Hypophosphatemia and Neuroleptic Malignant Syndrome

To the Editors:

The neuroleptic malignant syndrome (NMS) is a rare but potentially fatal adverse event associated with the use of conventional and atypical antipsychotic medications. In addition to the commonly observed symptoms of fever, muscular rigidity, autonomic dysregulation, and delirium, several abnormalities in laboratory indices are also associated with NMS. Laboratory abnormalities commonly associated with NMS include elevations of serum creatine phosphokinase, decreased serum iron, and abnormalities in serum sodium. Less commonly reported in NMS are abnormalities in serum phosphate, although derangements of serum phosphate concentrations may be common and potentially associated with substantial morbidity and mortality. We briefly report on cases of hypophosphatemia associated with NMS and review some potential implications of this finding.

Phosphate is widely distributed in the body and essential for many physiological processes. The highest concentrations of phosphate are present in the skeleton, skeletal muscle, and viscera. The reference range of serum phosphate in humans is between 0.80 and 1.45 mmol/L. Most complications associated with serum phosphate abnormalities occur in moderate (serum phosphate 0.32–0.65 mmol/L) or severe (<0.32 mmol/L) states of phosphate depletion. Hypophosphatemia is associated with cardiac arrhythmias, reduced cardiac performance, respiratory failure, seizures, and coma. Rhabdomyolysis is also a potential complication of both hypophosphatemia and NMS. Common causes of hypophosphatemia include internal redistribution from the serum into other body compartments, decreased intestinal absorption, and increased urinary losses.

We previously described a case of NMS during treatment with risperidone and clozapine that was associated with moderate to severe hypophosphatemia (serum phosphate level 0.36 mmol/L), and a chart review of NMS diagnoses at our hospital revealed another case of NMS complicated by hypophosphatemia during treatment with haloperidol and quetiapine (serum phosphate level 0.52 mmol/L). Review of the literature revealed 10 additional cases of hypophosphatemia associated with NMS with phosphate levels reported in 3 cases. The average serum phosphate level in the 5 cases reporting serum phosphate was 0.38 mmol/L (range, 0.23–0.52 mmol/L). Unfortunately, baseline serum phosphate levels before the development of NMS were not reported. Another case described the development of NMS in a patient with cancer who had severe hypophosphatemia (serum phosphate level 0.06 mmol/L) before receiving antipsychotics or displaying symptoms of hypophosphatemia. Hypophosphatemia is not reported as a risk factor or potential sequela of NMS in major review papers and textbooks of this subject, and serum phosphate levels are infrequently reported in published case reports of NMS in the medical literature.

There are many potential mechanisms by which NMS may be associated with hypophosphatemia. Phosphate deficiency is an uncommon cause of hypophosphatemia except in malabsorption syndromes and states of severe malnutrition. Increased renal excretion of phosphate is an unlikely cause of hypophosphatemia in NMS as NMS is associated with renal failure, a condition more often resulting in hyperphosphatemia. Redistribution of serum phosphate from the serum to body tissues is the most common cause of hypophosphatemia in clinical settings and likely explains the association between hypophosphatemia and NMS. Redistribution of phosphate may occur in several pathological conditions associated with nonspecific acute-phase responses including respiratory alkalosis from hyperventilation, systemic inflammation (eg, sepsis), and states associated with increased levels of circulating catecholamines. Tachypnea resulting in hyperventilation, markers of inflammation including leukocytosis, decreased serum iron, and elevated serum catecholamines are all associated features of NMS providing support for the redistribution of phosphate during NMS as the mechanism of hypophosphatemia with this disorder. Hyperphosphatemia has also been observed in NMS, although less frequently than hypophosphatemia.

Calcium is also linked to phosphate homeostasis, and intracellular calcium has also been implicated in the pathophysiology of NMS. Chronic states of calcium depletion, hyperparathyroidism through the action of parathyroid hormone on phosphate reabsorption, and vitamin D deficiency may all contribute to hypophosphatemia. Calcium levels in cases of NMS associated with hypophosphatemia have been reported as decreased or within normal limits when calcium levels are reported. At present, it is uncertain whether hypophosphatemia is a risk factor or a consequence of NMS. Published case reports of NMS infrequently noted phosphate levels, making it difficult to determine if most NMS episodes are associated with abnormal levels of serum phosphate or whether phosphate levels were measured and not reported because they were within normal limits. Considering the potential complications associated with hypophosphatemia, clinicians are advised to be aware of this finding and to evaluate and monitor serum phosphate levels carefully in all individuals suspected of having NMS.

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REFERENCES
Late-Onset Neuroleptic Malignant Syndrome in a Patient Using Olanzapine

To the Editors:

In a recent letter, a description of a neuroleptic malignant syndrome (NMS) induced by aripiprazole was presented. In the case described, the patient did not present the cardinal features of muscular rigidity, hyperthermia, autonomic dysfunction, and altered consciousness. In the absence of the cardinal symptoms, the authors relied on the fact that the patient developed the symptoms 2 weeks after being on aripiprazole, and the symptoms vanished after discontinuation. There is still controversy whether atypical antipsychotics that cause less extrapyramidal effects may induce a differential type of NMS without muscular rigidity. We describe a case where NMS developed after 1 year of exposure to olanzapine 20 mg/d.

A 48-year-old man with schizo-affective disorder had a history of long-term use of lithium carbonate 900 mg/d. For the past year, he had also used olanzapine 20 mg/d with good clinical response. He was also on topiramate 200 mg/d, used as a means to control weight gain induced by olanzapine. The patient presented a lithium-induced hypothyroidism and used T4 replacement, 50 µg/d. The patient had a previous history of using antipsychotic medications (levomepromazine, chlorpromazine, haloperidol, risperidone, and quetiapine), which were discontinued because of adverse effects. The patient had no previous history of NMS. At admission, the patient presented low-back pain, restless less, tremor, tachycardia, tachypnea, hypertension, insomnia, and fever (41°C). The patient became delirious and agitated in the next few hours after admission. No muscular rigidity was found on the physical examination. Laboratory tests showed leukocytosis (white blood cell count of 11,030/µL), increased aspartate aminotransferase (649 U/L), creatinine (1.9 mg/dL), and creatinine kinase (CK; 34,210 ng/mL). Chest radiographs, abdominal ultrasound, and electrocardiogram did not show abnormalities. A tentative treatment with antibiotics was initiated (intravenous [IV] administration of azithromycin 500 mg every 24 hours and IV cefpime 2 g every 12 hours) with no response within 48 hours. No evidence of HIV and other viral infections were found; both blood and urine cultures were negative. At this time, NMS was suspected, and the patient was treated with intensive IV hydration, bromocriptine 2.5 mg every 8 hours and diazepam. All other medications were discontinued. The clinical and mental condition improved, and the patient was asymptomatic after 72 hours. Creatinine kinase levels were normal after 3 weeks. The patient was discharged 27 days after admission. At the time of discharge, the patient was on clozapine 300 mg/d and lithium carbonate 900 mg/d. Although the use of lithium with neuroleptics seems to increase the risk of NMS, this treatment was kept throughout the episode because of its good previous response.

REFERENCES

Aripiprazole Augmentation for Treatment-Resistant Bipolar Depression

Sustained Remission After 36 Months

To the Editors:

Aripiprazole is an atypical antipsychotic introduced in the United States in November of 2002 for the treatment of schizophrenia.\(^1\) Since that time, aripiprazole has also gained Food and Drug Administration approval for the acute treatment of manic and mixed episodes associated with bipolar I disorder, as well as a maintenance indication for the prevention of new mood episodes in recently manic or mixed patients.\(^2,3\) In addition to its approved indications, aripiprazole is also used off-label as an augmentation agent in difficult to treat major depressive episodes.\(^4\) In this letter, we report on the long-term outcomes of patients with treatment-resistant bipolar disorder who responded acutely to aripiprazole augmentation and continued to experience benefit over the maintenance period. To our knowledge, this is the longest published account of sustained remission (36 months) with aripiprazole during the depressed phase of bipolar disorder.

