

Letters to the Editor

Olanzapine for Cocaine Cravings and Relapse Prevention

Sir: A letter published in the *Journal*¹ described olanzapine's effect in decreasing cocaine cravings and preventing relapse. We report similar positive outcome in a dual-diagnosis patient after olanzapine use.

Case report. Mr. A, a 46-year-old single, African American man with a history of schizoaffective disorder, bipolar type (DSM-IV criteria), was being treated with depot haloperidol 250 mg IM every month. He also met DSM-IV criteria for cocaine dependence. He had been to several addiction treatment programs, but relapsed often even while adhering to monthly depot haloperidol and other psychosocial treatments. He used about 2 g of cocaine per week, which often worsened paranoia and led to frequent hospitalizations. After his most recent hospitalization, he was transferred to our 28-day residential program. Here, he reported worsened drug use with depot haloperidol use. He agreed to try olanzapine instead.

Depot haloperidol dose was tapered and discontinued, while olanzapine was started at 10 mg at bedtime and then increased to 15 mg at bedtime. Mr. A reported improvement in his symptoms but still experienced distracting auditory hallucinations in the morning. An additional 5 mg of olanzapine was added in the morning. These scheduled doses of olanzapine improved his psychoses and decreased anxiety and frequency of "using" dreams and persistent thoughts of using cocaine. When asked to describe his cravings before olanzapine, he reported 7 on a 10-point Likert scale. His cravings decreased to 2 after olanzapine use. On discharge, he was referred to a halfway house and individual, group, and self-help therapy with Alcoholics Anonymous. At last contact, Mr. A had adhered to his outpatient program and completed 6 months of sobriety.

Typical antipsychotic medications reportedly do not impact substance use when prescribed to dual-diagnosis patients. Instead, reports suggest worsening drug abuse.²⁻⁴ This effect is probably mediated through strong dopamine-2 (D₂) receptor blockade in the nucleus accumbens, which, when stimulated by drugs or alcohol, causes the sensation of reward or experience of high.⁵ Since the atypical antipsychotics have relatively less D₂ blockade, their negative effects on the reward pathway in the nucleus accumbens may also be less. These effects would not, hypothetically, increase cravings for alcohol or drugs.⁵ Clozapine and quetiapine have reportedly shown decreased cravings and active substance use when prescribed for psychotic or bipolar disorders in dual-diagnosis patients. Littrell et al.⁶ conducted a 12-month open-label trial of olanzapine in 30 patients with schizophrenia and substance dependence and found that 70% of their sample achieved sobriety by the end of the study.

Olanzapine's potential in decreasing cravings and relapse is most likely multifactorial. Olanzapine decreases anxiety and

depression and causes sedation. Because these feelings often trigger drug use, their reduction may decrease relapse potential. Olanzapine reportedly decreased cocaine use in animals as well.⁷ Perhaps, similar or other unknown mechanisms are involved in olanzapine's anticraving effects in humans. More studies are needed before this is established. Until then, dual-diagnosis patients may benefit from olanzapine use in the reduction of cocaine cravings and relapse.

Dr. Sattar has served as a consultant for Lilly, AstraZeneca, and Abbott, served on the speaker/advisory board of AstraZeneca, and received honoraria from AstraZeneca; Dr. Bhatia has served as a consultant for and received honoraria from Lilly, Bristol-Myers, AstraZeneca, Janssen, and Pfizer.

REFERENCES

1. Longo LP. Olanzapine for cocaine cravings and relapse prevention in 2 patients [letter]. *J Clin Psychiatry* 2002;63:595-596
2. Bowers MB Jr, Mazure CM, Nelson JC, et al. Psychogenic drug use and neuroleptic response. *Schizophr Bull* 1990;16:81-85
3. Sirrius SG. Pharmacologic treatment of substance abusing schizophrenia patients. *Schizophr Bull* 1990;16:111-122
4. McEvoy JP, Freudenreich O, Levin ED, et al. Haloperidol increases smoking in patients with schizophrenia. *Psychopharmacology (Berl)* 1995;119:124-126
5. Green AI, Zimmet SV, Strous RD, et al. Clozapine for co-morbid substance use disorder and schizophrenia: do patients with schizophrenia have a higher reward-deficiency syndrome that can be ameliorated by clozapine? *Harv Rev Psychiatry* 1999;6:287-296
6. Littrell KH, Petty RG, Hilligoss NM, et al. Olanzapine treatment for patients with schizophrenia and substance abuse. *J Subst Abuse Treat* 2001;21:217-221
7. Meil WM, Schechter MD. Olanzapine attenuates the reinforcing effects of cocaine. *Eur J Pharmacol* 1997;340:17-26

