

Letters to the Editor

Two-Year Follow-Up of a Patient With Successful Continuation of Clozapine Treatment Despite Morning Pseudoneutropenia

Sir: Agranulocytosis occurs in 1% to 2% of patients treated with clozapine. Thus, if neutropenia (absolute neutrophil count [ANC] of $< 1500/\mu\text{L}$) occurs during clozapine treatment, physicians generally interrupt the drug treatment and do not reintroduce it. Lithium and granulocyte colony-stimulating factor may be used to reverse clozapine-induced granulocytopenia.¹ We have previously reported the case of a patient who was able to continue clozapine treatment despite developing "morning pseudoneutropenia" (MPN).² In this report, we describe the course of the clozapine treatment over the following 24 months.

Case report. In January 2002, clozapine treatment was administered to Mr. A, a 44-year-old white man with DSM-IV paranoid schizophrenia who had previously shown resistance to various other antipsychotics. Prior to treatment, the patient's total white blood cell count (WBC) and ANC were $7100/\mu\text{L}$ (normal range, $4500\text{--}11,000/\mu\text{L}$) and $5300/\mu\text{L}$, respectively. His clozapine dose was gradually increased to 200 mg/day, leading to a satisfactory improvement in symptoms. Concomitant medication consisted of valproic acid (2000 mg/day).

After 27 weeks of clozapine treatment, the patient's WBC and ANC had declined to $4100/\mu\text{L}$ and $1300/\mu\text{L}$, respectively. However, a subsequent physical examination, Mr. A's medical history, and baseline laboratory investigation did not indicate that chronic or acute inflammation or infection, or auto-immunologic or hematologic disease, had developed. After the first blood sample was taken at 8 a.m., a second blood sample was taken at 2 p.m. later that day, and the patient's WBC and ANC were in the normal range ($5500/\mu\text{L}$ and $2200/\mu\text{L}$, respectively).

Clozapine treatment was continued with a strict hematologic monitoring program: blood tests were performed at 8 a.m. and at 2 p.m. twice a week. During the following 3 weeks, Mr. A's ANCs were persistently between $1200/\mu\text{L}$ and $1900/\mu\text{L}$ at 8 a.m. (corresponding WBCs: $4100\text{--}4700/\mu\text{L}$) and between $2200/\mu\text{L}$ and $2700/\mu\text{L}$ at 2 p.m. (corresponding WBCs: $5400\text{--}5800/\mu\text{L}$).

Thereafter, monthly blood tests were systematically performed at 2 p.m. During the following 24 months, the patient's ANCs remained within the normal range. Clozapine treatment was thus continued, and the patient has since shown a great improvement in his social function.

Morning pseudoneutropenia is known to occur during clozapine treatment.^{2,3} However, due to short follow-up periods in previous reports, the duration and severity of this phenomenon were unknown. On the basis of this and other case reports,^{2,3} we hypothesize that MPN is a transient and harmless type of neutropenia rather than an early sign of incipient agranulocytosis.

The reasons behind the occurrence of MPN in patients undergoing clozapine treatment are unclear. However, it has been suggested that clozapine amplifies the circadian variations in the amount of circulating neutrophils by affecting the endogenous production of hematopoietic cytokines.^{2,4} The redistribution of marginated or bone marrow reserve neutrophils may also influence these diurnal variations.

As MPN does not necessarily predispose patients to agranulocytosis, those with MPN should not automatically be denied clozapine treatment.^{2,4} When ANCs and/or WBCs are below the normal range in the morning, we suggest that the tests be repeated in the afternoon before the decision to stop clozapine treatment is made.

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

REFERENCES

1. Boshes RA, Manschreck TC, Desrosiers J, et al. Initiation of clozapine therapy in a patient with preexisting leukopenia: a discussion of the rationale of current treatment options. *Ann Clin Psychiatry* 2001;13:233-237
2. Esposito D, Auouillé J, Rouillon F, et al. Morning pseudoneutropenia during clozapine treatment. *World J Biol Psychiatry* 2003;4:192-194
3. Ahokas A, Elonen E. Circadian rhythm of white blood cells during clozapine treatment. *Psychopharmacology (Berl)* 1999;144:301-302
4. Hummer M, Kurz M, Barnas C, et al. Transient neutropenia induced by clozapine. *Psychopharmacol Bull* 1992;28:287-290

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Ziprasidone in the Acute Treatment of Borderline Personality Disorder in Psychiatric Emergency Services

Sir: Patients with borderline personality disorder are regular users of psychiatric emergency services (PES) for symptoms such as severe behavioral dyscontrol, impulsive aggression, self-mutilation, psychotic-like symptoms, intense anger, and depressive "mood crashes." In PES, rapid, effective intervention in such crises is essential to control the situation, decrease the risk of violent behavior, and prevent psychiatric admissions.