A chart review was conducted at the Asher Depression Center of Northwestern University on 12 patients who received aripiprazole augmentation to treat symptoms of bipolar depression during November 27, 2002, through February 27, 2003, coinciding with the first 3 months of aripiprazole’s availability in the United States. All patients met criteria for bipolar disorder (I, II, or not otherwise specified [NOS]) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and were experiencing a nonpsychotic major depressive episode. Patients were considered treatment resistant during the current episode because all were experiencing depression that was nonresponsive to at least a 12-week trial of lithium and/or a mood-stabilizing anticonvulsant in combination with an antidepressant. All but 1 patient had previously been nonresponsive to augmentation with an atypical antipsychotic excluding aripiprazole.

Change in depressive symptoms had been prospectively assessed using the Montgomery-Asberg Depression Rating Scale (MADRS)\(^5\) as part of routine clinical care. To further assess treatment effectiveness for purposes of this report, a Clinical Global Impression of Improvement Scale score\(^6\) was retrospectively assigned by consensus of the treating physicians. Initial response to aripiprazole was defined as 50% or more reduction in MADRS total score. In those subjects who responded after 8 weeks of treatment with aripiprazole, naturalistic outcomes were evaluated for up to 36 months.

Four (33%) of the 12 patients treated with aripiprazole were considered initial responders. The effect of aripiprazole on maintaining response in these 4 patients was assessed over a period of 36 months. Three patients were diagnosed with bipolar II disorder and one with bipolar disorder NOS.

Two of the 4 responders discontinued aripiprazole before the 36-month assessment; one discontinued after 21 weeks of treatment secondary to persistent akathisia, and another discontinued after 24 weeks of treatment due to a depressive relapse.

However, 2 patients remained on aripiprazole for a period of 36 months without relapsing into a new mood episode and without any change in psychopharmacological treatment. Both patients were diagnosed with bipolar II disorder and met criteria for remission of depression, achieving a MADRS score less than 7 throughout the 36-month period. One patient achieving sustained remission was a 43-year-old woman who was concomitantly taking escitalopram, gabapentin, and lithium and had failed trials of clomipramine, paroxetine, and quetiapine in combination with lithium during the current episode. The other patient was a 44-year-old man with chronic depression who was concomitantly taking lithium, gabapentin, and temazepam. He had failed trials of divalproex, oxcarbazepine, and mirtazapine in addition to sertraline and clomipramine combined with lithium during the current episode.

Psychotropic drug regimens had been stable for at least 12 weeks before augmentation with aripiprazole.

DISCUSSION

Our chart review found that 2 of 4 patients who initially responded to aripiprazole augmentation for treatment-resistant bipolar depression achieved sustained remission for 36 months. As depressive symptoms are known to account for much of the chronicity of bipolar disorder,\(^9,10\) our findings suggest that aripiprazole augmentation in depressed bipolar patients may be useful to prevent the recurrence of future depressive episodes.

Our findings complement those reported by Keck et al\(^2\) who demonstrated that aripiprazole was more effective than placebo in delaying the time to relapse into any mood episode in a 26-week study of patients with bipolar I disorder but found no difference between aripiprazole and placebo in delaying the time to relapse specifically into depression. The study by Keck et al\(^2\) did not enroll patients with an index episode of depression. In contrast, our patients initially presented with depression and were diagnosed with bipolar disorders II and NOS, conditions characterized by even more depression than reported in bipolar I disorder.\(^9,10\)

The 2 patients responding to aripiprazole were taking doses of 10 and 2.5 mg/d, respectively. Prospective trials are warranted to substantiate whether doses of aripiprazole lower than currently recommended for acute mania or the maintenance treatment of bipolar disorder\(^11\) provide both antidepressant efficacy and a decreased incidence of side effects, and whether differential response patterns emerge for bipolar I and II disorders.

There are several methodological limitations to this chart review. The sample size is small and consists of

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Aripiprazole-Induced Obsessive-Compulsive Disorder

A Report of 2 Cases

To the Editors:

Previous reports suggest that most atypical antipsychotics exacerbate or produce de novo obsessive-compulsive symptoms (OCS), despite having antiobessional effects. In terms of frequency, most cases involve the use of clozapine as found in a large trial, followed by risperidone, olanzapine, and quetiapine. The cases of atypical antipsychotic-induced OCS have involved patients with psychotic disorders such as chronic schizophrenia, delusional disorder, major depressive episodes with psychotic features, unspecified psychoses, and exacerbation of OCS in obsessive-compulsive disorder (OCD). Aripiprazole is the new generation atypical antipsychotic that is a "dopamine system stabilizer." There is recent evidence for a beneficial effect of aripiprazole in OCD. However, unlike other atypical antipsychotics, there are no prior reports of new OCD emerging during treatment with aripiprazole. In the following case report, we describe 2 rare cases of de novo OCD possibly induced by aripiprazole.

CASE 1

An 18-year-old man having no contributory past or family history was brought to our clinic with history suggestive of an International Classification of Diseases, 10th Revision, psychotic manic episode. He was drug naive, and no symptom suggestive of OCD was present. We initiated treatment with aripiprazole 15 mg/d. After a month, parents reported significant improvement in manic symptoms but also reported repeated ritualistic hand washing by the boy which started 2 weeks after initiating treatment. There was no history of any throat infection or intake of any other medication during previous month. On mental state examination, we found an obsession with dirt and a compulsion of washing. Dose of aripiprazole was reduced to 10 mg/d. On next follow-up after a month, we found that manic symptoms had completely resolved, but OCD persisted. We stopped aripiprazole and initiated treatment with carbamazepine up to 600 mg/d. Obsessive-compulsive disorder disappeared completely.

CASE 2

A 16-year-old girl, with family history of bipolarity in mother and no contributory history, was brought for consultation with 2 weeks history suggestive of an International Classification of Diseases, 10th Revision, acute polymorphic psychotic disorder without symptoms of schizophrenia. The girl had an abrupt onset of ocular symptoms (OCS), with 2 weeks history suggestive of an obsessive-compulsive disorder (OCD). The girl had an abrupt onset of symptoms without any known stressor which was characterized by rapidly changing hallucinations and emotional state from day to day in absence of any schizophrenic symptom. We initiated treatment with aripiprazole 10 mg/d and added tablet zolpidem 10-mg HS for 7 days to take care of her early insomnia. On next follow-up after 2 weeks, we advised continuation of aripiprazole at the same dose, as she had shown significant improvement. After 3 months when she did not have any previous symptom left, she started complaining of recurrent doubts on her clarity of conversation with repeated reassurance seeking behavior for the past month. There was no history of fever, throat

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infection, rash, or joint pain after her first consultation with us. Aripiprazole dose was reduced to 7.5 mg/d, and she was sent for cognitive behavior therapy. As OCD persisted on subsequent follow-ups, she was shifted to tablet trifluoperazine 10 mg/d, and aripiprazole was discontinued. There was complete disappearance of OCD after discontinuation of aripiprazole.

**DISCUSSION**

In both of our case examples, OCD emerged de novo after introduction of aripiprazole and disappeared completely upon discontinuation of the drug. This observation strongly favors a probable link between emergence of OCS and aripiprazole treatment. We also considered the possibility of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) presenting as transient OCD considering our patients’ age group. However, PANDAS are unlikely to be the offending condition, as there was no history of fever, throat infection, rash, or joint involvements. Therefore, it is obvious from both of our case examples that emergence of OCD was linked to introduction of aripiprazole. However, this link perhaps remains tentative considering the fact that there was no rechallenge.

The neurobiological mechanisms of antipsychotic-induced OCS have been speculative in nature and definitive explanations are yet to come. Any attempt to explain the neurobiological mechanism is also complicated by the paradox of therapeutic improvement noted with atypical antipsychotics in OCD patients with or without comorbid psychosis. The 5-HT$_2A$ and 5-HT$_2C$ receptor antagonism has been postulated to play a role in the generation of OCS in patients with a comorbid psychiatric disorder. Furthermore, 5-HT$_2C$ receptors have been found in greater number in the basal ganglia, an area that has been linked to OCD in many imaging studies. However, given the complexity of the numerous 5-HT receptor systems, it is obvious from both of our case vignettes, OCD emerged at a relatively lower dose of aripiprazole (10 or 15 mg/d). We additionally propose that aripiprazole’s action via 5-HT$_2C$, D$_3$ receptors and antagonism of 5-HT$_6$ and 5-HT$_7$ serotonin receptors are still unknown and could have potential roles to play.

To the best of our knowledge, our case example is the first link between aripiprazole and new-onset OCD. Basic neuroscience research should now systematically investigate the obsessogenic property of atypical antipsychotics.

