# Letters to the Editor

## Mania Associated With Initiation of Ziprasidone

**Sir:** The efficacy of atypical antipsychotics in the treatment of psychotic disorders is well established. Although olanzapine carries an additional indication for bipolar disorder, there are cases of mania associated with risperidone[1,2] and olanzapine[3,4] treatment in some patients. We present a case report of mania that was apparently induced in a patient shortly after beginning therapy with another atypical antipsychotic, ziprasidone.

***Case report.*** Mr. A was a 20-year old man with a history of auditory hallucinations, paranoid delusions, flat affect, and social withdrawal. His symptoms worsened over several weeks, necessitating admission to our inpatient psychiatric unit. Haloperidol and risperidone trials had been attempted in the past, but he had refused treatment for 8 months prior to meeting us. Regarding this period, family members related waxing and waning of symptoms throughout, and they urged him to resume treatment. He had no history of drug/alcohol abuse, and his past medical/neurologic history was unremarkable.

With the patient meeting DSM-IV-TR diagnostic criteria for schizophrenia, we began ziprasidone, 20 mg b.i.d., with 20-mg b.i.d. increases over 4 days to 80 mg b.i.d. Due to daytime sedation, his dose was changed to 160 mg h.s. That night, because he slept poorly but related no other symptoms, ziprasidone was decreased to 80 mg h.s. The following night, he displayed increased energy with elated mood. He had increased religiosity and jumped over chairs, danced, and sang on a table. Lorazepam (2 mg) was emergently administered twice over 36 hours for his agitation and manic behavior. The ziprasidone therapy was discontinued, and olanzapine therapy was initiated as he refused lithium and valproic acid. The manic symptoms resolved over 48 hours, and his psychotic symptoms resolved over 30 days. Follow-up at 3 months, during which time he was maintained on 20 mg of olanzapine daily, revealed no further symptoms of mania, although some paranoid delusions remained.

On the basis of a recent literature search, this case represents the first report of mania associated with ziprasidone. Despite reports of the induction of mania by atypical antipsychotics, many authors find these agents (including ziprasidone[5]) helpful in treating manic symptoms seen in bipolar and schizoaffective disorders. In a review of risperidone/olanzapine-induced mania, it was speculated the cause was due to 5-$HT_2$/$D_2$ receptor occupancy.[6] However, ziprasidone differs from the older atypicals in its profound 5-$HT_{1D}$ and 5-HT/norepinephrine (NE) reuptake inhibition effect—similar to amitriptyline and imipramine. Perhaps the tricyclic-like antidepressant effect of ziprasidone precipitated our patient's mania.

We acknowledge that this case could represent a manic break in a patient who suffers from schizoaffective disorder. However, when the criteria proposed by Aubry et al.[6] are applied to our report, 6 of their 8 criteria favor our interpretation that ziprasidone was the cause of our patient's manic symptoms. Two criteria are not met, yet only because olanzapine was begun concurrent with ziprasidone discontinuation and because there was no rechallenge with ziprasidone. Our patient's lack of further manic symptoms despite no treatment with lithium or mood stabilizers in the 3 months following lends further credibility to our interpretation that ziprasidone was the cause of his mania.

Head-to-head trials among atypical antipsychotics with incidence of (hypo)mania development included as an outcome measure would be useful. This would allow productive speculation on a causative mechanism, based on the known differences in neuronal receptor affinities of agents in this class. For now, clinicians should be aware that ziprasidone, like other atypical antipsychotics, may induce mania in predisposed patients.

*Dr. Nolan reports no financial or other relationship relevant to the subject matter of this letter; Dr. Schulte is on the speaker/advisory boards of Pfizer, Lilly, Janssen, Abbott, and Forest.*

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## Burning Mouth Syndrome as a Side Effect of SSRIs

**Sir:** Maina et al.[1] recently published in the *Journal* a very interesting randomized trial of amisulpride, paroxetine, and sertraline for burning mouth syndrome (BMS). They cite case reports indicating that antidepressants have sometimes been helpful in treating BMS. A recent Cochrane Review summarizes previous treatment trials for BMS.[2] I report a case in which the

patient's BMS symptoms were the result of, rather than relieved by, antidepressants.

***Case report.*** When first seen, Ms. A was a 56-year-old woman presenting with DSM-IV dysthymia of at least 10 years' duration and superimposed major depressive disorder that had developed over the previous year. Her primary care physician had intermittently prescribed phentermine/fenfluramine during the preceding year, but these medications had been discontinued. She was experiencing menopausal symptoms. Her thyroid function was normal. Her primary care physician had started her on treatment with fluoxetine, 10 mg/day; following psychiatric evaluation, this dose was increased to 20 mg/day, and 1 month later, to 30 mg/day.