Benzodiazepines and typical antipsychotics appear to be effective in borderline personality disorder patients, although their use is limited due to poor tolerability and the risk of extrapyramidal side effects.¹ Atypical antipsychotics have a more

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favorable tolerance profile, and presently available data suggest they are effective for treating borderline personality disorder patients.^{2,3}

Ziprasidone is an atypical antipsychotic with a favorable efficacy/safety profile.^{4,5} No studies have yet been published on the use of ziprasidone to treat borderline personality disorder. The aim of this study was to evaluate the potential value and safety of ziprasidone in the acute treatment of adult borderline personality disorder patients in PES.

Method: Twelve borderline personality disorder patients (diagnosed with the Structured Clinical Interview for DSM-IV Axis II Disorders⁶ and Revised Diagnostic Interview for Borderlines⁷ semistructured interviews) who presented at PES provided written informed consent and were included in a 2-week open-label study. The research was conducted in accordance with Declaration of Helsinki guidelines. Data were collected from May to October 2003. Participants were evaluated in PES (V1) and at 2 days (V2), 1 week (V3), and 2 weeks (V4). At V1, a single intramuscular dose of ziprasidone 20 mg was administered. Oral treatment was subsequently administered at flexible doses (40–160 mg/day). Patients could continue treatment with benzodiazepines, antidepressants, and mood stabilizers, but doses could not be modified during the study.

Outcome measures included the following scales and self-reports related to affect, behavior, psychosis, general psychopathology domains, and clinical safety: Clinical Global Impressions-Severity of Illness scale (CGI-S),⁸ 17-item Hamilton Rating Scale for Depression (HAM-D-17),⁹ Hamilton Rating Scale for Anxiety (HAM-A),¹⁰ Brief Psychiatric Rating Scale (BPRS),¹¹ Symptom Checklist-90 Revised (SCL-90-R),¹² and Barratt Impulsiveness Scale (BIS).¹³

Results: The patients' mean age was 26.2 years (SD = 5.7; range, 20–40 years), and 83.3% (N = 10) were female. The patients were in a clinical situation of crisis: 4 patients due to self-injury/autolysis attempt, 3 due to aggressivity/hostility, 3 due to loss of impulse control, and 2 due to severe anxious-depressive symptoms. Nine patients (75%) completed the trial. The reasons for withdrawal were side effects in 1 patient, patient's decision in 1, and lack of efficacy and need for admission at V1 in 1.

Analysis of variance results indicated statistically significant improvements in the global clinical impression (CGI-S) (F = 61.7, df = 2.61, p = .000), depressive symptoms (HAM-D-17) (F = 20.25, df = 2.22, p = .000), anxiety symptoms (HAM-A) (F = 22.57, df = 2.14, p = .000), and psychotic symptoms (BPRS) (F = 13.13, df = 1.47, p = .001). The Wilcoxon signed rank test showed a significant difference on the SCL-90-R between V1 and V4 in most clinical subscales. The unplanned impulsivity subscale of the BIS was the only impulsive behavior measure that showed significant improvement (F = 7.39, df = 1.74, p = .006) (Table 1).

The mean daily dose of oral ziprasidone was 102.7 mg/day (SD = 33.5; range, 40–160 mg/day). The drug was shown to be safe, and no serious adverse effects occurred. Side effects included headache in 2 patients, gastrointestinal problems in 2 others, minor sedation in 1, and a complaint of sexual dysfunction in 1 male patient. Only 1 patient withdrew from the study due to side effects, as the result of headache. No movement disorders were observed with the Modified-UKU Side Effect Rating scale.¹⁴

Results from this open-label, uncontrolled study suggest ziprasidone may be effective, fast, and safe for treating acutely ill borderline personality disorder patients presenting to PES. The good tolerability of ziprasidone could translate into im-

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Table 1. Ratings Before (V1) Versus After (V4) 2 Weeks of Treatment With Ziprasidone in 12 Borderline Personality Disorder Patients^a

Scale	Timepoint		F	p
	V1 ^b	V4 ^c		
CGI-S	5.6	2.0	61.7	.000
HAM-D-17	24.2	13.1	20.3	.000
HAM-A	28.7	14.1	22.6	.000
BPRS	19.8	9.8	13.1	.001
BIS				
Cognitive	20.1	19.7	0.1	NS
Motor	28.4	27.8	0.5	NS
Unplanned	31.2	24.3	7.4	.006
Overall	79.7	72.0	1.9	NS
SCL-90-R				
Interpersonal sensitivity	2.51	1.88		.021
Anxiety	2.94	2.38		NS
Depression	3.21	2.36		.036
Anger/hostility	2.85	2.48		.049
Paranoia	2.63	2.29		.025
Psychoticism	2.45	1.58		.011
Phobic anxiety	2.52	1.74		.036
Somatization	2.46	2.02		NS
Obsessive-compulsive	3.00	2.33		NS

^aLast observation carried forward. All analyses were conducted on an intent-to-treat basis. The Wilcoxon signed rank test was used for the SCL-90-R analysis; analysis of variance was used for all other scales.

^bTime at which patients presented to the psychiatric emergency service.

^cTwo weeks after presentation to the psychiatric emergency service.

Abbreviations: BIS = Barratt Impulsiveness Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, NS = nonsignificant, SCL-90-R = Symptom Checklist-90-Revised.

proved adherence to treatment and lower dropout rates compared with current borderline personality disorder treatments.