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**REFERENCES**


**Pharmacokinetics Study for Hyperprolactinemia Among Schizophrenics Switched From Risperidone to Risperidone Long-Acting Injection**

**To the Editors:**

Hyperprolactinemia is an important but neglected consequence of antipsychotic medication and may be associated with both acute (galactorrhea, amenorrhea, decreased libido, etc) and chronic (predisposition to osteoporosis and cardiovascular disease) side effects. Turrone et al found a surge...
in prolactin concentration noted within 1 to 2 hours after oral risperidone administration, which remained significantly high for 8 hours and did not return to baseline until 24 hours. In contrast, elevation of prolactin after oral administration of olanzapine or clozapine lasted only for the first 1- to 5-hour period and returned to baseline values by 12 hours. The pituitary receptors involved in prolactin release lie outside the blood-brain barrier, and risperidone is less lipophilic than most antipsychotics and has a lower brain-to-plasma ratio. These might explain the phenomenon that risperidone has significantly higher and more sustained elevation of prolactin level than olanzapine and clozapine. Risperidone has 2 plasma active moieties, risperidone and 9-hydroxy (OH) risperidone. 9-Hydroxy risperidone has comparable potency of risperidone in stimulating prolactin but is less lipophilic and has longer half-life than risperidone. Knegtering et al found that plasma concentration of 9-OH risperidone, but not of risperidone, correlated significantly with plasma prolactin and concluded that the 9-OH metabolite plays a dominant role on prolactin release. The interesting question is whether the predominate role of 9-OH risperidone for prolactin level was also noted among patients receiving risperidone long-acting injections (RLAIs), which have been reported to produce 25% to 32% lower mean peak concentrations of the active moiety and lower prolactin levels than oral risperidone. In the present study, 25 symptomatic stable schizophrenic patients who had received oral risperidone for more than 3 months were switched to RLAIs every 2 weeks. The study was approved by the Ethics Review Committee of Yu-Li Veterans Hospital. Written informed consent was obtained before participating. Psychiatric symptoms, side effect profiles, and prolactin, risperidone, and 9-OH risperidone serum concentration measurements were performed at baseline, week 4, and week 12. Blood samples were taken at 7 AM, 12 hours after the evening dose and before the morning dose at baseline with oral risperidone. At weeks 4 and 12, blood samples were taken at 7 AM before the next RLAi. The plasma samples were stored at −60 °C until assayed. Plasma risperidone and 9-OH metabolite were measured using solid-phase extraction method and reversed-phase high-performance liquid chromatography with UV detection as described in detail by Lane et al. The standard curves of risperidone and 9-OH risperidone were linear over a range of 2 to 150 ng/mL. The intra-assay and interassay coefficients of variation were less than 15% in the range of 2 to 150 ng/mL for both compounds. The lower limits of detection for both compounds were 2 ng/mL. The ACCESS prolactin kit (Beckman Coulter), which enabled measurement of prolactin concentration with the upper limit detection of 200 ng/mL, was used to measure plasma prolactin level. The plasma concentration measurements were normalized by converting them to natural logarithm. Pearson correlations were calculated for plasma prolactin, risperidone, and its 9-OH metabolite. Continuous variables of clinical ratings and plasma level were analyzed with the repeated measurement analysis of variance. For all comparisons, the level of significance was set at 0.05. Finally, 24 patients, with mean age of 44.7 ± 9.2 years and original oral risperidone dose of 4.7 ± 1.7 mg/d, completed the 12-week study. At the end of the study, the mean RLAi dose was 32.0 ± 8.9 mg every 2 weeks. No significant changes in the severity of psychotic symptoms (Positive and Negative Syndrome Scale) were noted but with significant decreases in side effect profiles (Udvalg for Kliniske Undersogelser Scale, P = 0.005; Abnormal

| TABLE 1. Comparison of Characteristics Between Oral Risperidone and RLAi |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Serum prolactin (ng/mL)       | 68.44 ± 39.6    | 55.07 ± 45.54   | 50.57 ± 30.73   | <0.001          |
| Serum 9-OH risperidone (ng/mL)| 9.97 ± 5.90     | 4.68 ± 4.82     | 5.10 ± 2.80     | <0.001          |
| Serum risperidone (ng/mL)     | 6.30 ± 3.72     | 3.64 ± 4.97     | 2.75 ± 1.55     | <0.001          |
| Serum total active moiety      | 16.27 ± 8.18    | 8.28 ± 8.38     | 7.84 ± 3.52     | <0.001          |

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Values are mean ± SD.

AIMS indicates Abnormal Involuntary Movement Scale; BARN, Barnes Akathisia Scale; CGI, Clinical Global Impression Severity Scale; NS, not significant; PANSS, Positive and Negative Symptom Scale; SAS, Simpson Angus Scale; UKU, Udvalg for Kliniske Undersogelser Side Effect Rating Scale.
Patients Treated With CYP3A4 Inducers

To the Editors:

Reboxetine, a selective noradrenaline reuptake inhibitor administered as a racemic mixture, is used in the treatment of depression. No definite relationship between serum levels and effects has been established; nevertheless, serum concentration measurements of reboxetine are used as a means to monitor treatment.¹ Both enantiomers of reboxetine are metabolized mainly by the hepatic cytochrome P450 isoenzyme 3A4 (CYP3A4).² This enzyme is not subject to genetic polymorphism, but its activity can be inhibited and induced by a large number of drugs.

Ketoconazole, an antifungal drug known to inhibit CYP3A4 activity, has been shown to cause a significant elevation of the serum reboxetine levels.³ The authors of the study concluded that caution should be used when administering CYP3A4 inhibitors concomitantly with reboxetine, and a reduction in the reboxetine dose should be considered.

To our knowledge, there have been no reports on the effect of drugs inducing CYP3A4 on the serum concentrations of reboxetine. Among the most clinically relevant CYP3A4 inducers are the antiepileptic drugs carbamazepine, phenobarbital, and phenytoin. St. John’s wort, an herb used in the treatment of depression, also induces CYP3A4. We here present 2 patients with low serum concentrations of reboxetine in relation to dose who were both concomitantly treated with drugs inducing CYP3A4. We also compare their reboxetine levels to the serum concentrations found in 66 patients treated with drugs inducing CYP3A4 that we obtained from the TDM (TDM) database.

CASE REPORTS

Patient 1 was a 48-year-old woman with a diagnosis of bulimia nervosa who was
The 2 subjects treated with CYP3A4 inducers had serum concentrations of reboxetine that were considerably lower than the median concentration in patients not treated with CYP3A4 inducers. They both had relatively stable dose-adjusted serum concentrations in several consecutive measurements, as well as stable serum concentrations of the other drugs measured, indicating that noncompliance was not the explanation. Both patients were treated with a number of additional drugs (clozapine, olanzapine, clonazepam, alprazolam, and buspirone). However, there are no known pharmacokinetic interactions between these drugs and reboxetine, and there is no reason to suspect that these drugs may influence the enzyme activity of CYP3A4 significantly.

Three of 5 blood samples in the first patient were not drawn at trough levels. Thus, the median trough level in this patient was probably even lower than the value we have calculated, implying an even larger effect of carbamazepine on serum levels of reboxetine than shown here.

The S,S-enantiomer of reboxetine is 20 times more potent than the R,R-enantiomer in inhibiting noradrenaline reuptake. Although we have not used an enantiomer-selective method in this study, it is unlikely that an S,S selective method would have changed our principal findings, because both enantiomers are metabolized by CYP3A4 to approximately the same extent.

None of the patients had serum concentrations of reboxetine or any other medications measured to optimize the reboxetine dosages. However, because these recommendations are based on data from 2 patients only, a prospective study with serum concentration measurements of reboxetine with and without cotreatment with CYP3A4 inducers should have their serum drug reboxetine concentrations measured to optimize the reboxetine dosage. Therefore, these recommendations are based on data from 2 patients only, a prospective study with serum concentration measurements of reboxetine with and without cotreatment with CYP3A4 inducers would be helpful in quantifying the effect on the reboxetine concentration.