S. Pirezada Sattar, M.D.
Subhash C. Bhatia, M.D.

Creighton University School of Medicine
Omaha Veterans Administration Medical Center
Omaha, Nebraska

Serotonin Reuptake Inhibitors and Shocklike Paresthesia

Sir: Berigan et al.¹ have reported in the *Journal* 3 cases of transient paroxysmal, shocklike paresthesias associated with paroxetine initiation. At the Netherlands Pharmacovigilance Centre Lareb, which is responsible for collecting and analyzing reports concerning possible adverse drug reactions from health professionals on behalf of the Dutch Medicines Evaluation Board, we have received 9 reports of similar paresthesias related to the use of paroxetine and other serotonin reuptake inhibitors (SRIs). The reports were received between the date of

Table 1. Reports of Shocklike Paresthesia Associated With the Use of Serotonin Reuptake Inhibitors

Patient	Sex, Age (y)	Drug and Dose, Indication for Use	Concomitant Medications	Suspected ADR ^a	Other Reported ADRs	Time From Medication Start to Onset of Paresthesia, Outcome
A	F, 46	Fluvoxamine, 100 mg once daily, not specified	Moclobemide, alprazolam	"Shocks in the head"	Paresthesia, hyperhidrosis, paroniria, insomnia, fatigue	2 days, unknown
B	F, 56	Fluoxetine, 20 mg twice daily, not specified	None	"Small electric shocks"	Rash, joint swelling, back pain	6 months, medication continued
C	F, 35	Paroxetine, 20 mg once daily, depressive episode	None	"Sort of electric shocks"	Paresthesia, dizziness	2 months, medication continued
D	F, 27	Paroxetine, 20 mg once daily, depressive episode	None	"Electric shocks"	None	4 days after lowering dose, resolved
E	F, 45	Paroxetine, 20 mg once daily, obsessive-compulsive disorder	Levothyroxine	"Small electric shocks through arms"	Agitation, hyperhidrosis, abdominal discomfort	2 months, not yet resolved
F	F, 56	Paroxetine, 20 mg once daily, not specified	None	"Electric shocks in head and coccyx"	None	Shortly after dose increase, decrease, and withdrawal; resolved
G	F, 34	Paroxetine, 20 mg once daily, depressive episode	None	"Small shocks in the head 6 times a day"	Paresthesia in legs	8 months, first aggravation after withdrawal of paroxetine, resolved after 4–5 wk
H	F, 49	Fluvoxamine, 50 mg once daily, unspecified anxiety disorder	Oxazepam, estradiol/cyproterone acetate	"Small electric shocks"	Shivers	A few days, unknown
I	M, 29	Venlafaxine, 75 mg once daily, unspecified anxiety disorder	None	"Paroxysmal electric shock through whole body"	Dizziness	A few hours; first aggravation after withdrawal of venlafaxine; after 5½ months of treatment, resolved

^aDescriptions of the suspected ADRs are direct quotations from the reporting physician or pharmacist for each patient. Abbreviations: ADR = adverse drug reaction, F = female, M = male.

registration in the Netherlands for each drug and July 1, 2002. An overview of these reports is provided in Table 1.

The time to onset of the paresthesias is heterogeneous and varies from shortly after administration to 8 months after the start of treatment. In 1 report, the paresthesia occurred 4 days after dose reduction (patient D; see Table 1); in 1 report, it occurred after both dose increase and decrease and when the patient forgot to take her medication (patient F); and in 2 reports, the complaints at first worsened after withdrawal of the medication, then resolved fully. Six of 9 of the patients used no concomitant medication. In 3 of the reports, other types of paresthesias in addition to electric shocks were mentioned.

Selective serotonin reuptake inhibitors (SSRIs; fluvoxamine, fluoxetine, paroxetine, sertraline, and citalopram) inhibit presynaptic serotonin reuptake. The most frequent adverse effects of SSRIs include gastrointestinal complaints and effects on the central nervous system, such as headache, agitation, and insomnia. Venlafaxine, a nonselective SRI, inhibits serotonin reuptake, but also to a lesser extent norepinephrine reuptake.² The adverse reaction profile of the drug resembles that of the SSRIs.