This is the first prospective research on the effect of ziprasidone in borderline personality disorder patients, and our preliminary findings should be replicated in randomized, long-term, double-blind, placebo-controlled studies.

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REFERENCES

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Borderline Personality Disorder. *Am J Psychiatry* 2001;158(suppl 10):1–52
2. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 2001;62:849–854
3. Soler J, Pascual JC, Campins J, et al. A double-blind, placebo-controlled study of borderline personality disorder: olanzapine plus dialectical behavior therapy. *Am J Psychiatry*. In press
4. Tandon R. Ziprasidone appears to offer important therapeutic and tolerability advantages over conventional, and some novel, antipsychotics. *Br J Clin Pharmacol* 2000;49(suppl 1):1S–3S
5. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl)* 1998;140:173–184
6. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II, Version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1994
7. Zanarini MC, Frankenburg FR, Vujanovic AA. Interrater and

- test-retest reliability of the Revised Diagnostic Interview for Borderlines (DIB-R). *J Personal Disord* 2002;16:270–276
8. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
 9. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62
 10. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–55
 11. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799–812
 12. Derogatis LR. Symptom Checklist-90 (Revised): Administration, Scoring, and Procedures Manual, I. Baltimore, Md: Clinical Psychometric Research; 1977
 13. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 1995;51:768–774
 14. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: A New Comprehensive Rating Scale for Psychotropic Drugs and a Cross-Sectional Study of Side Effects in Neuroleptic-Treated Patients. *Acta Scand Psychiatr Suppl* 1987;334:1–100

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Alternative Pharmacotherapy for Trichotillomania: A Report of Successful Bupropion Use

Sir: Trichotillomania is classified in the spectrum of impulse-control disorders, with phenomenological overlap with obsessive-compulsive disorder (OCD), tic, and affective spectrum disorders.^{1,2} The role of serotonin has been postulated in trichotillomania based on overlapping features with OCD and positive treatment response observed with selective serotonin reuptake inhibitors (SSRIs) in open-label studies.^{3,4} In controlled studies, however, not all patients have benefited from SSRIs.^{5,6} We describe a patient with trichotillomania who failed an SSRI trial but experienced symptom remission with a trial of bupropion.

Case report. Ms. A, a 31-year-old academic, presented to the outpatient clinic in May 2003 for evaluation of DSM-IV trichotillomania. She reported a 10-year history of trichotillomania that was exacerbated by stressors such as psychological stress and seasonal allergies. She denied presence of both obsessive-compulsive symptoms and mood disorders. Her personal medical history was unremarkable, although her family history was notable for presence of trichotillomania in a maternal aunt.

The current episode of trichotillomania had been present for 2½ years, and Ms. A had been receiving treatment with sertraline 100 mg daily along with psychotherapy, with minimal benefits. Further dosage increases of sertraline were not tolerated by the patient due to adverse effects on her libido. The patient had also received a previous trial of gabapentin, due to ongoing symptoms of insomnia and anxiety, which was not particularly helpful. Concurrent treatment with cognitive-behavioral therapy (CBT) did not result in sustainable gains.

Due to nonresponse of her condition to combination SSRI treatment and CBT, a decision was made, at Ms. A's request, to try alternative treatment with bupropion sustained release. A dose of 100 mg/day was initiated and, once tolerated, was further

adjusted to 150 mg/day at 2-week follow-up. At her next visit 2 weeks later, the patient reported a slight decrease in hair pulling, and therefore she accepted a dosage increase to 150 mg twice daily. At this dose, the patient noted an almost complete remission of her symptoms. The patient has been maintained at this dose and at 12-week follow-up reported ongoing remission.

Although a role for serotonin has been postulated in trichotillomania and other impulse-control disorders, pharmacotherapy with SSRIs appears inadequate, presumably because of additional pathways that may be involved. Both the opioid and dopamine systems have also been implicated in the pathophysiology of trichotillomania.^{7,8} Some researchers have reported beneficial results with naltrexone, very likely as a result of antagonism of opioid receptors and blockade of the internal reward pathways involved with hair pulling.⁹

Others have conceptualized trichotillomania as a variant of OCD and have suggested a role for dopamine,⁸ although, until now, treatment with dopamine-augmenting agents has not been described in the literature. In smoking, and possibly alcohol and caffeine, cessation, bupropion appears to modulate the dopaminergic internal reward pathways, leading to decrease in self-administration of these substances.¹⁰ By extension, bupropion may lead to decreased goal-directed behaviors in conditions such as trichotillomania by diminishing the heightened arousal and pleasurable relief that are involved during hair pulling. Therefore, given the positive results with this patient, further investigation of bupropion in trichotillomania is warranted.