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Duloxetine in the Treatment of Social Anxiety Disorder

To the Editors:

Duloxetine is a new selective serotonin and norepinephrine reuptake inhibitor (SSNRI) antidepressant that has demonstrated efficacy to reduce anxiety and physical symptoms associated with depression. Recently, we reported a case of a 26-year-old woman with panic disorder with agoraphobia successfully treated with duloxetine. These data suggest that this compound may also be effective in the treatment of social anxiety disorder (SAD). We report, for the first time to our knowledge, 2 cases of patients with generalized SAD successfully treated with duloxetine as evaluated by standardized clinical rating scales.

CASE REPORTS

Both patients, naive to SAD treatment, were assessed with the Portuguese version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and met criteria for SAD without comorbid conditions. Open-label protocol was to start duloxetine at 60 mg daily for the first 4 weeks, which could be increased to 120 mg/d for the last 4 weeks of the trial if partial or no response and no limiting side effects were found. A maximum dosage of 120 mg/d was chosen because it is well-known that the SSNRI dosage for SAD is similar to the standard dosages used for depression and to try to achieve maximal improvement. The study was approved by the local ethical committee (HCRP no. 15549/2005), and no other patient was treated as part of this trial. Ms A., a 24-year-old woman, since early adolescence avoided various social situations because she always experienced symptoms of anxiety, such as palpitations, tremors, gastrointestinal discomfort, and blushing. Symptoms impaired her social and educational performance, as the patient was considering abandoning the university before graduating because she could not interact with her colleagues without feeling anxiety. Duloxetine (60 mg/d) was then introduced, leading to partial reduction of SAD symptoms within 4 weeks. Hence, duloxetine was increased to 120 mg/d. Eight weeks after starting duloxetine, the overall clinical picture improved, showing reduction in anticipatory and performance anxiety and improvement in interpersonal relationships and social and educational functioning. The Brief Social Phobia Scale baseline score decreased from 64 to 31 and 17 after 4 and 8 weeks, respectively. The Clinical Global Impression Scale scores confirmed the above outcome (from 7 to 4 and 2, respectively).

Ms B., a 49-year-old woman, had a history of excessive shyness and fear of speaking, eating, and writing in front of unfamiliar people since early childhood because of fear of acting in a humiliating way. The exposure to the social or performance situations provoked an immediate anxiety response with palpitations, tremors, sweating, and muscle tension, which interfered significantly with the patient’s daily routine and social life. She was given 60 mg/d duloxetine for 4 weeks with partial anxiety and physical symptoms improvement. After that period, dosage was increased to 120 mg/d, but needed to be reduced back to 60 mg/d within 1 week as she reported insomnia, tremors, and dry mouth. After 8 weeks of the trial, symptoms of anxiety in social situations lessened considerably. She was able to talk to others and became more confident and relaxed, although some discomfort in social situations were still present. The Brief Social Phobia Scale baseline score decreased from 60 to 38 and 24, and Clinical Global Impression Scale scores decreased from 6 to 5 and 2, after 4 and 8 weeks, respectively. A 6-month follow-up of both patients with duloxetine showed no relapse of the symptoms.

Previous studies showed that venlafaxine, another representative of SSNRI, could be an option for SAD. The progressive rating scales decreases after 4 and 8 weeks in both patients confirm the idea that long-term antidepressant pharmacotherapy for SAD results in continued improvement of the symptoms. The present cases thus confirm a potential usefulness of SSNRI and suggest that duloxetine may also be effective for the treatment of SAD, although double-blind, controlled studies would be necessary to further confirm this observation.

ACKNOWLEDGMENT

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REFERENCES


Sexual Disorders in Subjects Treated for Mood and Anxiety Diseases

To the Editors:

The incidence of sexual dysfunction obtained unsystematically in clinical...
trials is likely underestimated because it relies on spontaneous reporting of side effects.

We evaluated the rate of hypoactive sexual desire disorder, sexual arousal disorder, and orgasmic disorder in a group of 103 subjects with mood and anxiety disorders consecutively recruited in the outpatient clinic of the University of Siena Medical Center.

The University of Siena’s biomedicai institutional review board approved all recruitment, assessment, and treatment procedures. All subjects who met inclusion and exclusion criteria provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions. Subjects were 103 outpatients with a mood and/or anxiety disorder and without an organic disease that could interfere with sexual functions.

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**TABLE 1.** Demographic and Clinical Characteristics of 103 Subjects With Mood and Anxiety Disorders

<table>
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<tr>
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<th>%</th>
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<tbody>
<tr>
<td>Age, mean (±SD)</td>
<td>41.4 (±10.1)</td>
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</tr>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
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<td>47.6</td>
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<tr>
<td>Female</td>
<td>54</td>
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<td>Psychiatric diagnosis</td>
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<tr>
<td>Mood disorders</td>
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<td>Major depressive disorder</td>
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<td>3.88</td>
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<tr>
<td>Anxiety disorders</td>
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<td>66.9</td>
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<td>Social phobia</td>
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<td>1.94</td>
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<tr>
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<td>11.65</td>
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<td>Specific phobia and generalized anxiety disorder</td>
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<tr>
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<td>28.2</td>
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<tr>
<td>Sertraline†</td>
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<td>Fluoxetine</td>
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<tr>
<td>Venlafaxine</td>
<td>4</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*4 Subjects endorsed both a mood and an anxiety disorder.
†Rates referred to the patients who assumed therapies.
sexual desire, and 7 (15%; 3 women, 4 men) reported difficulty with arousal.

Among the 4 patients with comorbid mood and anxiety disorders, 2 (50%; women) reported reduced sexual desire. 

**DISCUSSION**

Our results are in agreement with the findings of other authors, such as Clayton and Montejo,4 Montejo et al,5 and Stevenson,6 and confirm that the prevalence of sexual dysfunction in subjects with mood and anxiety disorders is higher than it is reported in the many clinical trials that rely on spontaneous reporting of side effects. We observed that sexual fantasies and desire for sexual activity were severely reduced or absent in approximately half of our 103 patients (49% of the men and 43% of the women). These percentages are higher than the prevalence reported for the general population, which is itself a reason for concern. For instance, a recent population-based study found that “only” 15% of men and 18% of women reported a lack of sexual interest.7 Forty-two percent of our 103 subjects reported orgasmic dysfunction. Not surprisingly, the prevalence of orgasmic dysfunction was particularly high (66%) in the subjects that were receiving antidepressant medications.

However, the percentage of subjects in our sample that reported difficulty with arousal (10%) is lower than we were expecting and lower than what was reported in studies in the general population1 and in subjects with mood and/or anxiety disorders. For instance, this percentage is lower than the 52% reported in a population-based survey of men aged 40 to 70 years.8 However, it is noteworthy that our subjects were younger than those participating in the study mentioned above. Sexual health can be adversely affected by many medical conditions, such as neurological illnesses, cardiovascular disease, urogenital disorders, hormonal dysfunctions, and other medical illnesses. Clearly, psychological distress and psychiatric disorders can contribute to impairment of sexual health, both directly and/or via iatrogenic factors because of the use of medications liable for sexual dysfunctions. In fact, it is often very difficult to disentangle whether sexual dysfunction is part of the psychiatric syndrome being treated, the result of its treatment, or a result of a preexisting psychosexual or medical disorder. Few would argue that the use of antidepressants such as the selective serotonin reuptake inhibitors can cause or contribute to the sexual dysfunction.1,4 However, it is noteworthy that in our study, 86% of the 29 subjects who were not receiving antidepressant medications reported a sexual dysfunction. Of interest, most (80%) of these subjects reported reduced sexual desire, whereas a much lower percentage reported difficulty with arousal (20%) or orgasm dysfunctions (0%). Not surprisingly, this distribution is different from the distribution observed in the group of our patients that were treated with antidepressants in which we observed a higher rate of erectile and orgasmic dysfunction.

Although we did not run any statistical comparison between the patients with mood and anxiety disorders, it is interesting to observe that hypoactive sexual desire disorder was clearly more prevalent in subjects with mood disorders than in subjects with anxiety disorders. This is not surprising, given that a reduced sexual interest is one of the core symptoms of mood disorders, whereas, in our observations, the sexual function of patients with anxiety disorders is more likely to be affected by performance anxiety.

Among the limitations of this study, we acknowledge its cross-sectional design and the fact that patients with substance-induced sexual dysfunction with impaired desire, arousal, or orgasm were considered as part of the group of patients with hypoactive sexual desire disorder, sexual arousal disorder, or orgasmic disorder, respectively.

Despite the limitations previously mentioned, we believe that the results of this study are of interest.

