

# Letters to the Editor

## Efficacy of 17 $\beta$ -Estradiol on Depression: Is Estrogen Deficiency Really Necessary?

**Sir:** Ahokas and colleagues<sup>1</sup> recently published the results of an open-label study in which 23 women who suffered from severe postpartum depression (mean  $\pm$  SD Montgomery-Asberg Depression Rating Scale [MADRS] total score = 40.7  $\pm$  2.8; range, 35–45) received micronized 17 $\beta$ -estradiol (E<sub>2</sub>) sublingually for 8 weeks. The results were impressive: 39% of subjects experienced full remission of depression (MADRS total score  $\leq$  7) after 1 week of treatment, and almost 83% experienced full remission after 2 weeks. Two patients sustained antidepressant benefit at 4 weeks following treatment discontinuation. At baseline, 16 of 23 subjects were hypogonadal (serum E<sub>2</sub> level < 110 pmol/L), and all subjects had a serum E<sub>2</sub> level < 200 pmol/L. The authors suggest that an increase in serum E<sub>2</sub> levels with E<sub>2</sub> treatment may explain the antidepressant benefit obtained with the treatment as assessed by decrease in mean MADRS total scores. Ahokas and colleagues concluded that the antidepressant effect of estrogen replacement therapy may depend on the presence of a hypoestrogenic state.

The lack of a control group and, most importantly, the fact that the study recruited only depressed women with a low serum E<sub>2</sub> concentration (most of them with a serum E<sub>2</sub> level lower than the threshold value of gonadal failure) constitute evident limitations to examining this hypothesis. E<sub>2</sub> may treat postpartum major depressive disorders for reasons and/or mechanisms unrelated to restoration of normal serum E<sub>2</sub> level.

We recently examined the efficacy of E<sub>2</sub> for the treatment of depression in endocrinologically confirmed perimenopausal women.<sup>2</sup> We were unable to find a significant association between clinical response to treatment and serum E<sub>2</sub> levels at study entry or higher serum concentration of E<sub>2</sub> after 12-week E<sub>2</sub> treatment.<sup>2</sup> Of note, some depressed women had a satisfactory response to treatment with E<sub>2</sub> even though their serum E<sub>2</sub> levels remained relatively low (< 200 pmol/L) over the course of the study.

Ahokas and colleagues' finding of antidepressant effect of E<sub>2</sub> for the treatment of postpartum depression is in line with the results of a previous study<sup>3</sup> and consistent with the literature on perimenopausal and postmenopausal women. To date, trials in menopausal women that failed to detect antidepressant benefit of estrogens have used oral conjugated equine estrogen or estropipate.<sup>4,5</sup> In contrast, at least 2 double-blind, placebo-controlled trials with E<sub>2</sub> (delivered transdermally) have shown superior efficacy of E<sub>2</sub> for the treatment of major and minor depression.<sup>2,6</sup>

Our remarks should not diminish the potential role of hormone interventions as a monotherapy or augmenting strategy for the treatment of reproductive-related mood disturbance. However, the exact mechanism by which estradiol may exert an antidepressant effect in puerperal or perimenopausal women remains unclear and probably involves a series of steps<sup>7</sup> that extend beyond the correction of a presumed estrogen deficiency.

*The authors report no financial affiliation or other relationship relevant to this topic.*

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### Dr. Ahokas and Colleagues Reply

**Sir:** We are grateful to Dr. Soares and colleagues for their comments on postpartum depression and our finding of positive treatment effect with natural 17 $\beta$ -estradiol (E<sub>2</sub>)<sup>1</sup> and for reporting their similar observation in perimenopausal women.<sup>2</sup>

We wish to clarify some of the points raised. Our study population was not chosen on the basis of low serum estradiol concentration; consecutive patients were recruited because they had major depression with postpartum onset. The patients' low serum E<sub>2</sub> concentrations at baseline were a study finding. Many of our patients (14/23) had been resistant to conventional psychiatric treatment methods, but responded successfully to treatment with E<sub>2</sub>. The aim of weekly measurement of serum E<sub>2</sub> concentration during treatment was to ensure the absorption of E<sub>2</sub> and the maintenance of serum E<sub>2</sub> levels within physiologic limits. Antidepressants were used as an adjunct therapy in 2 patients with low serum E<sub>2</sub> concentration and insufficient treatment effect with E<sub>2</sub> alone. Furthermore, the suggestion by Dr. Soares and colleagues that E<sub>2</sub> may treat postpartum major

depression without restoration of normal serum E<sub>2</sub> level is at least yet speculative and is not referenced.