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REFERENCES

1. Christenson G. Trichotillomania. In: Gelder MG, Lopez-Ibor JJ, Andreasen N, eds. *New Oxford Textbook of Psychiatry*, vol 1. Oxford, England: Oxford University Press; 2000:986–990
2. Diefenbach GJ, Mouton-Odum S, Stanley MA. Affective correlates of trichotillomania. *Behav Res Ther* 2002;40:1305–1315
3. Palmer CJ, Yates WR, Trotter L. Childhood trichotillomania: successful treatment with fluoxetine following an SSRI failure. *Psychosomatics* 1999;40:526–528
4. Iancu I, Weizman A, Kindler S, et al. Serotonergic drugs in trichotillomania: treatment results in 12 patients. *J Nerv Ment Dis* 1996;184:641–644
5. Streichenwein SM, Thornby JJ. A long-term, double-blind, placebo-controlled crossover trial of the efficacy of fluoxetine for trichotillomania. *Am J Psychiatry* 1995;152:1192–1196
6. van Minnen A, Hoogduin KA, Keijsers GP, et al. Treatment of trichotillomania with behavioral therapy or fluoxetine: a randomized, waiting-list controlled study. *Arch Gen Psychiatry* 2003;60:517–522
7. Stein DJ, O'Sullivan RL, van Heerden B, et al. The neurobiology of trichotillomania. *CNS Spectrums* 1998;3:47–51
8. Goodman WK, McDougle CJ, Price LH, et al. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry* 1990;51(8, suppl):36–43
9. Carrion VG. Naltrexone for the treatment of trichotillomania: a case report [letter]. *J Clin Psychopharmacol* 1995;15:444–445
10. Berigan TR, Harazin J. Bupropion related alcohol cessation. *Psychiatry On-Line* [serial online]. Available at: <http://www.priory.com/psych/bupropion.htm>. Accessed January 15, 2004

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Possible Increased Efficacy of Low-Dose Clozapine When Combined With Aripiprazole

Sir: Clozapine has been shown to be superior to typical antipsychotics in treatment-refractory schizophrenic patients. However, patients are sometimes unable to tolerate full therapeutic doses of clozapine because of significant adverse central nervous system and gastrointestinal effects at high doses. Aripiprazole is a new antipsychotic with a novel mechanism of action. We recently observed 3 inpatient cases in which aripiprazole appeared to have increased the efficacy of low doses of clozapine. We determined Brief Psychiatric Rating Scale (BPRS)¹ scores for each patient at admission and discharge, including subscale scores for the positive symptoms factor (suspiciousness, hallucinations, unusual thoughts, bizarre behavior) and the negative symptoms factor (blunted affect, emotional withdrawal, motor retardation). We also obtained serum clozapine levels for each patient.

Case 1. Ms. A., a 65-year-old white woman with DSM-IV schizoaffective disorder, was admitted in June 2003 for worsening auditory hallucinations. She had a 30-year history of multiple hospitalizations for refractory psychotic symptoms. She had been on aripiprazole treatment prior to this admission at 15 mg/day for over 2 months without significant improvement. Her aripiprazole dose was increased to 30 mg/day, and treatment with clozapine was started and titrated over a 1-week period to 150 mg/day.

On admission, Ms. A's total BPRS score was 62, her positive symptoms factor score was 11, and her negative symptoms factor score was 15. At discharge 15 days later, the patient's total BPRS score was 46 (26% reduction), her positive symptoms factor score was 9, and her negative symptoms factor score was 11. At discharge, Ms. A's serum clozapine level was 110 ng/mL, and her serum norclozapine level was 71 ng/mL. Substantial improvement was thus achieved with low-dose clozapine when combined with aripiprazole.

Case 2. Mr. B., a 38-year-old white man with a history of DSM-IV bipolar disorder with psychotic features, was admitted in May 2003 for visual hallucinations, somatic delusions, and increasing depressive symptoms. He had a 12-year history of multiple hospitalizations for affective psychosis. He had been titrated upward on aripiprazole treatment from 15 to 45 mg/day for over a month prior to this admission without substantial improvement. Clozapine was added and titrated over a 1-week period to a dose of 200 mg/day. The patient's aripiprazole dose was decreased and maintained at 30 mg/day.

Mr. B's total BPRS score on admission was 77, his positive symptoms factor score was 25, and his negative symptoms factor score was 14. At discharge 8 days later, the patient's total BPRS score was 36 (53% reduction), his positive symptoms factor score was 6, and his negative symptoms factor score was 8. At discharge, the patient's serum clozapine level was 159 ng/mL, and his serum norclozapine level was 59 ng/mL. Improvement was again noted with low-dose clozapine when combined with aripiprazole.

Case 3. Ms. C., a 38-year-old white woman with a history of chronic DSM-IV paranoid schizophrenia, was admitted in May 2003 for paranoid delusions. She had a 14-year history of multiple hospitalizations for psychotic symptoms. On admission, she had been on treatment with aripiprazole for over 4 months (titrated from 15 to 30 mg/day during this time), but her symptoms had not decreased. Clozapine was added and titrated to 150 mg/day over a 2-week period.

Ms. C's total BPRS score on admission was 66, her positive symptoms factor score was 23, and her negative symptoms factor

score was 16. At discharge 2 weeks later, the patient's total BPRS score was 50 (24% reduction), her positive symptoms factor score was 15, and her negative symptoms factor score was 10. At discharge, the patient's serum clozapine level was 460 ng/mL, and her serum norclozapine level was 150 ng/mL. Again, relatively low-dose clozapine provided symptom decrease when used in conjunction with aripiprazole.