After 2 weeks of treatment with this dose, Ms. A reported painful burning sensations in her tongue, with no visible oral changes. No evidence of a systemic medical disorder was observed. Fluoxetine was discontinued, and the patient's glossodynia disappeared. She was started on treatment with sertraline, 50 mg/day, and after the dose was gradually raised to 100 mg/day, she promptly redeveloped glossodynia. Examination by a dentist/oral pathologist found no evidence of any oral or dental disease. Ms. A's symptoms disappeared with discontinuation of sertraline, but recurred during a trial of venlafaxine. She was unable to tolerate bupropion, nefazodone, mirtazapine, or methylphenidate because of unrelated side effects. During this period of antidepressant trials, Ms. A also received trials of hormone replacement therapy and hysterectomy for dysfunctional uterine bleeding; neither appeared to have any effect on her depression or oral pain.

Because the patient had experienced the most benefit from fluoxetine, she asked to retry it. As before, she was able to tolerate 20 mg/day without side effects, but the dose was ineffective. At a dose of 40 mg/day, intolerable glossodynia recurred. Fluoxetine was again discontinued, with subsequent disappearance of oral pain. Ms. A was started on treatment with citalopram, and with a dose of 40 mg/day, her depression completely remitted. She has continued taking this dose of citalopram for the past 3.5 years with no recurrence of depression or oral pain.

Glossodynia has been associated with menopause[3] and with involutional depression.[4] Neither appeared to account for this patient's oral pain, since it began after her depression had responded to trials of antidepressants. Whenever the antidepressant was discontinued, her depression worsened, but the glossodynia resolved. Hormone replacement did not affect the course of her symptoms. I could find no reports in the literature of glossodynia caused by antidepressants. Glossitis has been reported as an antidepressant side effect,[5,6] but in those cases there was visible evidence of inflammation, which was entirely absent in this case. This patient did not experience glossodynia while taking nonserotonergic antidepressants (bupropion, mirtazapine, nefazodone), but was on treatment with each only a short time. She experienced glossodynia with fluoxetine, sertraline, venlafaxine, and retrial of fluoxetine. For unclear reasons, she has not had this problem with citalopram. Continued follow-up has revealed no evidence of any underlying medical or neurologic disorder.

*Dr. Levenson has been a consultant for Lilly.*

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## Drs. Maina and Bogetto Reply

**Sir:** We read with great interest the letter to the editor by Levenson on burning mouth syndrome (BMS) as a side effect of selective serotonin reuptake inhibitors (SSRIs). To our knowledge, it is the first report in the literature of BMS associated with antidepressants.

Three aspects of the case report must be noted: (1) diagnosis: the BMS symptoms appeared in a patient treated for a double depression; (2) drugs: the BMS symptoms appeared and recurred with 2 SSRIs (fluoxetine and sertraline) and with venlafaxine, but not with citalopram; and (3) doses: BMS symptoms were experienced with fluoxetine, 30 mg/day, but not with fluoxetine, 20 mg/day, and with sertraline, 100 mg/day, but not with sertraline, 50 mg/day (the daily dose of venlafaxine was not cited).

Concerning diagnosis, the occurrence of BMS in a patient with double depression is an infrequent clinical condition. In our experience,[1] major depressive disorder co-occurs in almost 20% of patients with a principal diagnosis of BMS, with a significant difference in comparison to matched non-BMS controls, but a lifetime diagnosis of dysthymia is present in less than 7% of these patients, with no statistical difference from controls. In conclusion, the infrequent occurrence of BMS in patients with double depression may further suggest that this association depends on drug treatment.

Conversely, the association of BMS symptoms with several antidepressants and not with others is difficult to interpret. Moreover, we found another case report[2] describing the onset of BMS symptomatology after 4 weeks of therapy with clonazepam in a 52-year-old woman treated for anxiety disorder; previous treatment with alprazolam did not improve anxiety symptoms, but was not associated with BMS. The association of BMS with a wide range of drugs conflicts with the observation of great differences among drugs of the same class, and this leads us to believe that BMS is not related to a pharmacologic effect.

Concerning the daily dose, oral symptoms occurred with 30 mg/day of fluoxetine and with 100 mg/day of sertraline, but did not occur with lower doses (from Levenson's letter, we do not know what dose of venlafaxine was associated with BMS). This is another interesting finding, but we are unable to discuss it.