The comparison of 2 age groups, young postpartum women versus perimenopausal women, and 2 treatment methods, sublingual versus transdermal, is difficult due to physiologic reasons. Serum E<sub>2</sub> concentration declines sharply from about 100,000 to 100 pmol/L or lower within a few days after parturition.<sup>3</sup> Ovarian E<sub>2</sub> production may recover slowly, and postpartum E<sub>2</sub> deficiency can be prolonged and profound, mimicking menopause. In perimenopausal women, estrogen levels fluctuate in a slowly declining manner, allowing several adaptation mechanisms for, e.g., the brain.

Furthermore, there are great interindividual and intraindividual variations in estradiol metabolism and serum concentrations.<sup>4</sup> The use of the transdermal method (patches) includes the risk of poor/nonabsorbers.<sup>5</sup> Measuring serum E<sub>2</sub> concentration only at baseline and endpoint of 12-week treatment<sup>2</sup> does not tell very much about the absorption and serum concentration of E<sub>2</sub> during the treatment, thus limiting the evaluation of the study.

The parenteral use of natural estrogen E<sub>2</sub> in our study<sup>1</sup> and in the study by Soares et al.<sup>2</sup> resulted in a similar positive treatment effect in different age groups. Obviously, there is a difference between parenterally administered natural estrogen and oral (e.g., equine) estrogens. Much further research is needed in the underrecognized, underresearched, and undertreated group of patients with postpartum psychiatric disorders.

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### Dystonia Induced by Mirtazapine

**Sir:** Mirtazapine is a new antidepressant that exerts its effects through antagonism at central  $\alpha_2$  receptors instead of through an uptake or enzyme inhibitor.<sup>1</sup> Unlike tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), mirtazapine enhances central noradrenergic and serotonergic activity by acting as an antagonist at central presynaptic  $\alpha_2$ -

adrenergic inhibitory autoreceptors and presynaptic  $\alpha_2$  heteroreceptors.<sup>2</sup> Mirtazapine is also a potent antagonist of serotonin 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, with minimal affinity for the 5-HT<sub>1</sub> receptor, thus incurring minimal occurrence of serotonergic side effects. To our knowledge, no report has linked dystonia as a side effect of mirtazapine. Here, we report a case of dystonia that ensued after mirtazapine therapy for depression.

**Case report.** Mr. A, a 63-year-old man with a history of hypertension, type 2 diabetes mellitus, and heroin snorting, presented with acute onset of upper-extremity dystonia for 1 day. At presentation, examination revealed stable vital signs. The only positive findings were the visible slow, irregular, and myoclonic involuntary movements of his proximal upper extremities and neck and twitching of the pectoralis major muscles. His strength was 5/5 and symmetrical in all extremities. No sensory deficit or cerebellar signs were present. His deep tendon reflex was 2+ and symmetrical. A computed tomographic (CT) scan of Mr. A's head showed an old lacunar infarct. Magnetic resonance imaging (MRI) and magnetic resonance angiography of his head and neck were performed. The results were consistent with those of the CT scan. He was taking quinapril for hypertension, which was well controlled. Ten days prior to admission, Mr. A was started on mirtazapine, 15 mg p.o. q.d., by his psychiatrist for DSM-IV depression. At admission, complete blood count, electrolytes, renal, and liver function test results were within normal range. His last heroin use was 3 days prior to admission. A urine toxicology screen showed the presence of opiates and showed no trace of cocaine, amphetamine, phencyclidine, marijuana, and barbiturates. Mr. A did not take mirtazapine on the day of admission. After admission, mirtazapine was discontinued. On the second day, his symptoms slightly improved. Two days later, his symptoms completely resolved.