For these 3 patients, we observed a reduction in both positive and negative BPRS symptom scores at relatively low doses of clozapine and, for 2 patients, at low serum clozapine levels. Aripiprazole alone had produced no significant improvement despite adequate trial periods. Published reports suggest that serum clozapine levels greater than 350 ng/mL may be necessary for a therapeutic response.²⁻⁴ However, 2 of our patients demonstrated substantial clinical improvement despite low serum clozapine levels. A pharmacokinetic interaction between clozapine and aripiprazole may explain the elevated clozapine level found in our third patient. However, the low levels observed in 2 of our patients suggest a possible pharmacodynamic interaction between clozapine and aripiprazole. The basis for this mechanism may lie in the unique receptor profiles of clozapine and aripiprazole. The reduction in positive symptoms with the combination of clozapine and aripiprazole may be due to greater D₂ receptor antagonism in mesolimbic pathways. Other possible hypotheses include combined D₂ and D₄ antagonism (although the role of D₄ receptors in antipsychotic efficacy is unclear) and the possible role of fast dissociation of the antipsychotic from receptors as the basis of atypicality.^{5,6}

The reduction in negative symptoms among our patients was particularly notable. This reduction may be secondary to the balance of adequate dopamine activity in nigrostriatal pathways and increased dopamine activity in mesocortical pathways when clozapine is combined with aripiprazole. Another possible explanation is a modest antidepressant effect due to the moderate affinity of aripiprazole for serotonin reuptake sites combined with the binding of clozapine to norepinephrine reuptake sites.^{7,8}

There are several case reports and open trials of risperidone augmentation of clozapine; most⁹⁻¹¹ (but not all¹²) show clinical improvement in "clozapine-refractory" patients. However, clozapine doses in those patients were significantly greater (350-900 mg) than in our patients. These higher doses, however, are frequently associated with adverse effects such as sedation, sialorrhea, and seizures, which can often result in noncompliance or necessitate discontinuation of treatment. Our findings suggest that combined clozapine and aripiprazole treatment may result in reduction in both positive and negative symptoms with relatively low doses of clozapine. We have tentatively chosen to consider aripiprazole as the augmenting agent. Although clozapine was the second agent used, aripiprazole alone had produced minimal symptom improvement in all 3 cases. All of our patients had substantial clinical responses with minimal adverse effects.

We have considered the possibility that these patients could have improved clinically with clozapine monotherapy. However, in our experience, doses of clozapine this low would not be expected to produce the degree of clinical improvement evident in our treatment-refractory psychotic patients. One additional treatment-refractory schizoaffective patient, who had undergone an extensive clozapine monotherapy trial with minimal improvement at both low and high doses, demonstrated a robust response when low-dose clozapine was reintroduced and combined with aripiprazole. Further observations with combinations of clozapine and aripiprazole appear warranted.

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REFERENCES

1. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799-812
2. Kronig MH, Munne RH, Szymanski S, et al. Plasma clozapine levels and clinical response for treatment-refractory schizophrenic patients. *Am J Psychiatry* 1995;152:179-182
3. Perry PJ, Miller DD, Arndt SV, et al. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. *Am J Psychiatry* 1991;148:231-235. Correction 1991;148:1427
4. Potkin SG, Bera R, Gulaskaram B, et al. Plasma clozapine concentrations predict clinical response to treatment-resistant schizophrenia. *J Clin Psychiatry* 1994;55(suppl B):133-136
5. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology (Berl)* 1996;194:2-34
6. Kapur S, Remington G. Dopamine D₂ receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psych* 2001;50:873-883
7. Abilify [package insert]. Princeton, NJ: Bristol-Myers Squibb; March 2003
8. Breier A. Clozapine and noradrenergic function: support for a novel hypothesis for superior efficacy. *J Clin Psychiatry* 1994;55(suppl B): 122-125
9. DeGroot IW, Heck AH, van Harten PN. Addition of risperidone to clozapine therapy in chronically psychotic inpatients [letter]. *J Clin Psychiatry* 2001;62:129-130
10. Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. *J Clin Psychiatry* 1996;57: 395-397
11. Raskin S, Katz G, Zislin A, et al. Clozapine and risperidone: combination/augmentation treatment of refractory schizophrenia: a preliminary observation. *Acta Psychiatr Scand* 2000;101:334-336
12. Adesina A, Pantelis C. Adjunctive risperidone treatment in patients with "clozapine-resistant schizophrenia" [letter]. *Aust N Z J Psychiatry* 2000;34:533-534

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The Successful Use of Meclizine in Panic Disorder

Sir: A variety of pharmacologic treatments have been recommended in panic disorder, including the selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, benzodiazepines, and monoamine oxidase inhibitors.¹ This does not exclude the effectiveness of other medications (e.g., venlafaxine, gabapentin) that may not have been formally studied for the disorder. Meclizine, an H₁ receptor antagonist, has not undergone empirical study as a pharmacologic intervention in panic disorder, although Jacob² indicates its potential effectiveness among individuals with both panic disorder and vestibular symptoms. We present the case of a female patient, seen in a primary care setting, who had been treated with the traditional pharmacotherapies for panic disorder (SSRIs, tricyclic anti-

depressants, benzodiazepines), but responded well only to meclizine.