In fact, we confirmed that sexual dysfunctions are highly prevalent among patients with mood and anxiety disorders even when they are not treated with medications and hope that our results contribute to draw the clinicians’ attention on the importance of adequately assessing and, when possible, appropriately treating sexual dysfunction, given its multiple and negative correlations with poor quality of life9 and/or feelings and symptoms like unhappiness, frustration, sense of inadequacy, loss of self-esteem, and depression.5

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Recurrent Hyponatremia After Substitution of Citalopram With Duloxetine

To the Editors:
The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a well-known side effect of selective serotonin reuptake inhibitors (SSRIs), although the exact mechanism is unknown. The occurrence of hyponatremia as a severe side effect of treatment with duloxetine, a dual serotonin and norepinephrine inhibitor, has been reported only once. In this case report, we describe a patient who initially developed symptomatic hyponatremia on treatment with citalopram. After substitution with duloxetine, hyponatremia reoccurred. This patient’s treatment was subsequently changed to nortriptyline, and repeated investigations showed no abnormalities of serum sodium levels.

CASE REPORT
Mrs K., an 85-year-old woman was admitted with a suspected cerebral vascular accident. Clinical features included somnolence, facial paralysis, and abnormal gait. Neuroimaging using computed tomography of the brain showed no significant abnormalities; however, laboratory blood investigation revealed severe hyponatremia (116 mM).

The patient had a history of depression and was recently started on antidepressant medication (citalopram). After discovery of hyponatremia, citalopram was discontinued. In addition, the patient was treated with intravenous fluids. Serum sodium concentration normalized (134 mM), and the neurological symptoms disappeared.

The patient continued to express depressive symptoms and was admitted to our psychiatric hospital for reinstatement of antidepressant medication. We started treatment with duloxetine 30 mg BD with regular monitoring of serum sodium levels. After 2 days of treatment, a significant decrease in serum sodium levels (120 mM) was noted. To prevent further deterioration and recurrence of neurological symptoms, duloxetine was discontinued. A diagnosis of hyponatremia due to SIADH was made on the basis of serum hypo-osmolality (272 mOsm/kg), serum hyponatremia (120 mM), and increased urinary sodium excretion (66 mM). Further investigations including chest radiograph, serum cortisol, thyroid function, renal function, and liver function tests were normal. Oral fluid intake was restricted, and sodium serum levels were measured daily. Ten days after discontinuation of duloxetine, the serum sodium level returned to normal (135 mM). The patient was restarted on the tricyclic antidepressant nortriptyline 10 mg BD. Daily monitoring revealed no effect of nortriptyline on serum sodium levels.

DISCUSSION
Our case report demonstrates that duloxetine is capable of causing SIADH. This particular side effect of duloxetine has been reported only once previously. Duloxetine is a relatively new drug, and therefore, reports of significant side effects remain important. Our case report also suggests that, in patients with hyponatremia secondary to treatment with SSRIs, the possibilities for substitution with other antidepressant drugs may be limited because of a possible increased risk of recurrence of hyponatremia. The occurrence of hyponatremia has been reported with SSRIs, reboxetine, venlafaxine, mirtazapine, and tricyclic drugs such as imipramine and clomipramine. There have been no reports of hyponatremia in patients treated with nortriptyline. It is possible that nortriptyline is the most appropriate choice for patients with a recurrence of SIADH on antidepressant medication. However, further investigation is necessary to support this suggestion.

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Treatment-Resistant Depression Response to Low-Dose Transdermal But Not Oral Selegiline

To the Editors:
The author reports a case of treatment-resistant depression not responsive to the combination of a selective serotonin reuptake inhibitor and lithium that was treated first with oral selegiline, then transdermal selegiline.

CASE REPORT
A 67-year-old man with a 30-year history of recurrent depression presented in the midst of a major depressive episode of several months in duration. Symptoms were consistent with melancholic depression and included anhedonia, amotivation, a sense of being “ill at ease,” “self-described “flat affect” and “jealousy of others’ joy,” poor appetite with 17-lb weight loss, excessive worry with ruminating thoughts, lack of interest in work or sex, and difficulty initiating and maintaining sleep despite use of sleep medication. He noted a diurnal variation to his symptoms, with depression and lack of motivation at its worst upon awakening, leveling through most of the day except for brief periods after physical exercise, and receding in the evening with

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enjoyment of television and reading possible. His medications were escitalopram 30 mg, lithium 600 mg, olanzapine 5 mg nightly, zolpidem 10 to 20 mg nightly, clonazepam 0.5 mg daily for anxiety, and 1 mg nightly for sleep. He also took a multivitamin and a supplement with concentrated ω-3 fatty acids.

Prior to 3 years ago, the patient experienced depressive episodes only every few years. Symptom presentation was variable but always included anhedonia and lack of motivation. Single agents including amitriptyline and fluoxetine or the combination of lithium and fluoxetine successfully treated these episodes to remission typically within 2 to 3 weeks. Three years ago and after the death of his psychotherapist of more than 20 years, he began having depressive episodes every 8 to 12 months. These recent episodes were less responsive to treatment, with little to no benefit from a single agent (selective serotonin reuptake inhibitors, buspirone) and partial response to fluoxetine plus lithium or escitalopram plus lithium.

Initial management consisted of discontinuation of escitalopram and olanzapine followed by initiation of oral selegiline. Selegiline was begun as 5 mg daily with breakfast then increased 2 days later to 5 mg twice daily with breakfast and lunch. After 1 week, all 10 mg were taken together with breakfast. After 4 weeks of oral selegiline treatment, there were little to no appreciable changes in symptoms. Oral selegiline was discontinued, and the newly available transdermal selegiline 6 mg/24 h was begun. By the end of the first week of treatment, the patient reported that he felt substantially better and had received numerous comments that he looked better. At 2-weeks’ follow-up, the patient exhibited brighter affect, improved mood, and increased motivation; he expressed satisfaction with work and admitted to a sense of joy in thinking about his grandchild. His appetite improved and sexual activity resumed. Although still present, anxiety decreased, and the patient was able to stop the use of clonazepam during the day. Worsening of anxiety or depression at the latter was tolerable with a 3-site rotation.

In this case of treatment-resistant melancholic depression, low-dose oral selegiline was started because of its availability, the lack of dietary restrictions required, a positive case report, and its effectiveness and tolerability at higher doses in an older population. Given the lack of response to oral dosing as well as the emerging availability, theoretical advantage, and apparent efficacy of the transdermal system, the patient’s medication was switched with the notable results described above.

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Clomipramine-Induced Mood and Perceived Performance Changes in Selected Healthy Individuals

To the Editors:

Antidepressants can induce positive changes in the subjective state of some individuals, independently of the presence of anxiety or depression.1–3 Patients treated for panic disorders with low to moderate doses of antidepressants report, besides symptom remission associated with their primary disorder, secondary depression, or health-related worries, unexpected changes regarding their usual premorbid emotional state.4 More specifically, decreased irritability, increased well-being, self-confidence, and cognitive efficiency have been observed in normal volunteers.1,3,5 Also, a shift toward positive affect and...
a “care less” attitude were reported in both clinical and normal subjects.2,5–7

The present report is part of a broader study aiming to extend the scope of our previous investigations about the effects of low doses of antidepressants on the emotional response of healthy subjects. In this way, personality, mood, and other psychological variables, as well as their relationship to cognitive processing, circadian rhythms, eating behavior, and neuroimaging correlates, will be assessed. Moreover, pharmacogenomic techniques will be used to study individual variability in emotional response.

We conducted 2 controlled experiments using low, flexible doses of clomipramine or propantheline (active placebo) in healthy volunteers without personal or family history of psychiatric disorders (selected through Self-Reporting Questionnaire 20, psychiatric interview through the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, a family history questionnaire,8 laboratory tests, electrocardiogram, and physical examination). Clomipramine was chosen based on our previous experience with this drug inducing extratherapeutic effects.4,4

In the first double-blind, balanced, parallel-design trial, subjects received clomipramine (10–40 mg/d; n = 24) or propantheline (30 mg/d; n = 21) for 6 weeks (mean age [SD], 32.4 [6.9] years; 69% female). Thirty subjects were asymptomatic, and 15 displayed symptoms such as emotivity, worry, and tension of insufficient severity to meet any diagnostic criteria at baseline.