The patients with BMS whom we treated with amisulpride and with SSRIs (paroxetine and sertraline) were different from the patient described in Levenson's case report, because we excluded patients with comorbid major depressive disorder.[3] Furthermore, our sample was treated with a low dose of drug (sertraline was given at 50 mg/day). No worsening of BMS was observed in any patients at any time.

We are now studying the clinical and therapeutic features of BMS comorbid with major depressive disorder, because we hypothesize that in these cases BMS has a different course and prognosis. Our preliminary impression is also that in these patients the treatment of BMS is much more difficult. We did not find a relationship between previous or ongoing treatment with antidepressants and onset of BMS, but we now believe the issue merits investigation in light of the interesting report by Levenson.

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

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## Nutritional Approach to Bipolar Disorder

**Sir:** Kaplan and colleagues[1] are to be commended for their pioneering nutritional approach to treating bipolar disorder. Their clinical report described the open-label trials of 14 adults with bipolar disorder who were treated with E.M.Power+ (EMP), a mixture of essential minerals, vitamins, and other nutrients, developed by David L. Hardy and Anthony F. Stephan, which is marketed by Evince International. While perhaps startling initially, this novel treatment approach appears to offer substantial benefit. Popper[2] has briefly described successful clinical use in some cases, and I report here on my own experience with this same nutrient supplement.

Impressed by a striking response in a patient who learned of this supplement on the Internet, I began to discuss this option with other patients in my private clinical practice. After discussing alternative available treatments, the nature of this new approach, and the lack of controlled data regarding its use, I gave some treatment-resistant patients the option to try EMP under careful observation. I have now worked with EMP in treating 19 adults (mean age = 38 years; range, 18–68) with DSM-IV-TR bipolar I (N = 14) or bipolar II (N = 5) disorder, who were followed for a mean of 13 months (range, 5–21). At the time of starting EMP, 16 patients were already receiving pharmacotherapy (mean = 2.7 psychiatric medications). After gaining some experience in using EMP, I elected to start 3 unmedicated (at the time; not medication-naive) patients on this supplement.

Following the usage described by Hardy and Stephan[3] for acute phase treatment of adults, the patients were started on 32 EMP capsules daily (taken as 8 q.i.d.). Most patients experienced mild transient gastrointestinal symptoms, including nausea (6 patients), loose bowels or diarrhea (7 patients), burning stomach pain (2 patients), and stomach ache (1 patient). Most patients experienced nausea if they took EMP without food. One patient developed apparent moderate gastritis with stomach ache that responded well to standard medical treatment. Two patients described mild transient headaches. Two patients switched from depressed mood to mild hypomania.

By clinical global estimate, 12 of the 19 patients showed marked clinical improvement, 3 showed moderate improvement, and 1 showed mild improvement. Thirteen patients (10 marked responders, 3 moderate responders) were able to completely discontinue psychiatric medications over a mean of 5.2 weeks (range, 3–10 weeks) and remain stable on EMP alone. Of the 12 showing marked improvement, 10 have remained on EMP (current follow-up mean length = 13 months; range, 5–21). One of the 3 moderate responders has also continued on EMP, so that 11 of 19 patients have chosen to remain on EMP rather than psychiatric medications.

Of the other 8 patients, 1 was lost to follow-up. Four discontinued EMP because of gastrointestinal problems. Three had recurrent symptoms, stopped EMP, and resumed psychiatric medication.

It is clear that the effectiveness and safety of EMP remain to be established in controlled trials, but this approach does appear to represent an exciting potential direction for new research in bipolar disorder.

*Dr. Simmons reports no financial or other relationships relevant to the subject matter of this letter.*

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## Drs. Simpson and Kaplan Reply

**Sir:** Dr. Simmons' observations confirm our report[1] that a micronutrient treatment has therapeutic effects in bipolar effects in bipolar patients, a finding supported also by Popper's clinical experience.[2] With a third observer describing a high response rate, this nutritional approach might begin to take on increasing credibility, but it is important to note that no controlled trials have been reported yet.

The conciseness of Dr. Simmons' report prevented his providing details of the transition from conventional medications to this micronutrient treatment, but the prior reports describe interactions between micronutrients and conventional psychiatric medications that are unexpectedly strong and significantly complicate the clinical management of drug-treated patients. We support Popper's advice[2] to physicians against use of E.M.Power+ in patients currently taking psychiatric medications, unless they have solid and ongoing consultation with an experienced advisor. Instead, physicians who are inexperienced in the use of micronutrient treatment would be wise to restrict its use to unmedicated patients.