Case report. Ms. A, a 38-year-old, white, divorced woman, presented in June 2003 to her internal medicine physician with a history of panic attacks and background anxiety since the age of 12 years. She described attacks that routinely lasted 15 minutes and were characterized by dyspnea, increased respiratory rate, palpitations, tremulousness, paresthesias of the fingers, diaphoresis, impaired concentration, perceptual distortions (i.e., derealization), depersonalization, feelings of being overwhelmed, and fears of going crazy or dying. Ms. A experienced no light-headedness, nausea, vomiting, other gastrointestinal symptoms, or agoraphobia. Prior to effective treatment, episodes occurred 3 to 4 times per week, precipitated by acute psychosocial stressors such as frustrating interpersonal events. (We are unaware of any non-cued panic attacks.) Attacks subsided with self-talk, leaving the immediate area, and/or partner coaching. Ms. A's history included multiple emergency room visits for symptom treatment and various medication trials including fluoxetine, citalopram, amitriptyline, desipramine, diazepam, and alprazolam. During treatment with these various medications, Ms. A experienced either excessive sedation (benzodiazepines, tricyclics) or, at times, paradoxical dysphoria (SSRIs), which precluded adequate drug trials.

The patient denied any history of comorbid depression, alcohol or other substance abuse or dependence, or social phobia, but acknowledged ongoing background anxiety (e.g., hypervigilance, fatigue, impaired concentration, irritability, feeling "keyed up," muscular tension) that intensified with psychosocial stressors (i.e., generalized anxiety disorder). She displayed no avoidant personality features; indeed, during contacts with the primary care physician, she was engaging, verbally elaborative without prompting, and spontaneous.

Ms. A had no family history of panic disorder, history of childhood separation difficulties, or past airway compromise. She reported a history of childhood sexual, emotional, and physical abuse that began at around 3 years of age and continued through adolescence. (The patient's symptoms of posttraumatic stress disorder were not explicitly explored during the medical visit.) At the time of initial presentation, the patient's medications were clopidogrel (following a transient ischemic attack while taking oral contraceptives), meclizine, naproxen, and ranitidine. During the primary care visit, the internist specifically inquired about vestibular symptoms because of the patient's request for a prescription refill of meclizine. The patient denied any history of hearing loss, vestibular symptoms, or tinnitus; her tympanic membranes were clear on physical examination.

When asked about the indication for meclizine, Ms. A explained that on one of her past visits to the emergency room, a European physician recommended 12.5 mg 3 times per day specifically for the treatment of her panic symptoms. Ms. A began treatment, and 4 years later reports a sustained 70% reduction in symptoms (i.e., approximately 2 episodes per month). To our knowledge, the patient has never discontinued meclizine treatment since its inception to determine the effect on panic symptom status. Higher doses have resulted in excessive sedation.

Meclizine, which is prescribed for the treatment of nausea and dizziness that are associated with motion sickness as well as vertigo, is structurally and pharmacologically similar to buclizine, cyclizine, and hydroxyzine.³ Interestingly, in a double-blind, placebo-controlled study, hydroxyzine was found effective in the treatment of generalized anxiety disorder,⁴ a disorder that is frequently comorbid with panic disorder. We suspect that the majority of clinicians do not consider the use of

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meclizine in panic disorder patients who are not responding well to the currently recommended medications. As illustrated in this case, meclizine may be effective even in patients without predominant vestibular symptoms. To our knowledge (i.e., following searches of PubMed and PsycINFO databases from 1966 to 2004 using the keywords *meclizine*, *panic*, and *anxiety*), ours appears to be the first documented case of effective meclizine treatment in panic disorder.

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

REFERENCES

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Panic Disorder. *Am J Psychiatry* 1998;155(suppl 5):1–34
2. Jacob RG. Panic disorder and the vestibular system. *Psychiatr Clin North Am* 1988;11:361–374
3. Hochadel MA. *Clinical Psychopharmacology Online*. Tampa, Fla: Gold Standard Multimedia; 2003
4. Lader M, Scotto J-C. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. *Psychopharmacology (Berl)* 1998;139:402–406

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Successful Switch to Aripiprazole After Induction of Hyperprolactinemia by Ziprasidone: A Case Report

Sir: Hyperprolactinemia is a frequently encountered clinical sign in antipsychotic treatment that is highly dependent on the antidopaminergic properties of the drug.¹ Two aspects of the development of hyperprolactinemia must be taken into consideration in this context. First, the propensity to induce hyperprolactinemia is highly substance dependent, with amisulpride and risperidone usually involved.² Ziprasidone seems to be less frequently associated with hyperprolactinemia (leading, when the condition does occur, to small prolactin increases and a transient course),³ and aripiprazole may even lower prolactin levels.^{1,4} Second, it is noteworthy that there is no clear connection between the level of prolactin and acute clinical side effects.⁵ In the case we describe here, a patient who developed hyperprolactinemia with ziprasidone was successfully switched to aripiprazole with complete normalization of serum prolactin concentrations and restoration of sexual function.

