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 (D_2) 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 D_2 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.

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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

[a]Descriptions 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.

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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, T_4, 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 galactorrhea[1–3] and mammoplasia,[4,5] there is only 1 article reporting the development of gynecomastia secondary to SSRI therapy. Benazzi[6] 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 reports[1] indicating that there is no simple correlation between prolactin levels and galactorrhea.

SSRIs produce complex changes in dopaminergic neurotransmission both in man[7] 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]

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