We implicate mirtazapine for the appearance of dystonia in this patient. The onset of dystonia after initiation of mirtazapine and prompt recovery after drug discontinuation led to the impression that it was a drug-induced phenomenon. Dystonia and akathisia may be mediated through the 5-HT<sub>2</sub> receptors. 5-HT<sub>2</sub> antagonists have been shown to have some activity to promote motor function in states of reduced dopamine release.<sup>2</sup> Mirtazapine has been shown to be effective in treating resting tremor in patients with Parkinson's disease.<sup>3</sup> Dystonias and akathisia have been reported with SSRIs.<sup>2</sup> The mechanism involved was the stimulation of 5-HT<sub>2</sub> receptors that induced an inhibitory action on dopamine release. However, mirtazapine is an intrinsic 5-HT<sub>2</sub>-receptor blocker. The mechanism of mirtazapine-induced dystonia is unclear. In our case, drug-drug interaction is unlikely; the patient is taking only an angiotensin-converting enzyme inhibitor, quinapril, for hypertension and insulin for diabetes mellitus. Drug interaction with mirtazapine mainly involves centrally acting drugs, such as clonidine.<sup>4</sup> We cannot be certain that heroin influenced this reaction; therefore, we searched MEDLINE using the keywords *heroin* and *dystonia*. Only 1 case of generalized dystonia after first-time intranasal heroin abuse was reported.<sup>5</sup> In that case, MRI of the brain demonstrated diffuse organic cerebral damage. In our case, the patient has a long history of intranasal heroin abuse. More importantly, MRI of the brain showed no acute process. So, we conclude that heroin is unlikely to be the cause of Mr. A's dystonia. Why he had only upper-extremity dystonia remains unclear. Recently, mirtazapine-induced restless legs syndrome has been reported.<sup>6</sup> Dystonia is a rare side effect of mirtazapine, with an incidence of 1/100 to 1/1000.<sup>7</sup> To our knowledge, no case report associating dystonia and mirtazapine has been published in the literature. Herein, we report a single case of dystonia that

occurred after the introduction of mirtazapine, with rapid resolution after discontinuation of the drug. While an infrequent event, dystonia is a possible adverse effect of mirtazapine. Therefore, the risk of dystonia should be taken into consideration when initiating mirtazapine therapy.

*The authors report no financial affiliation or other relationship relevant to this topic.*

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**Resolution of Hyperglycemia on Risperidone Discontinuation: A Case Report**

**Sir:** Because atypical antipsychotic agents are being increasingly prescribed as first-line agents in the treatment of psychotic symptoms, concern about treatment-emergent weight gain and hyperglycemia has increased. A MEDLINE search from 1995 to 2001 using the keywords *hyperglycemia*, *risperidone*, *diabetes*, *olanzapine*, *quetiapine*, and *clozapine* revealed several reports of hyperglycemia associated with clozapine<sup>1–5</sup> and olanzapine,<sup>5–9</sup> but only 2 reports of risperidone-associated hyperglycemia.<sup>10,11</sup> Diabetes mellitus was an infrequently observed (0.1%–1%) event during premarketing evaluation of risperidone.<sup>12</sup> We describe a patient whose hyperglycemia resolved soon after discontinuation of risperidone treatment.

**Case report.** Ms. A, a 39-year-old white woman, was hospitalized continuously at our long-term care facility from June 1994 to June 2000 with chronic undifferentiated schizophrenia (DSM-IV criteria). She was human immunodeficiency virus (HIV)- and hepatitis C antibody-seropositive. Her laboratory values between 1994 and 1997 showed elevated triglyceride, elevated liver enzyme, and normal fasting blood glucose levels.

Throughout hospitalization, her HIV-seropositive status was stable. She was taking a constant dose of nevirapine, stavudine, and didanosine. She had no active signs of hepatitis, hypercholesterolemia was well controlled on a constant dose of gemfibrozil, and the degree of hypertriglyceridemia did not significantly fluctuate.

In June 1994, at the time of admission, Ms. A was taking a combination of haloperidol decanoate, 200 mg/month; paroxetine,

20 mg/day; and risperidone, 6 mg/day. From October 1995 through February 1998, her risperidone dose was raised to 8 mg/day. Haloperidol decanoate treatment was discontinued on December 1, 1997, to evaluate whether the patient's improvement could be maintained with risperidone alone. In February 1998, her dose of risperidone was raised to 12 mg/day. However, because of extrapyramidal symptoms, the dose was reduced to 6 mg/day within 1 month. She remained on this dose until March 1999, when haloperidol decanoate was reintroduced into her treatment regimen. Risperidone was then tapered and discontinued by May 1999 along with paroxetine. She was discharged in June 2000 on haloperidol decanoate treatment.

The first indication of abnormal glucose tolerance was a fasting blood glucose level result in October 1997 that was marginally abnormal at 127 mg/dL. A fasting blood glucose level result in February 1998 was abnormally high at 328 mg/dL. Ms. A was started on glipizide treatment, and by mid-December 1998, good glycemic control was achieved at a dose of 7.5 mg in the morning and 5 mg in the evening.

Within a month of discontinuation of risperidone, Ms. A's blood glucose values began to decline consistently. In June 1999, her dose of glipizide was decreased to 2.5 mg in the morning and 5 mg in the evening; in July 1999, to 5 mg every other day; and in August 1999, to 2.5 mg every other day. Finally, glipizide was discontinued in October 1999. The patient's fasting blood glucose levels remained normal until her discharge in June 2000.