Case report. Ms. A, a 21-year-old woman, had a 3-year history of DSM-IV paranoid schizophrenia and was admitted in June 2003 for psychotic relapse with delusions and psychomotor agitation. Her Positive and Negative Syndrome Scale (PANSS)⁶ score was +32/–21. She had had no previous serious illnesses and was receiving no medication. On our ward, she was treated with risperidone up to 6 mg/day with a good effect on positive symptoms (PANSS score on discharge = +14/–21). This medication was well tolerated except for side effects of amenorrhea and decreased sexual drive. The patient's serum prolactin concentration was 217 $\mu\text{g/L}$ (normal range, 2.8–29 $\mu\text{g/L}$) when

total serum concentration of 48 ng/mL of risperidone and its main metabolite 9-hydroxyrisperidone was measured.

Since the side effects mentioned were intolerable for the patient, especially in an outpatient setting, she was switched to ziprasidone. Because of insufficient suppression of psychotic features with lower dosages, Ms. A was treated with ziprasidone up to 120 mg/day and then a maintenance dosage of 80 mg/day. After approximately 2 weeks of maintenance treatment and 6 weeks total of treatment with ziprasidone, which was about 8 weeks after discontinuation of risperidone, when no risperidone or 9-hydroxyrisperidone could be detected in the patient's plasma, she again complained of amenorrhea and loss of sexual desire. Magnetic resonance imaging of the head showed no pathology (particularly no hypophyseal mass), but the patient's prolactin levels were increased to 52 $\mu\text{g/L}$.

After a laboratory control confirmed the prolactin finding, Ms. A was switched to aripiprazole, 15 mg, in the morning. Only 3 days after the beginning of aripiprazole treatment, the patient's prolactin levels were within normal range again (18 $\mu\text{g/L}$) and have remained so for 9 months (ranging from 12–18 $\mu\text{g/L}$). About 1 week after the start of aripiprazole treatment, clinical side effects (e.g., menstrual abnormalities) disappeared with no deterioration in psychopathology.

Sexual dysfunction as a result of hyperprolactinemia not only may be troublesome for many patients but also may negatively influence adherence to medication.⁷ This case report presents a young woman with an obviously high susceptibility to this side effect of antidopaminergic drugs, since she had developed hyperprolactinemia not only with risperidone but also—though to a lesser extent—with ziprasidone. A switch to the partial dopaminergic agonist aripiprazole reversed the elevated serum prolactin levels and also the clinical side effects. From a critical point of view, one could argue that the normalization of prolactin concentrations could be due to the discontinuation of ziprasidone per se. One could at least arrive at the conclusion, then, that aripiprazole did not negatively influence prolactin levels in this highly susceptible patient. The very rapid time course of normalization, however, strongly supports the first interpretation, i.e., that aripiprazole has an independent effect on prolactin levels.⁸ The power of the intrinsic dopaminergic action of aripiprazole is dopamine dependent, since receptor occupancy is not just antagonism.⁹

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REFERENCES

1. Goodnick PJ, Rodriguez L, Santana O. Antipsychotics: impact on prolactin levels. *Expert Opin Pharmacother* 2002;3:1381–1391
2. Maguire GA. Prolactin elevation with antipsychotic medications: mechanism of action and clinical consequences. *J Clin Psychiatry* 2002;63(suppl 4):56–62
3. Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. *Clin Ther* 2002; 1:21–37
4. Inoue A, Seto M, Sugita S, et al. Differential effects on D₂ dopamine receptor and prolactin gene expression by haloperidol and aripiprazole in the rat pituitary. *Brain Res Mol Brain Res* 1998;55:285–292
5. Compton MT, Miller AH. Antipsychotic-induced hyperprolactinemia and sexual dysfunction. *Psychopharmacol Bull* 2002;36:143–164
6. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health System; 1986
7. Petty RG. Prolactin and antipsychotic medications: mechanism of action. *Schizophr Res* 1999;S67–S73
8. Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics,

Reprinted with correction (see Pascual et al., page 1281).

tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol* 2004;44:179–187

9. Gründer G, Carlsson A, Wong DF. Mechanism of new antipsychotic medications: occupancy is not just antagonism. *Arch Gen Psychiatry* 2003;60:974–977

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A Case of Parenteral Zolpidem Dependence With Opioid-Like Withdrawal Symptoms

Sir: Zolpidem, an imidazopyridine hypnotic agent, is suggested to have minimal risk of abuse or dependence.¹ Nonetheless, there are some case reports documenting its abuse, dependence, and withdrawal effects.^{2–4} We present a case of intravenous zolpidem abuse with opioid-like withdrawal symptoms.