In addition to their association with initiation of paroxetine as described by Berigan et al.,¹ shocklike paresthesias are also associated with the withdrawal of SSRIs. Three patients experienced shocklike sensations after discontinuation of paroxetine/sertraline; all 3 patients were young men who used the SSRI for treatment of obsessive-compulsive disorder, anxiety attacks, or depression.³ Another report describes a 39-year-old woman who

experienced the sensation of electrical shocks through her back and limbs after abrupt discontinuation of paroxetine. The symptoms could be provoked by flexion of the neck and were alleviated with readministration of paroxetine.⁴

The pathophysiology of drug-induced shocklike paresthesias is not clear, but in some cases resembles Lhermitte's sign: "sudden 'electrical' pains occurring with neck flexion down the spine and into the upper extremities."^{1(p176)} Lhermitte's sign has been associated with various spinal cord disorders^{4,5} and described as an adverse effect of cisplatin and oxaliplatin.^{5,6} Here, Lhermitte's sign is assumed to be due to hyperexcitability of the ascending neurons.

The cases in the Lareb database show that shocklike sensations may occur with SRIs, irrespective of the indication for use. This type of paresthesia strongly resembles Lhermitte's sign and therefore may be due to neuronal hyperexcitability.

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

REFERENCES

- Berigan TR, Cannard AW, Cannard KR. Transient, paroxysmal, shock-like paresthesias associated with paroxetine initiation [letter]. *J Clin Psychiatry* 1997;58:175–176
- Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, NY: McGraw-Hill; 1996
- Frost L, Lal S. Shock-like sensations after discontinuation of selective

- serotonin reuptake inhibitors [letter]. *Am J Psychiatry* 1995;152:810
- Reeves RR, Pinkofsky HB. Lhermitte's sign in paroxetine withdrawal [letter]. *J Clin Psychopharmacol* 1996;16:411-412
 - Walther PJ, Rossitch E Jr, Bullard DE. The development of Lhermitte's sign during cisplatin chemotherapy: possible drug-induced toxicity causing spinal cord demyelination. *Cancer* 1987;60:2170-2172
 - Taieb S, Trillet-Lenoir V, Rambaud L, et al. Lhermitte sign and urinary retention: atypical presentation of oxaliplatin neurotoxicity in four patients. *Cancer* 2002;94:2434-2440

Linda de Graaf, Pharm.D.
Eugène P. van Puijenbroek, Ph.D.
 Netherlands Pharmacovigilance Centre Lareb
 's-Hertogenbosch, the Netherlands

Case of Gynecomastia During Paroxetine Therapy

Sir: A 30-year-old man had been followed since age 19 for panic disorder with agoraphobia (DSM-IV). After a major depressive episode at the age of 25, the patient began psychotherapy and was started on paroxetine, 40 mg daily. Several months later, he noticed that his left breast was slightly enlarged, but waited almost 5 years before reporting this to his physician. Over the course of therapy with paroxetine, which he continued during these 5 years, the gynecomastia gradually became more marked. In addition to paroxetine, the patient used incidentally a benzodiazepine (diazepam) for anxiety attacks, but was not taking any other concomitant medication. There was no history of organic illness and no family antecedent except breast cancer in a paternal aunt. Gynecomastia had developed insidiously several months after starting paroxetine, when the patient was 25 years old. Gynecomastia had not been present during adolescence.

The breast examination revealed overt enlargement of the left breast with minimal enlargement of the right breast. All other clinical findings were in the normal range. Blood biochemistry ruled out hepatic, renal, or metabolic diseases. Hormone levels (thyroid-stimulating hormone, T₄, testosterone, estradiol, luteinizing hormone, β -human chorionic gonadotropin) were within the limits of normal values and prolactin concentration was 14 ng/mL (normal range, 4.1-18.5 ng/mL). A contrast-enhanced brain computed tomographic scan of the sella turcica did not detect any pituitary lesions. The breast examination (mammography and ultrasonography) confirmed the marked enlargement of the left breast, with an abundant retroareolar glandular component. Multiple-site biopsies were performed, and the cytological analysis showed the absence of malignant cells (Papanicolaou class I). Although paroxetine was considered to be the most likely cause of the gynecomastia, cosmetic surgery was proposed, since this was a condition that had been present for some time (with fibrotic tissue replacing the initial ductal hyperplasia) in which elimination of the causal factor might not lead to clinical improvement. Thus, 52 g of tissue were surgically removed and postoperative histological examination confirmed the gynecomastia and revealed no evidence of malignancy. After cosmetic surgery, the patient was treated with mirtazapine, 30 mg/day. A 2-year follow-up showed no evidence for gynecomastia.