While the accumulation of similar anecdotal observations from multiple clinicians should counter initial skepticism, con-

trolled studies are needed to clarify whether micronutrient treatment represents an important new direction for bipolar research.

*The open-label trial[1] was supported in part by the Alberta Children's Hospital Foundation and the Alberta Science and Research Authority, Edmonton, Alberta, Canada; and Evince International, Farmington, Utah (who provided the E.M.Power+ supplement free of charge).*

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## A Case Report of Olanzapine-Induced Fecal Incontinence

**Sir:** Fecal incontinence is a socially devastating and embarrassing condition. We report a case of primary insomnia that did not respond to various anxiolytics and sedative drugs. Eventually, olanzapine was added to the patient's regimen of minor tranquilizers. Although the patient showed improvement in sleep duration, he developed fecal incontinence. Withdrawal of olanzapine resulted in complete recovery from the incontinence.

***Case report.*** Mr. A, a 65-year-old man, presented with a history of primary insomnia (DSM-IV criteria) of 20 years' duration. The patient claimed that he would sleep for only 1 to 2 hours per night, and, in the daytime, due to lack of sleep, he would feel restless, irritable, and anxious and had poor concentration and decreased memory. During a 5-year period, he was treated with various anxiolytic and sedative drugs with no improvement in sleep. In July 2001, he was put on treatment with lorazepam, 2 mg, and zolpidem, 10 mg, at night for 15 days. Due to lack of response, olanzapine, 2.5 mg, was added at nighttime.

With this combination, Mr. A's total sleep time was increased from 2 hours to 4 hours with no daytime symptoms, but he noticed passage of stool in his clothes without being able to control the motion before reaching the toilet. This fecal incontinence would occur mostly in the morning, even after the patient had attended to proper toilet activities. The frequency of incontinence varied from 1 to 3 times per day, and it was so obvious that others could notice the patient's soiled clothes. The patient continued the same drug regimen for 20 days and continued to have fecal incontinence during this period.

In August 2001, during follow-up, oral olanzapine treatment was stopped. The next day, Mr. A observed complete recovery of fecal incontinence. He was seen by a gastroenterologist on the second day after stopping olanzapine to rule out any organic cause for the fecal incontinence. The findings of a per rectal examination were normal. No rectal prolapse was found, and anal sphincter tone was normal. No hemorrhoids or excoriations were found. A sigmoidoscopic examination showed normal rectal and sigmoid colon. A laboratory examination also did not suggest organic lesions as a cause of the incontinence. Mr. A had no history of urinary incontinence and was not suffering from any medical or neurologic disorder.

The literature contains reports of clozapine- and olanzapine-induced urinary incontinence that were treated successfully by using an α-adrenergic agonist (ephedrine).[1,2] To our knowledge, this case report is the first in which fecal incontinence was observed in association with olanzapine treatment. The specific mechanism of incontinence in this case is difficult to determine. The internal anal sphincter receives a stimulatory adrenergic innervation. A previous study[3] showed that abnormalities in the adrenergic innervation of the internal anal sphincter were seen in cases of idiopathic fecal incontinence. Recent research has successfully demonstrated the feasibility of an adrenergic agonist (topical phenylephrine) in raising resting anal tone in patients with fecal incontinence.[4] Olanzapine also possesses significant α-adrenergic antagonist effects,[5] which may be a possible explanation for the occurrence of fecal incontinence.

One can argue that the combined effect of olanzapine and other sedative drugs could have caused fecal incontinence, but complete recovery from incontinence following withdrawal of olanzapine is sufficient evidence to document that olanzapine can cause fecal incontinence. Our case would have been more convincing had we reexposed the patient to experimentally prove the point, but we believed this approach to be unethical.

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

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## Adjunctive Quetiapine Treatment of the Polydipsia, Intermittent Hyponatremia, and Psychosis Syndrome: A Case Report

**Sir:** Excessive fluid intake by psychotic patients can produce significant morbidity and possibly death due to water intoxication and hyponatremia. In patients with chronic schizophrenia, the prevalence of polydipsia is estimated between 6% and 20%.[1] In a subset of these patients, fluid intake overwhelms the kidney's normal excretory capacity and produces symptomatic, dilutional hyponatremia, known as the *polydipsia, intermittent hyponatremia, and psychosis syndrome* (PIP).[2] The symptoms of PIP range from mild cognitive deficits to seizures, coma, and death. While the pathophysiology is poorly under-