To our knowledge, this patient had no family history of diabetes and none of the classic risk factors (being African American, male, obese, etc.) commonly associated with the development of adult-onset diabetes mellitus except for hypertriglyceridemia that remained constant. Furthermore, development or resolution of diabetes mellitus cannot be attributed to body weight changes, since she had a fairly stable body mass index of 24 throughout hospitalization. A MEDLINE search from 1995 to 2001 using the keywords *diabetes* and *paroxetine* revealed no studies suggesting that paroxetine might contribute to the development or perpetuation of hyperglycemia. On the contrary, one study<sup>13</sup> suggests that SSRIs (fluoxetine) might improve insulin sensitivity.

Our patient was on risperidone treatment for almost 3 years before her hyperglycemia was recognized, making the causal relationship between risperidone and hyperglycemia somewhat questionable. However, the prompt remission of hyperglycemia on discontinuation of risperidone indicates its role in the perpetuation of hyperglycemia. We believe this to be the third published report suggesting a possible association between risperidone and hyperglycemia. These reports suggest a need for careful monitoring of fasting serum glucose level in patients being treated with risperidone.

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### Urinary Incontinence With Mirtazapine

**Sir:** Urinary incontinence is an uncommon side effect of antidepressant therapy. To our knowledge, based on a literature review incorporating a MEDLINE search from 1996 to present, there is no report of urinary incontinence with mirtazapine. We report a patient who developed nocturnal urinary incontinence while taking mirtazapine.

**Case report.** Mr. A, a 48-year-old white single man with a history of major depressive disorder without psychotic symptoms (DSM-IV criteria), was seen at an inpatient psychiatry unit for management of treatment-resistant depressive symptoms with suicidal ruminations. He also had permanent anxiety symptoms. He had failed treatment with paroxetine, fluoxetine, and electroconvulsive therapy. At the time of admission, his medications were venlafaxine, 450 mg/day; trazodone, 100 mg at bedtime; and hydroxyzine, 25 mg 3 times a day. He was receiving his present regimen of treatment for the last 4 weeks without much response. After reviewing his history, the treatment team decided to switch him to mirtazapine. On the fourth day after admission, he was started on mirtazapine, 15 mg at bedtime, and venlafaxine was reduced to 300 mg. On the same day, hydroxyzine was stopped and clonazepam, 1 mg twice a day, was started for his anxiety. Trazodone was also discontinued that day, and venlafaxine was tapered and subsequently discontinued over the next week. By the end of 2 weeks, his medications were mirtazapine, 30 mg at bedtime, and clonazepam, 1 mg 3 times a day. At that time, Mr. A complained of an episode of enuresis, which recurred after 3 days. He was examined by an internist, and results of repeat routine laboratory tests were within normal limits. By the end of the third week, his anxiety symptoms improved, but he had only some improvement in

his depressive symptoms, so his mirtazapine dosage was raised to 45 mg/day. Two days after his mirtazapine dosage was raised, he again had an episode of enuresis, which was reported on a daily basis after that; his clonazepam dosage was reduced to 1 mg/day that same day. Four days after his clonazepam dosage was reduced, he continued to have enuresis. Seven days after clonazepam was reduced, with no improvement in enuresis, mirtazapine was reduced to 30 mg. His enuresis improved, but he still had enuresis about once every 2 to 3 days. For control of his anxiety symptoms, clonazepam was slowly raised back to 3 mg/day. His anxiety symptoms improved, but there was no change in the frequency of enuresis. He was advised restriction of fluid intake in evening and also awoke at night to void urine. These measures afforded little help, and the patient was very distressed due to this problem. After a risk-benefit discussion with the patient, he opted to be taken off mirtazapine treatment. He was started on citalopram, 20 mg/day, and his mirtazapine dosage was reduced to 15 mg/day. Enuresis decreased in frequency and finally disappeared after mirtazapine was completely stopped. At the time of this report (3 months since mirtazapine was discontinued), the patient has reported no episode of enuresis. His present medications are citalopram, 40 mg/day, and clonazepam, 3 mg/day, on which he was discharged from the hospital.