This case is the first to implicate a selective serotonin reuptake inhibitor (SSRI) alone in induction of gynecomastia. Paroxetine was considered a possible cause of gynecomastia based on a detailed history and the diagnostic findings described above. While there are many studies and case reports

that directly confirm the potential of SSRIs to cause galactorrhea¹⁻³ and mammaplasia,^{4,5} there is only 1 article reporting the development of gynecomastia secondary to SSRI therapy. Benazzi⁶ reports a case of gynecomastia in a patient taking fluoxetine, associated with risperidone. In contrast to this case report, our patient had never taken antipsychotic drugs, thereby allowing us to postulate that the SSRI alone was the underlying cause.

Prolactin levels were not measured until 5 years after onset of gynecomastia and were within normal limits, which is consistent with many reports¹ indicating that there is no simple correlation between prolactin levels and galactorrhea.

SSRIs produce complex changes in dopaminergic neurotransmission both in man⁷ and in rats,⁸ and hyperprolactinemia is due to adaptive changes in dopaminergic neurons.⁹ Several authors have suggested that SSRIs inhibit dopaminergic transmission not by their effects on secretion, reuptake, or dopaminergic receptors, but indirectly via serotonergic pathways.^{1,10} Two mechanisms of action have been proposed to explain serotonergic stimulation of prolactin release: presynaptic inhibition by serotonergic receptors of dopamine release, a most likely mechanism according to Egberts et al.,¹ or direct stimulation of hypothalamic postsynaptic serotonergic receptors.³

Poster presented at the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum; June 23-27, 2002; Montreal, Quebec, Canada.

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

The authors thank E. Diepart, M.D., and S. Beyenburg, M.D., for their comments.

REFERENCES

- Egberts AC, Meyboom RH, De Koning FH, et al. Nonpuerperal lactation associated with antidepressant drug use. *Br J Clin Pharmacol* 1997;44:277-281
- Bonin B, Vandel P, Sechter D, et al. Paroxetine and galactorrhea. *Pharmacopsychiatry* 1997;30:133-134
- Bronzo MR, Stahl SM. Galactorrhea induced by sertraline. *Am J Psychiatry* 1993;150:1269-1270
- Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic antidepressant therapy. *J Affect Disord* 1997;46:151-156
- Hall MJ. Breast tenderness and enlargement induced by sertraline. *Am J Psychiatry* 1994;151:1395-1396
- Benazzi F. Gynecomastia with risperidone-fluoxetine combination. *Pharmacopsychiatry* 1999;32:41
- Tanda G, Carboni E, Frau R, et al. Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? *Psychopharmacology* 1994;115:285-288
- Gardier AM, Lepoul E, Trouvin JH, et al. Changes in dopamine metabolism in rat forebrain regions after cessation of long-term fluoxetine treatment: relationship with brain concentrations of fluoxetine and of norfluoxetine. *Life Sci* 1994;53:51-56
- Cowen PJ, Sargent PA. Changes in plasma prolactin during SSRI treatment: evidence for a delayed increase in 5-HT neurotransmission. *J Psychopharmacol* 1997;4:345-348
- Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* 1999;19:67-85

Cristian Damsa, M.D.
 University of Geneva Psychiatric Center
 Geneva, Switzerland
Robert Sterck, M.D.
 Jolimont-Lobbes Hospital
 La Louviere, Belgium
Pierre Schulz, M.D.
 Belle-Idée Hospital
 Geneva, Switzerland

Olanzapine-Associated Bilateral Pedal Edema

Sir: Bilateral pedal edema is most commonly associated with multiple medical etiologies that include hepatic cirrhosis, lymphedema, congestive heart failure, hypoproteinemia, and renal disease.¹ However, a significant number of medications such as nonsteroidal anti-inflammatories, antihypertensives, steroids, and immunosuppressive agents can also cause both localized and generalized edema.² I report a case of bilateral pedal edema developing in a young woman shortly after initiation of treatment with the atypical antipsychotic agent olanzapine. Although there has been 1 other case report of a person with congestive heart failure developing peripheral edema secondary to the use of olanzapine,³ this is the first report of this adverse event occurring in a medically healthy subject who was being treated with this agent.