**Table 1. Studies and Case Reports of Clozapine, Risperidone, and Olanzapine Treatment of PIP**

| Publication | Type | Study Duration | Drug | Parameters | Results |
|---|---|---|---|---|---|
| Kar et al, 2002[10] | Case report | 2 y | Risperidone | $Osm_{serum}$, $Osm_{urine}$ | – |
| Kawai et al, 2002[11] | Open-label study (N = 6) | 9 mo | Risperidone | DW, USG, Osm, $Na_{serum}$ | – |
| Kruse et al, 2001[12] | Case report | 2 y | Olanzapine, risperidone | DW | Risperidone +/– Olanzapine +/– |
| Canuso and Goldman, 1999[4] | Open-label study (N = 8) | 24 wk | Clozapine | $Osm_{serum}$ | + |
| Kern et al, 1997[13] | Case series (N = 2) | 24 wk | Risperidone | DW | + |
| Littrell et al, 1997[14] | Case report | 1 y | Olanzapine | $Na_{serum}$ | + |
| Millson et al, 1996[15] | Open-label study (N = 8) | 11 mo | Risperidone | DW | – |
| Spears et al, 1996[8] | Open-label study (N = 11) | 1 y | Clozapine | $Na_{serum}$, DW, $Osm_{serum}$, $Osm_{urine}$ | + |
| Wakefield and Colls, 1996[9] | Case report | 18 mo | Clozapine | $Na_{serum}$, $Osm_{serum}$ | + |
| Landry, 1995[16] | Case report | 13 mo | Risperidone | $Na_{serum}$ | + |
| Henderson and Goff, 1994[5] | Observational study (N = 40) | 6 mo | Clozapine | $Na_{serum}$ | + |
| Lyster et al, 1994[7] | Retrospective study (N = 4) | 20 mo | Clozapine | $Na_{serum}$ | + |
| Lee et al, 1991[6] | Case report | 20 wk | Clozapine | DW | + |

Abbreviations: DW = diurnal weight change, Na = sodium, Osm = osmolality, PIP = polydipsia, intermittent hyponatremia, and psychosis syndrome, USG = urine specific gravity. Symbols: + = sustained symptom improvement, – = little improvement in symptoms, +/– = some improvement, but not sustained.

stood, some authors have attributed the hyponatremia to disturbances in antidiuretic hormone function.[3] Primary management involves limiting water intake, often difficult in the outpatient setting. There have been some published case reports and open-label studies suggesting clozapine as an effective pharmacotherapy for PIP.[4–9] Published case reports of resolution of PIP with olanzapine and risperidone are contradictory (Table 1).[10–16] There have been no published reports of treating PIP with quetiapine.

***Case report.*** Mr. A is a 42-year-old white man with a history of chronic disorganized schizophrenia (DSM-IV) since 1982. He has had 8 psychiatric admissions since his diagnosis, and his baseline mental state is characterized by negative symptoms, thought disorganization, and limited executive functioning. Once a successful Air Force medical specialist and college student studying premedicine, he is now considered totally disabled and lives in a closely supervised group home. His initial treatment with traditional antipsychotics (haloperidol, thioridazine, and fluphenazine) was unsuccessful, and he is considered treatment refractory. As newer agents became available, trials of risperidone and olanzapine were attempted with limited success. The patient refused to consider clozapine.