Case report. Mr. A, a 35-year-old man, began abusing multiple substances at the age of 16 years, but did not use any one drug exclusively. He intravenously injected heroin several times at 33 years of age, but quit injecting it because of its unaffordable expense and its illegality. He then purchased zolpidem over the counter at a local pharmacy and began taking 10 mg/day orally at 34 years of age, initially for insomnia. About 1 week later, he tried injecting zolpidem intravenously by dissolving the pills in normal saline. He experienced a stronger stimulating effect and euphoria through intravenous administration. Over the past year, Mr. A had increased the dosage of intravenous zolpidem from 20 mg/day to 300 to 400 mg/day because he experienced tolerance to lower doses. In addition, he experienced yawning, rhinorrhea, and lacrimation several hours after injection of zolpidem and had alternating hot and cold sensations after about 2 days of abstaining from zolpidem; after this attempt at abstinence, he resumed zolpidem use due to his withdrawal symptoms.

With intravenous use of zolpidem, the patient also suffered from cyanotic change of his hands on 3 occasions, which resolved spontaneously within 2 weeks each time. After injecting zolpidem again, he suffered from cyanosis of his left hand, with a cold and unbearable painful sensation. Mr. A then sought medical attention and was admitted to the hospital in June 2003 for treatment. Drug abuse screening, including amphetamine, opioids, benzodiazepines, and alcohol, was performed at his admission and showed negative findings. A distal embolism was found in the patient's left radial artery on angiography. He was treated with anticoagulant and antibiotic therapies, as well as hyperbaric oxygen therapy. Diclofenac sodium 25 mg 4 times daily was prescribed to relieve his pain, but tramadol 200 mg/day was soon added due to unsatisfactory pain relief. Lorazepam 1.5 mg at bedtime was prescribed to help him sleep. No obvious withdrawal symptoms of zolpidem were noted during hospitalization. Three weeks later, he was discharged with improvement in the cyanosis of his left hand.

Previous reports of the withdrawal symptoms of oral zolpidem abuse, like those of benzodiazepine withdrawal symptoms, described tremor, agitation, anxiety, and seizure.^{2–4} To our knowledge, ours is the first report of intravenous zolpidem

abuse with opioid-like withdrawal symptoms (i.e., yawning, rhinorrhea, and lacrimation) complicated by arterial embolism.

Zolpidem is a short-acting hypnotic that acts on omega 1 receptors (GABA_A-receptor subtypes containing alpha 1 subunits).¹ Animal studies have shown that withdrawal of zolpidem induces changes in GABA_A-receptor gene expression,⁵ and stimulation of GABA_A-receptors reduces yawning behavior.⁶ Both of these findings could explain the yawning symptom our patient experienced while withdrawing from large-dose intravenous zolpidem abuse. Another possible explanation for the opioid-like withdrawal symptoms is that zolpidem may have an indirect effect on the opioid system through GABA_A-receptors; animal studies show coexpression of opioid and GABA_A-receptors by the same neuron in rat brain.⁷ The intoxication symptoms of zolpidem are similar to those of narcotic overdose,⁸ and our patient illustrated zolpidem-related opioid-like withdrawal symptoms. The possible pharmacologic effect of zolpidem on the opioid system may warrant further exploration.

Our case is similar to a previous report that a former substance abuser was at risk of zolpidem dependence⁹; thus, clinicians should be cautious when prescribing zolpidem, especially for those with a prior history of substance abuse.

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REFERENCES

1. Darcourt G, Pringuey D, Salliere D, et al. The safety and tolerability of zolpidem: an update. *J Psychopharmacol* 1999;13:81–93
2. Madrak LN, Rosenberg M. Zolpidem abuse [letter]. *Am J Psychiatry* 2001;158:1330–1331
3. Aragona M. Abuse, dependence, and epileptic seizures after zolpidem withdrawal: review and case reports. *Clin Neuropharmacol* 2000;23:281–283
4. Goder R, Treskove V, Burmester J, et al. Zolpidem: the risk of tolerance and dependence according to case reports, systematic studies and recent molecular biological data [in German]. *Fortschr Neurol Psychiatr* 2001;69:592–596
5. Follsea P, Mancuso L, Biggio F, et al. Changes in GABA_A receptor gene expression induced by withdrawal of, but not by long-term exposure to, zaleplon or zolpidem. *Neuropharmacology* 2002;42:191–198
6. Melis MR, Argiolas A. Reduction of drug-induced yawning and penile erection and of noncontact erections in male rats by the activation of GABA_A receptors in the paraventricular nucleus: involvement of nitric oxide. *Eur J Neurosci* 2002;15:852–860
7. Kalyuzhny AE, Dooyema J, Wessendorf MW. Opioid- and GABA_A-receptors are co-expressed by neurons in rat brain. *Neuroreport* 2000;11:2625–2628
8. Lheureux P, Debailleul G, De Witte O, et al. Zolpidem intoxication mimicking narcotic overdose: response to flumazenil. *Hum Exp Toxicol* 1990;9:105–107
9. Bottlender R, Schutz C, Moller HJ, et al. Zolpidem dependence in a patient with former polysubstance abuse. *Pharmacopsychiatry* 1997;30:108

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