Case report. Ms. A is a 34-year-old white woman with a history of DSM-IV bipolar disorder, type II, who had been treated for several weeks in 2002 with a combination of bupropion sustained release, 150 mg twice per day; diazepam, 10 mg/day; and gabapentin, 600 mg 3 times per day. Although she reported no adverse side effects, she continued to report cycling mood symptoms. As a consequence, she consented to a taper of the gabapentin and the initiation of olanzapine, 10 mg/day. Approximately 10 days after beginning the evening dose of olanzapine, Ms. A called to complain of “swollen feet and ankles.” She denied other associated symptoms of rash, fever, shortness of breath, or dizziness. Other than the aforementioned psychotropic agents, she was taking no other medications and denied all alcohol and illicit substance use. Ms. A had no history of cardiac, pulmonary, vascular, hepatic, or immunologic disorders.

Her physical examination was significant only for a bilateral 2+ pitting edema in the ankles and dorsum of the feet. There was no evidence of rash, skin thickening, ulceration, or changes in pigmentation. Results of a comprehensive metabolic profile that included assays of albumin and hepatic enzymes were without abnormality. Serum electrolytes, including sodium, evidenced no abnormalities. Results of a complete blood count with differential, renal function tests, thyroid-stimulating hormone level, and sedimentation rate were also within normal limits. It was decided with Ms. A to withhold the olanzapine for a period of time to better determine whether this agent was causing her edema. Approximately 2 weeks later, Ms. A called saying that her edema had resolved and requesting another trial of the olanzapine since her sleep and anxiety had improved while taking it. The medication was reinitiated at 10 mg/day, and within 10 days her bilateral edema recurred. At that time, the decision was made to discontinue the atypical agent, resulting in the resolution of her edema over a 1-week period.

Although the on-off-on naturalistic trial described in this case report strongly underscores the association between the initiation of olanzapine and the development of bilateral pedal edema, the precise mechanism behind this adverse event remains open to speculation. A number of possible etiologies should be considered, including neuroendocrine changes caused by the antipsychotic agent as well as an adverse interaction between the medications taken by this patient (e.g., diazepam and olanzapine). However, drug-induced pedal edema by a single agent is not uncommon and has been associated with antihypertensive agents that have properties of α -adrenergic antago-

nism.² There is also evidence in the literature associating idiopathic edema with hypodopaminergic states, which may respond favorably to the use of bromocriptine, a dopamine agonist.¹ Olanzapine, an atypical antipsychotic agent, has the pharmacologic capacity to antagonize both α_1 - and α_2 -adrenergic receptors as well as block a pleomorphic range of dopamine receptors.⁴ Whether one or a number of these mechanisms adequately account for the development of an olanzapine-induced peripheral edema is subject to further clinical observation, discussion, and research.

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

REFERENCES

1. Braunwald E. Edema. In: Braunwald E, Fauci AS, Kasper DC, et al, eds. *Harrison's Principles of Internal Medicine*. 15th ed. New York, NY: McGraw-Hill; 2001:217–222
2. Chertow GM, Thibault GE. Approach to the patient with edema. In: Goldman L, Braunwald E, eds. *Primary Cardiology*. Philadelphia, Pa: Saunders; 1998:112–121
3. Yovtcheva SP, Yazel JJ. Olanzapine-induced bilateral pedal edema: a case report [letter]. *Gen Hosp Psychiatry* 2000;22:290–291
4. van Kammen DP, Marder SR. Serotonin-dopamine antagonists. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*, vol 2. 7th ed. Baltimore, Md: Williams & Wilkins; 2000:2455–2474

Richard C. Christensen, M.D., M.A.
University of Florida College of Medicine
Jacksonville, Florida

Corrections

In the article “Venlafaxine in Treatment-Resistant Obsessive-Compulsive Disorder” by Eric Hollander, M.D., et al. (May 2003 issue, pp. 546–550), the corrected percentages of nonresponders to prior serotonin reuptake inhibitors in Table 3 on page 549 (far right column) are as follows:

Table 3. Venlafaxine Response in Obsessive-Compulsive Disorder Patients

CGI-Improvement Score	All Patients (N = 39)		Prior SRI Nonresponders (N = 29)	
	Frequency	Percentage	Frequency	Percentage
Responders	27	69.2	22	75.9
1 (very much improved)	19	48.7	16	55.2
2 (much improved)	8	20.5	6	20.7
Nonresponders	12	30.8	7	24.1
3 (minimally improved)	8	20.5	5	17.2
4 (no change)	4	10.3	2	6.9

Abbreviations: CGI = Clinical Global Impressions, SRI = serotonin reuptake inhibitor.

In the Letter to the Editor “Oral Magnesium Ion Shortens Prolonged QTc Interval” (June 2003 issue, pp. 733–734) by Daniel M. Bachman, M.D., the correct location of the Eastern Oregon Psychiatric Center is Pendleton, Oregon.