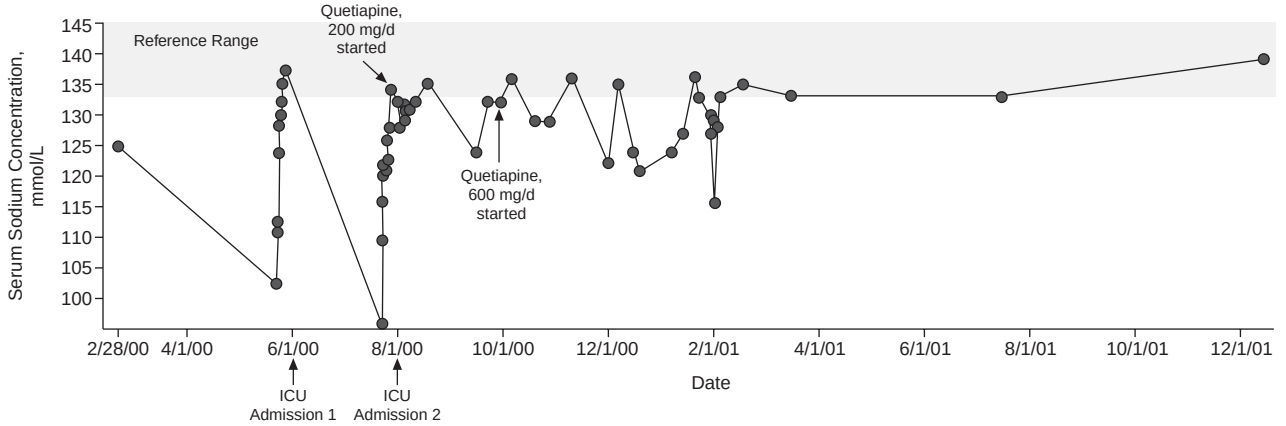
At routine follow-up in February 2000, Mr. A's laboratory results revealed a serum sodium concentration of 125 mmol/L and urine specific gravity of 1.005. Three months later, the patient was hospitalized for symptomatic hyponatremia with serum sodium concentration of 104 mmol/L, urine specific gravity of 1.009, serum osmolality of 233 mOsm/kg $H_2O$, and urine osmolality of 126 mOsm/kg $H_2O$ on admission. At the time, his psychotropic regimen consisted of olanzapine (20 mg/day) and haloperidol (30 mg/day). In July 2000, he presented to the local Veterans Affairs medical center complaining of slurred speech, unsteady gait, and frequent falls with injuries to his face and neck. His live-in caregiver provided additional history that the patient had been consuming 20 to 30 liters of water per day for several months. In the emergency department, the patient's serum sodium concentration was 96 mmol/L; urine specific gravity, 1.002; serum osmolality, 200 mOsm/kg $H_2O$; and urine osmolality, 27 mOsm/kg $H_2O$. The patient was admitted to the intensive care unit (ICU). Despite profound hyponatremia, no seizures were reported, and neurologic examination revealed only dysarthria. Management in the ICU consisted of complete free water restriction, intravenous infusion of normal saline at 70 $cm^3$/h, and close monitoring of serum sodium concentration. A correction of less than 12 mmol/L/day of sodium was desired to prevent central pontine myelinosis. Following stabilization of hyponatremia, the patient was started on treatment with quetiapine (200 mg/day) and continued on treatment with haloperidol (30 mg/day).

At the time of discharge, outpatient treatment involved behavioral and pharmacologic interventions to manage both the PIP and schizophrenia. Over the course of 2 months, quetiapine was increased to 600 mg/day and haloperidol was tapered down to 5 mg/day. With the exception of 1 acute psychotic deterioration that occurred when haloperidol was discontinued, the patient's psychiatric symptoms responded well to treatment. In the first 20 weeks after his discharge from the hospital, Mr. A's compulsive drinking behaviors continued, as evidenced by both residential staff reports and afternoon urine specific gravities in the low-normal range (1.007–1.008). Despite evidence of continued excessive water intake, the patient's afternoon serum sodium concentrations improved with less variability within a few weeks and normalized within 6 months (Figure 1).

Chronic $D_2$ blockade has been shown in animals to induce abnormal release of angiotensin II, a dipsogen.[3] In humans, chronic $D_2$ blockade is associated with increased peripheral response to angiotensin II. Although the profound effects of angiotensin II on thirst and drinking in animals have not been reproduced in healthy human subjects, angiotensin II levels are elevated in pathologic conditions associated with increased thirst such as diabetes mellitus. These findings suggest that chronic treatment with first-generation antipsychotic agents may actually increase the likelihood of polydipsia. Furthermore, the corrective and stabilizing effect of the second-generation antipsychotic clozapine on PIP has been attributed to its relative dopamine $D_2$ receptor sparing.[3]

Like clozapine, quetiapine has a higher affinity for 5-$HT_2$ than dopamine $D_2$ receptors,[17] and research suggests that quetiapine has significantly lower binding affinity for $D_2$ than risperidone or olanzapine.[18] If $D_2$ receptor sparing is an important component of treating PIP, then quetiapine could be hypothesized to have greater benefits in treating PIP compared with other second-generation antipsychotics.

**Figure 1. Serum Sodium Concentrations in a Schizophrenia Patient With PIP[a]**




[a]Reference values for serum sodium concentration: low, 133 mmol/L; high, 145 mmol/L.
Abbreviations: ICU = intensive care unit, PIP = polydipsia, intermittent hyponatremia, and psychosis syndrome.

One limitation to this report is that during the treatment phase with quetiapine, haloperidol was being tapered and discontinued. Chronic haloperidol treatment could have contributed to the patient's developing PIP; thus, tapering off this first-generation antipsychotic with high $D_2$ affinity could have improved his water balance. In addition, staff efforts at water restriction, though perceived as unsuccessful, may have played a greater role in the patient's sodium stabilization than medication. Nonetheless, the role of $D_2$ receptor binding in PIP, and quetiapine's potential in particular, warrants further study.