Nineteen subjects (6 on placebo) reported feeling calmer and less irritated. To evaluate emotional alterations after clomipramine treatment, subjective rating scales were used initially, but a ceiling effect precluded its usefulness to detect those changes. Thus, we opted for a qualitative approach using semi-structured interviews based both in our observations and in previous reports of antidepressant extratherapeutic effects.7 This strategy identified 4 subjective domains: interpersonal tolerance (decreased irritability and tension in social interactions), efficiency (improved decision making, ability to prioritize demands, and self-confidence), well-being (feeling better, brighter mood), and feeling substantially changed from usual self. A complete response was categorized as sustained changes in 3 of 4 of these domains as independently rated by 2 blinded psychiatrists.

According to these criteria, 5 individuals (3 asymptomatic on clomipramine (21%) and 1 (asymptomatic) on placebo were considered complete responders.

A second study confirmed the specificity of this response. Another 24 healthy volunteers (16 asymptomatic and 8 symptomatic) received clomipramine (single-blind; 10–40 mg/d) for up to 6 weeks. Ten subjects (34.5%, 7 asymptomatic) reached the above response criteria and were then included in a double-blind, balanced-order, crossover trial with clomipramine or propantheline, same doses, for 3 weeks. While on clomipramine, all 10 subjects maintained (or reacquired) response criteria. Response ceased during placebo.

These results confirm that at low doses clomipramine may induce qualitative changes in subjective state in the absence of psychopathology in some, but not all, individuals. Such perceived effects on mood, performance, and social interaction were consistently established and lost in a matter of days and were not associated with sedation, psychostimulation, or drug-induced hypomania. One might suppose that the observed effects are merely caused by improvement of mild subclinical symptoms not amounting to complete diagnosis. In this case, the subject would be considered a partial responder (1 or 2 of 4 subjective domains) and would not be included in the subsequent analysis. Moreover, this argument does not hold true when we consider that among responders, the majority was asymptomatic.

Given the low dosage, the small response rate (35%) is unlikely to be explained by pharmacokinetic factors.1 The mechanisms of action, individual responsibility, and the clinical usefulness of this selective effect on mood regulation deserve further investigation.

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REFERENCES

Psychosis With Sibutramine

To the Editors:

Sibutramine (1-(4-chlorophenyl)-N,N-dimethyl-a-(2-methylpropyl)-cyclobutanemethanamine (Meridia and Reductil), a norepinephrine and serotonin reuptake inhibitor originally developed as an antidepressant,2 has met with considerable success in the treatment of obesity.2,3 Typical adverse effects are dry mouth, constipation, tachycardia, hypertension, and headache. Regarding the central nervous system, anxiety, depression, and somnolence are well-known side effects, whereas delusions or hallucinations have been reported only once, without fully establishing causality.3 We report 2 additional cases of psychosis apparently induced by sibutramine.
CASE 1

A 48-year-old German prison officer was admitted because of impertinent voices telling him to shoot his superior. He reported hearing these voices during the past 3 months and also lately receiving signs and reading thoughts. There was no personal or family history of mental disorder and no history of somatic illness. However, he had used sibutramine 10 mg BID for weight reduction during the past 6 months because inmates and colleagues had teased him and his superior had urged him to reduce weight or otherwise leave the service. Allegedly, he had used no other substances and had no experience with illicit drugs. On admission, he was fully oriented but agitated and anxious, whereas his mood appeared at most slightly depressed. He could refrain from obeying the voices but could not distance himself from other psychotic experiences with the same ease. For example, he anxiously avoided the city for fear of dangerous trams chasing him. He had already lost 53 kg and was only slightly overweight at 88 kg (body mass index [BMI], 27.8 kg/m²). Diagnostic procedures yielded normal results; particularly, brain magnetic resonance imaging, arteriography, cerebrospinal fluid, blood and urine analysis including measurement of serum levels of vitamins and trace elements, prolactin, thyroid, parathyroid, adrenocortical, and sex hormones were in the normal range. Treponema pallidum hemagglutination, autoantibodies as well as antibodies against hepatitis B and C, Borrelia, cytomegalovirus, toxoplasma, Epstein-Barr virus, and human immunodeficiency virus I/II tested negative. Urinary screening for amphetamines, cannabinoids, opiates, cocaine, LSD, and benzodiazepines was negative. The medication with sibutramine was stopped, and the patient was treated with sertrindole 16 mg OD; full recovery was achieved within 3 weeks.

CASE 2

A 43-year-old Thai woman was admitted after setting her furniture on fire, because it appeared “dark,” and attacking her husband fiercely, biting and scratching him when he tried to rescue her from the fire. She had been treated before this incidence with antiobesity pills in Thailand for a duration of 8 weeks. According to her spouse, similar but less extreme behavior had occurred twice before, 1 and 2 years before admission, during their annual leave in Thailand. In all 3 cases, she had taken the same pills for a duration of 8 weeks, losing about 15 kg of weight on each occasion. The 2 earlier episodes of mental derangement reportedly lasted 6 to 8 weeks and remained untreated. The patient showed no insight pertaining to her mental disorder and appeared to be fully satisfied with the effects of her medication. She usually felt overweight and was thus motivated to lose weight when on vacation in Thailand even with an initial BMI substantially below 30. There was otherwise no personal or family history of mental disorder, especially no Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision eating or personality disorder. On admission, we saw a distrustful but fully oriented woman with a minor attention deficit, severe delusional jealousy, persecutory delusions, and visual hallucinations. Apathy and depression alternated with aggressive outbursts. Body mass was 49.5 kg (BMI, 20.6 kg/m²), and results of extensive blood and urine analysis including thyroid and parathyroid hormone levels, vitamins, and trace elements were normal. Urine drug screening was negative. The patient refused brain imaging and lumbar puncture. Mass spectrometry of the drug revealed sibutramine and no other active content. The patient was treated with olanzapine 15 mg OD and recovered completely within 4 weeks.

DISCUSSION

We report 2 cases of psychotic disorders after substantial weight reduction and use of sibutramine in otherwise healthy persons. These cases confirm the single case reported by Taflinski and Chojancka. Sibutramine is chemically related to the amphetamines, but its mechanism of action is different because it acts via inhibition of serotonin, norepinephrine, and dopamine reuptake rather than via direct monoamine release. Both serotonergic and adrenergic mechanisms are involved in its appetite suppressant action, and peripheral effects may also play a role. Although psychotic syndromes do frequently occur with amphetamines, they are not common with reuptake inhibitors. There are a few reports of psychoses as adverse effects of antidepressive therapy, practically all in patients with preexisting psychosis. Actually, in several, but not all, controlled studies in schizophrenia, reuptake inhibitors, including antidepressants and sibutramine, did not even precipitate exacerbations when added to antipsychotic therapy. The only antidepressant reuptake inhibitor unequivocally associated with first-episode psychoses is bupropion (Zyban, Wellbutrin, and Elnoril), which is also the only antidepressant to inhibit dopamine reuptake such as sibutramine. Increased synaptic dopamine concentrations might, therefore, be a common ground of the psychotomimetic effects of bupropion and sibutramine, in line with the dopamine hypothesis of schizophrenia and the known psychotomimetic effects of dopaminergic drugs.

In Germany, warnings have been issued about certain Asian antiobesity drugs, so-called LiDas (derived from “Li Da Lidameiticha Meizi Tea”) because of excessive sibutramine content. Against that background, sibutramine content may have been high in our second case, thereby explaining the occurrence of otherwise unknown adverse effects. However, the pills used in our case appeared to be forged Meridia 5-mg capsules, which may indicate low dosage, and quantitative analysis was not available. In case 1, the dosage was within recommended limits.

