K. Perospirone. *CNS Drugs* 2001;15:329-337
2. Aubry J-M, Simon AE, Bertschy G. Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000;61:649-655
3. Benazzi F. Quetiapine-associated hypomania in a woman with schizoaffective disorder [letter]. *Can J Psychiatry* 2001;46:182-183
4. Davis R, Risch SC. Ziprasidone induction of hypomania in depression? [letter] *Am J Psychiatry* 2002;159:673-674

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