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

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## Treatment of Leuprolide-Induced Depression With Intramuscular Testosterone: A Case Report

**Sir:** Hypogonadal states occur naturally or with gonadotropin-releasing hormone (GnRH) agonist administration. Hypogonadism in men, defined as testosterone levels < 350 ng/dL, may cause fatigue, memory loss, and diminished libido.[1] Naturally occurring hypogonadism in men and women has been associated with depressed mood.[2,3] Cases of depression and mania have been associated with GnRH agonists.[4–6]

GnRH agonists are often utilized for treatment of prostate cancer, the most common malignancy in men. The rationale is that some prostatic malignancies may be exacerbated by testos-

terone and that tumor size may be reduced by decreasing testosterone. The following case describes the emergence of major depressive disorder with the use of the GnRH agonist leuprolide in the treatment of prostate cancer.

***Case report.*** Mr. A is a 70-year-old white man who presented with depressed mood of 7 weeks' duration, with onset, per the patient's report, within 1 week of receiving a depot leuprolide intramuscular injection for adenocarcinoma of the prostate. He reported weakness; anhedonia; decreased energy, appetite, concentration, and sleep; hot flushes; anxiety; restlessness; and suicidal ideation. A DSM-IV diagnosis of major depressive disorder was made 1 month after the leuprolide injection. Under the care of a physician, Mr. A received sertraline, 50 mg/day, for 2 weeks, without benefit, and citalopram, 20 mg/day, for 5 days, with intolerable anxiety. He then used lorazepam, 0.5 mg/day, for 2 weeks with minimal benefit. Mr. A had no prior psychiatric history, and at the time of presentation to our clinic, he was using no psychotropic medications. He refused treatment with antidepressants. Electrolytes, glucose, calcium, thyroid-stimulating hormone, liver function tests, and a complete blood count were within normal limits. The patient's prostate-specific antigen (PSA) level was 1.8 ng/mL (normal range, 0–4.0 ng/mL), and his total testosterone level was 26 ng/dL (normal range, 350–720 ng/dL), decreased from a PSA level of 6.0 ng/mL and total testosterone level of 139 ng/dL 1 year prior. It is undetermined why the patient's testosterone level was low 1 year prior; the patient's urologist attributed it to diurnal fluctuations in testosterone levels.

The patient attributed his depressive symptoms to "testosterone deficiency" and pursued testosterone therapy after a discussion of the risks and benefits. The following day, Mr. A received 200 mg of depot testosterone intramuscularly. Within 1 day, he reported his depression "gone." His appetite and libido improved. He denied anhedonia and reported improved sleep and concentration and decreased anxiety. One week later, he received another injection of 200 mg. A week after the second injection, his total testosterone level was 673 ng/dL and free testosterone level was 142.1 pg/mL, both within normal limits. Two months later, Mr. A was "back to normal" without anxiety or depressive symptoms. A follow-up PSA test revealed a level of < 0.1 ng/mL; total testosterone was 45 ng/dL, and free testosterone was 8.7 pg/mL, both below the normal range.

Treatment with GnRH agonists may precipitate depression. The package insert for leuprolide lists depression as an adverse event that occurs in approximately 23% of patients treated for 6 months.[7] Also, the package insert for another GnRH agonist, goserelin acetate, lists the incidence of depression at 54%.[8] GnRH agonists may cause depression by induction of a hypogonadal state. This has never been definitively proved, and the possibility that GnRH agonists cause depression independently of the production of a hypogonadal state cannot be ruled out. A bidirectional, saturable transport of GnRH across the blood-brain barrier has been demonstrated,[9] supporting a possible central effect of GnRH agonists that could mediate mood.

This is the first case report of testosterone therapy for leuprolide-induced depression. However, a placebo-controlled study of testosterone replacement in hypogonadal men with depression failed to demonstrate a significant difference between testosterone and placebo.[10] The subjects had a mean baseline testosterone level of 266.1 ng/dL, only slightly below the normal range. Therefore, the degree of hypogonadism may be important in the emergence of depressive symptoms and the response to treatment. It is also possible that a rapid decline in testosterone precipitates depression in a subgroup of men.

Our patient still exhibited low levels of serum testosterone 2 months after receiving testosterone injections, despite cessation of leuprolide therapy. Normalization of testosterone levels after GnRH therapy requires, on average, several months.[11] In this case, although total and free testosterone levels were decreased below normal 2 months after the testosterone injection, the decline may have been slower than that which occurred after the leuprolide injection.