The patient in case 1 lost 38% of his initial weight (0.29 kg/d) during 6 months, and the other patient lost 23% of his initial weight (0.27 kg/d) during 8 weeks of treatment with sibutramine. Obviously, this is exceptional stress that might provoke neuropsychiatric disorders even without any additional toxic exposure. Consecutive thiamine deficiency could cause Wernicke encephalopathy, and fluctuations of serum sodium levels could provoke myelolyses in the brainstem, callosum, or cerebral hemispheres. Cirignotta et al reported 22 subjects that developed psychotic syndromes after gastric bypass surgery. Their average daily weight reduction was 0.36 kg, and the average duration from surgery to onset of psychosis was 93 days, consistent with the numbers observed in our patients, underscoring the possibility of a shared pathogenesis. On the other hand, these disorders typically produce structural lesions and focal neurological deficits that were lacking in our patients. Also, there was no vitamin deficiency or electrolyte disturbance in our patients. All patients in the study by Cirignotta and coworkers experienced daily vomiting, whereas both our patients did not vomit. A Medline
search for “‘weight loss’ OR ‘weight reduction’ OR anorexia) AND (psychosis OR psychotic)” yielded 255 references, 90% of which were concerned with weight gain as a side effect of antipsychotic therapy. Only a single article reported psychosis as a consequence of weight loss during dieting. The authors mention from their own experience “approximately 30 cases in which weight loss was from 8% to 28%. In some of them this appeared to be the crucial and central factor of their illness.” Yet, their article actually describes no more than 3 cases of psychosis during dieting in previously mentally healthy persons. We do not know whether these patients could have been recognized by structural lesions had brain imaging been available. Still, diet alone may not be a frequent cause of psychosis in the absence of structural pathology.

Additional drug abuse was not suspected in either case because there were no specific clues yet could not be completely excluded because our drug screening was not exhaustive. Furthermore, the husband’s report in case 2 may have been incomplete, inaccurate, or subjective. We, nevertheless, believe, on account of these new cases, that there is increasing evidence that sibutramine may induce psychotic symptoms.

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Glutamate Antagonists Seem to be Slightly Effective in Psychopharmacologic Treatment of Autism

To the Editors:
Cholinergic drugs, mainly used for patients with Alzheimer disease, are described to be effective in treating patients who have autism. Chez et al published an open-label study demonstrating that rivastigmine leads to gains in overall autist behavior and expressive speech. Hertzmann2 reported improvements in verbal fluency, caused by galantamine treatment, but also mentioned verbal and behavioral regression when the patient was on donepezil. We have not found yet any data with regard to memantine’s efficacy for those patients.

For late stages of Alzheimer disease, glutamate antagonists (memantine) have also been recommended and proven to be effective.

For that reason, we checked this substance in an open trial for 4 patients (ages 17.4 ± 3.2 years; IQ 68 ± 11, Wechsler Intelligence Scale) without medical or neurological illnesses, with autistic disorder (2 patients have type Asperger, 1 patient has type Kanner, and 1 patient has atypical autism) diagnosed by International Statistical Classification of Diseases, Tenth Revision and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, who had been medication-free for at least 2 weeks and received memantine (20 mg daily) for 4 weeks. Subjects were included in the study if their irritability, motoric activity, eye contact, and expressive language were significantly impaired, according to the Aberrant Behavior Checklist.3 Combined both parent and teacher ratings of irritability (off, 13.8 ± 1.26; on, 12.3 ± 2.1; P = 0.033), hyperactivity (off, 21.3 ± 1.3; on, 21.8 ± 1.0; P = .034) and inappropriate speech (off, 5.5 ± 1.3; on, 5.8 ± 1.7; P = 0.033) improved significantly. Drowsiness (off, 2.0 ± 0; on, 2.0 ± 1.41; P = 0.084) and inadequate eye contact (off, 8.2 ± 0.5; on, 8.3 ± 1.0; P = 0.078) did not show any improvement. None of the subjects appeared to have headaches or stomachaches, although report of such side effects was limited by the expressive language and social skills of these subjects.

Memantine seems to be not only effective in treating Alzheimer disease, but may be also very modestly effective in the short-term treatment of irritability in children with autistic disorder in some cases.

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Open Trials in Psychiatry

Comments on Article by Uchida et al

To the Editors:

A randomized trial with provocative results on accelerating antidepressant response with sulpiride augmentation appeared in the December issue of the Journal. The median time to response of 2 weeks in the combination group was impressive, as were the very high remission rates early in treatment. Although the authors correctly stated that bigger, blinded trials are needed, their discussion falls short of explaining why this is so.

The double-blind method has been criticized both in general medicine and psychiatry, as patients in controlled trials may not be adequately blinded. Nevertheless, in disciplines where outcomes are highly subjective, such as psychiatry, binding is still thought as essential in controlling for expectations and preserving the possibility of making causal inferences. Especially in the trial of Uchida et al, where treatment groups were asymmetrical regarding the number of medications and pill counts, and, through informed consent, patients were educated on the possibilities of allocation, a differential expectation of improvement could have biased the results in favor of the combination group. Furthermore, the authors imply that raters were not blinded; even in open trials, rater binding is usually possible and regarded as fundamental.

The issue of onset of antidepressant action is sensitive to psychiatrists. The delay in the onset of the therapeutic action of antidepressants may result in patient suffering and diminished treatment adherence. As a result, psychiatrists may be inclined to try novel treatment strategies to improve patient outcome; caution in this matter has been urged before.

If limitations are not more thoroughly discussed and the direction of possible bias made clear, a precarious adoption of inadequately tested combinations may occur. Overall, the open nature of the Uchida trial and the small number of subjects recruited make the results highly sensitive to bias. Although potentially relevant, we believe that the results of the study of Uchida et al should not be translated into clinical practice until more reliable trials are conducted.

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REFERENCES

Reply to Comments by Dr Magalhães

To the Editors:

We are grateful to Dr Magalhães for raising important issues. We agree in that the unblinded procedure constitutes a major limitation in our study, and our results should be replicated in more methodologically rigid trials. Dr Magalhães pointed out that shortcomings of the study design adopted in our trial should have been more thoroughly discussed. Considering that the primary objective of our trial was not to examine the pros and cons of this open label procedure, we believe that our descriptions regarding this issue met readers’ requirements because we clearly mentioned disadvantages of our study design. Drawbacks of a weak study design are to be critically evaluated. However, more thorough discussion regarding advantages and disadvantages of each study design should be done somewhere else in papers that deal primarily with methodology issues. Dr Magalhães also stated that results from not strictly designed trials such as ours should not be translated into clinical practice. Our standpoint is that the combination therapy presented in our trial could be performed in clinical practice. Results from “reliable” trials should be more highly prioritized than “unreliable” ones; still, physicians could learn much even from a case report. With regard to our trial, sulpiride has been approved as an antidepressant drug and widely prescribed in Japan. Prolactin elevation caused by dopamine blockers has been reported to be reversible. Increased prolactin level was, in fact, diminished also in our subjects who agreed to discontinue sulpiride after this trial (Uchida et al, October 2005, unpublished data). Moreover, evidence concerning antidepressant effect of dopamine-mediated agents has been accumulated, although it is still insufficient. As long as serious side effects do not occur, we could devise a better treatment even from preliminary findings. Of course, this attitude must be always accompanied by full deliberation and should be valid.

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Baclofen Suppresses Alcohol Intake and Craving for Alcohol in a Schizophrenic Alcohol-Dependent Patient

A Case Report

To the Editors:

Alcohol use disorders (AUDs) are common in patients with schizophrenia. The Epidemiologic Catchment Area Study indicated that approximately one third of patients with schizophrenia have a lifetime diagnosis of AUDs. An excessive alcohol intake produces negative consequences on schizophrenic patients, such as increased relapses, more hospitalizations, and increased violence and suicide attempts. Therefore, decreasing alcohol consumption in patients with schizophrenia should be considered a major goal in their treatment programs. It has recently been demonstrated that the prototypic agonist of the γ-aminobutyric acid (GABA) B receptor, baclofen, widely used to control spasticity, reduced alcohol consumption and obsessive thinking of alcohol, as well as symptoms of alcohol withdrawal syndrome in human alcoholics. A recent paper also reported that higher doses of baclofen completely suppressed alcohol consumption and craving for alcohol. These studies also reported that use of baclofen in alcohol-dependent patients appeared to be safe and manageable. Baclofen was tested in schizophrenic patients to evaluate its effect on tardive dyskinesia, an adverse effect of neuroleptic drugs, or schizophrenic symptoms. The results of these studies suggested that baclofen was similar to placebo in both effects. However, baclofen administration—up to 90 mg daily—did not result in any worsening of schizophrenic symptoms. Moreover, a recent case report described the efficacy and safety of baclofen in decreasing craving for cocaine in a patient with cocaine dependence and schizoaffective disorder. Considering the efficacy of baclofen in reducing alcohol intake in alcoholics and in view of the fact that it did not worsen schizophrenic symptoms, baclofen administration to the patient described here was aimed at evaluating the effectiveness and safety profile of baclofen in an alcohol-dependent schizophrenic patient.