Mirtazapine is a potent antagonist of central  $\alpha_2$ -autoadrenergic and  $\alpha_2$ -heteroadrenergic presynaptic receptors and serotonin-2A/2C (5-HT<sub>2A/2C</sub>) and 5-HT<sub>3</sub> receptors as well as histaminergic H<sub>1</sub> postsynaptic receptors.<sup>1</sup> Mirtazapine is also a peripheral  $\alpha_1$ -adrenergic antagonist, which might be responsible for relaxation of the trigone and the sphincter muscles in the base of urinary bladder leading to the decreased resistance to urinary outflow.<sup>2,3</sup> True urinary incontinence has not been reported as a well-known side effect of antidepressant therapy in the review literature, although the Physicians' Desk Reference lists it as infrequent with mirtazapine (1/100–1/1000 patients). There have been 2 cases reported of urinary incontinence on venlafaxine treatment.<sup>4</sup> The mechanism of action of drug-induced urinary incontinence is not fully understood, but genitourinary and sexual side effects associated with antidepressant therapy should be monitored to increase patient comfort and compliance with the treatment.

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

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### Efficacy of Continuation Treatment With *Hypericum perforatum* in Depression

**Sir:** Several studies<sup>1-3</sup> have suggested that *Hypericum perforatum* (St. John's wort) is efficacious for the treatment of mild-to-moderate depression. Most of these studies involved short-term treatment of an acute depressive episode.<sup>1,2</sup> There are no extensive data from studies on whether *Hypericum* is an efficacious maintenance treatment for depression. We have previously reported<sup>3</sup> that a standardized extract of *Hypericum* (LI-160, 900 mg/day) was as effective as sertraline (75 mg/day) in reducing depression in a group of 28 patients with a DSM-IV diagnosis of single or recurrent major depressive disorder and an initial mean 17-item Hamilton Rating Scale for Depression (HAM-D) score of 21.5 during a double-blind trial of 7 weeks of treatment with either *Hypericum* or sertraline.

This letter reports a follow-up study of a subset of 18 patients in the original study who received open-label *Hypericum* (LI-160, 900 mg/day) continuation therapy for a 6-month period. The study was approved by the Institutional Review Board of St. John's Episcopal Hospital, and all study patients provided informed written consent before entering the study. These patients had shown a clinical response to double-blind study medication treatment with either sertraline or *Hypericum*. Of the 18 patients who entered the continuation study, 2 were terminated early because of insufficient response (i.e., possible relapse; criteria were a HAM-D<sup>4</sup> increase  $\geq 50\%$  and/or Clinical Global Impressions scale<sup>5</sup> change score of much worse). Additionally, 1 patient was terminated early due to an insomnia complaint, and 2 patients withdrew consent. In the last-observation-carried-forward analysis, the mean HAM-D score at the beginning of open-label treatment was 10.6 and at endpoint was 10.2. The 7 patients randomly assigned to *Hypericum* in the prior double-blind study showed a further small mean decrease in HAM-D scores by the end of the continuation phase (approximately 3 points; 25% decrease compared with continuation trial entry score), while the 11 patients originally randomly assigned to sertraline showed a small mean increase in HAM-D score at endpoint (approximately 1 point; 10%). These differences were not statistically significant in this small sample.

Our results suggest that *Hypericum* may be an efficacious continuation treatment for depression. Mean depression scores did not increase during longer-term continuation treatment, but remained around 10 and tended to show a minimal further decrease. The 11% (2/18) relapse rate is fairly similar to relapse rates reported in other studies of maintenance therapy of depression. In a meta-analysis of 27 antidepressant maintenance studies, Viguera and associates<sup>6</sup> computed an average relapse rate of 1.85%/month for patients maintained on continued antidepressant treatment; this is an 11.1% relapse rate at 6 months of maintenance treatment. In a study<sup>7</sup> of continuation therapy with venlafaxine, the relapse rate was 11% at 6 months in the antidepressant patients. In a study<sup>8</sup> of continued maintenance treat-

ment with fluoxetine or placebo, the relapse rate was estimated at 26.41% at 6 months of continued fluoxetine treatment. In one Italian study<sup>9</sup> of sertraline and fluvoxamine, relapse rates were somewhat lower; at 7 months, the rates were 6.2 for sertraline and 3.4 for fluvoxamine. One-year depression relapse rates for both drugs were 9.4%. The limitations of our study include the absence of a placebo group, a small sample size, and a relatively short duration. Further research, including longer-term, placebo-controlled, double-blind studies with a comparator drug, is needed to evaluate our preliminary finding. The recently published study by Shelton et al.<sup>10</sup> addressed some of these issues, but has not yet revealed continuation results.

*The authors report no financial affiliation or other relationship relevant to this topic.*

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