The interaction between mood and testosterone may be especially important in a subgroup of patients. Seidman et al.[12] have demonstrated that some men may be genetically predisposed to experience depressive symptoms when total testosterone levels are low. In their study of 1000 men, depression was inversely related to total testosterone levels only in those men with a specific isotype of the androgen receptor (those with shorter CAG repeat length [RL]). Pope et al.[13] also demonstrated that the relationship between mood and testosterone may vary greatly and that subgroups of men may be differently affected by administration of exogenous testosterone. In men who received supraphysiologic doses of testosterone, although the majority of men (84%) exhibited a minimal psychiatric response, 16% demonstrated significant symptoms of hypomania or mania.

The benefits of treating GnRH agonist–induced depression in men with testosterone must be balanced against the risks of exacerbating prostate cancer. Prostate cancer is considered a contraindication to androgen therapy.[14] However, while data support a role for androgens in the development of prostate cancer, data are lacking to demonstrate that testosterone administration causes progression of prostate cancer.[15] Androgens appear to promote prostatic cell division and the indirect development of prostate cancer.[16] Although androgens are a necessary component for cell proliferation, evidence suggests that they do not directly stimulate cell proliferation. Careful discussion and consideration of the risks and benefits must occur before testosterone is used for depression in men with prostate cancer.

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

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## Hydroxyzine for Generalized Anxiety Disorder

**Sir:** A recent comprehensive review of pharmacologic approaches to generalized anxiety disorder (GAD)[1] referenced only 2 of the 5 publications available on the use of hydroxyzine in treatment of GAD. I present 2 other publications that report the effectiveness of hydroxyzine in relieving GAD and 1 that reports its effectiveness in relieving benzodiazepine withdrawal anxiety.[1]

One study enrolled 55 outpatients with comorbid anxiety and cardiovascular disease.[2] Patients received hydroxyzine for 28 days (daily dose = 50 mg). In 47 of 50 patients, Hamilton Rating Scale for Anxiety (HAM-A) scores dropped by a mean of 10 points. The reduction was most obvious in patients suffering from somatic anxiety. Hydroxyzine was reported to be "well tolerated and safe"(p45) in this patient group.[2] In another study, 29 patients with GAD were treated with hydroxyzine.[3] The patients were examined both before the treatment and on days 14 and 28 of treatment. Excellent and good Clinical Global Impressions scale results were observed in 66% of the patients. Unsatisfactory results were found in 10% of the cases. Reduction of the HAM-A total score by 50% or more was observed in 48% of the patients.[3] A multicenter, randomized, placebo-controlled study published data on 154 outpatients with GAD, who had been on treatment with 2 mg of lorazepam daily for at least 3 months.[4] They were withdrawn using hydroxyzine or placebo. Results proved a significant improvement of anxiety, a decrease of side effects in both of the groups treated with hydroxyzine, and a reduction of withdrawal symptoms in the hydroxyzine 50-mg group within 28 days.[4]

Hydroxyzine is a great alternative for benzodiazepine in acute and chronic anxiety reduction. Since 1993, I have prescribed hydroxyzine to hundreds of patients for this purpose. In a majority of the cases, the anxiety relief has been very positive. Having no addictive potential, hydroxyzine is a great alternative to all the benzodiazepines, barbiturates, and other sedatives used in treating anxiety symptoms. When switching a patient from a sedative to hydroxyzine, one must still take a good history and make sure to taper down the sedative (e.g., alprazolam) to reduce the likelihood of withdrawal seizures. I use a conversion formula of "25 mg of hydroxyzine is equal to 1 mg of lorazepam (or equivalent dose of a benzodiazepine)." In acute anxiety situations that require an intramuscular injection of 2 mg of lorazepam, I have given the "equivalent" 50-mg intramuscular injection of hydroxyzine with success. Dosing frequency is between 6 and 12 hours, depending on individual response. I do not recommend exceeding a total daily dose of 400 mg. In cases of alcohol intoxication or for patients who have a known seizure disorder, pending alcohol or other sedative, hypnotic, or anxiolytic withdrawal, I choose the traditional benzodiazepine (along with thiamine injection in case of known alcohol-induced neurotoxicity).

Hydroxyzine may also prove to be an efficacious agent for patients suffering from GAD. Most of the available literature on hydroxyzine presents it as an effective pharmacologic agent in GAD. Hydroxyzine is a better option than benzodiazepines and may deserve to be the secondary agent used to treat GAD if (or when) buspirone is not effective.

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

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