CASE REPORT

In 1999, a 49-year-old male outpatient was admitted to the Division of Psychiatry, University of Cagliari, Italy, having persecutory and referential delusions, visual hallucinations, affective flattening, and avolition. Details provided by his relatives revealed an early onset of heavy alcohol drinking and schizophrenic symptoms at approximately the age of 28 years. Daily alcohol intake, as reported by both the patient himself and his relatives, averaged approximately 2 L of wine (approximately 16 drinks per day). After frequent episodes of alcohol intoxication and/or exacerbation of schizophrenic symptoms, he had been admitted several times to medical and psychiatric hospitals with a diagnosis of alcohol dependence and paranoid schizophrenia (in accordance with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria) and treated with haloperidol and benzodiazepines. He had also been treated with disulfiram and had attended Alcoholics Anonymous meetings, without any apparent beneficial effect in terms of reduction of alcohol intake. From 1999 to 2005, he was admitted to the hospital approximately once a year because of severe episodes of acute alcohol intoxication. In July 2005, we proposed to the patient and his family a new pharmacological treatment to decrease his alcohol consumption. Specifically, the possibility of using baclofen was discussed. Written informed consent was obtained. Before the first baclofen administration, a blood sample was collected for evaluation of the following indicators of heavy alcohol drinking: mean corpuscular volume of red blood cells, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. A schedule was drawn up providing for patient examination once a day for the first 3 days, once a week for the first 4 weeks, and subsequently once every 2 weeks. A breathalyzer test, using the Alco-Sensor IV breathalyzer apparatus (Syen Elettronica, Gardigiano di Scorze, Venezia, Italy), was administered at each visit to evaluate the patient’s breath alcohol concentration. At each visit, the following rating scales were administered to the patient: Zung Self-rating Depression Scale, Spielberger State Anxiety Inventory, Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI)–Improvement and –Severity Scales, a visual analog scale (VAS) of craving severity and Obsessive and Compulsive Drinking Scale (OCDS) in its validated form in Italian. Alcohol intake was self-reported by the patient and confirmed by a family member. Possible side effects related to baclofen therapy were also recorded. Treatment with baclofen started with the dose of 5 mg, per os, 3 times a day for 3 days; starting from day 4, the dose was increased to 10 mg, 3 times a day. The patient attended all scheduled visits and regularly took the baclofen pills as indicated by counting the returned tablets. He did not report any side effect, with the sole exception of a mild degree of sedation at the very beginning of the treatment. He stopped drinking from the first week of treatment; breath alcohol concentrations were negative throughout the treatment. OCDS and VAS scores were virtually suppressed from the first 4 weeks of treatment (Table 1). Indexes of severity of schizophrenic symptoms tended to decrease during treatment (Table 1). Conversely, anxiety and depression severity scores were not modified by baclofen administration. In line with the reduction in alcohol intake, value of mean corpuscular
volume decreased from 101 to 94 fL over treatment with baclofen. The patient reported the consumption of 1 drink in week 18. Subsequently, taking into account the recently reported beneficial effects induced by relatively high doses of baclofen (up to 270 mg/d) on alcohol consumption and craving for alcohol,7 the dose of baclofen was increased to 25 mg, 3 times a day. After 1 year of treatment, the latter remains the only episode of alcohol drinking, as the patient demonstrated near-complete suppression of alcohol drinking and craving for a 48-week period.

DISCUSSION

Suppression, or at least reduction, of alcohol drinking is 1 of the major goals in the treatment of patients affected by schizophrenia and alcohol dependence.2 However, research to evaluate effective pharmacotherapies for patients diagnosed with AUDs and psychiatric comorbidity is still in its infancy. To our knowledge, this is the first case of a schizophrenic alcohol-dependent patient treated with baclofen in an attempt to decrease his alcohol consumption. Consistent with previous reports,11–13 treatment with baclofen did not worsen schizophrenic symptoms in our patient, as indicated by the scores of BPRS and CGI. Vice versa, treatment with baclofen resulted in a virtually complete suppression of alcohol drinking, without occurrence of any relevant side effects. This observation is in agreement with the results of 2 recent studies which demonstrated that treatment with baclofen induced a significant reduction in alcohol intake and craving for alcohol.4,5 Of interest, another GABAergic medication has recently been suggested to be effective in alcohol-dependent schizophrenic patients. A recent case report indeed described how the GABAergic antiepileptic drug, topiramate, suppressed alcohol intake in a patient affected by alcohol dependence and schizophrenia.17 In conclusion, the present observation suggests that baclofen may be evaluated in future, properly designed studies as a novel pharmacotherapy for patients affected by alcohol dependence and schizophrenia.

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REFERENCES

Comments on “Postpartum Depression” Article by Dr Wisner and Colleagues

To the Editors:

I write as a concerned reader about the article “Postpartum Depression—A Randomized Trial of Sertraline Versus Nortriptyline” published in August 2006. My concern centers on the apparent extent of the methodological flaws within this study. The main problems with the research, as I see them, are as follows.

Although the basic assumption, that postpartum depression may be a different clinical entity, is worthy of research, a number of the scientific assumptions used in this article do not stand up to scrutiny. This includes the statement that previous research shows that selective serotonin reuptake inhibitors (SSRIs) compare favorably with tricyclic antidepressants (TCAs) in postpartum depression. This statement was based on Ref. 7, an article based on research done on 6 patients, and Ref. 8, a nonrandomized trial that quotes a 12% benefit in treatment by SSRIs as compared with TCAs in 35 patients. Aside from the trial being an open one, a power calculation shows that for this result to be statistically significant, there should be at least 43 patients in each arm of the trial. Lastly, this result was then compared with Ref. 10, a randomized controlled trial in non-postpartum depression and, therefore, an entirely inappropriate comparison.

I also think the statement, “Women with PPMD also have significantly more aggressive obsessional thoughts (14) than non postpartum women with depression. Although these women did not have obsessive-compulsive disorder, they may comprise a subtype of depressed women who are particularly responsive to SSRIs, which are effective for obsessive-compulsive disorder, whereas TCAs are not,” is incorrect.

Clomipramine was one of the first medications to be used successfully in obsessive-compulsive disorder and remains as the first- or second-line treatment in many guidelines. It also fails to point out that Ref. 14 shows no difference in overall obsessional symptoms; only a difference in content exists between the 2 groups. I am unaware of any research that shows the content of obsessions has any bearing on their response to particular pharmacological treatments.

The article then goes on to state exact and valid hypotheses that it wishes to test but fails to maintain the focus of the study, as exemplified by the addition of the arm of women with chronic depression after study inception, and 25% of their conclusions (6 and 8) did not appear relevant to their hypotheses.

The description of the drug intervention seemed contradictory at times:

- “All subjects were treated with a fixed-dose strategy.”
- “Thereafter, the doses were increased to 50 mg/d SERT and 25 mg/d NTP and increased until either response or side effects prohibited further dose escalation. The maximum doses were 200 mg/d SERT and 150 mg/d NTP.”
- “We emphasize that doses were not titrated to response for either drug.”

Other methodological flaws include no description of the process of concealment of randomization. This is particularly pertinent because only 61% of the 420 patients who inquired about the study were actually interviewed, and there was a statistically significant imbalance in the ethnic minority entrance into each arm (40% sertraline, 19% nortriptyline).

The power calculation appears to have been done retrospectively rather than prospectively. It showed that the study could only detect a difference of more than 30% in treatment effect, a figure that even if you take into account the flawed references quoted at the beginning of the article (showing at the very extremes of the SDs a 29% difference) is optimistic.

About the results, only 53% (n = 109) of the 206 patients eligible were enrolled, and of those enrolled, only 76% (n = 83) remained in the study at 8 weeks, and only 27% (n = 29) completed the full 20 weeks of the study. These attrition rates are not compatible with valid statistical analysis and the drawing of reasonable conclusions. There is an intention-to-treat analysis, but the only positive result that has been drawn from the study, that responders to sertraline can be predicted earlier than those who respond to nortriptyline, does not appear to be drawn from the intention-to-treat analysis.

Even if this study was well constructed and had valid conclusions, there is no way for the reader to assess its own patient populations because no demographic details have been given at all. The authors state that despite the marked difference in ethnicity between the 2 study groups, there are no differences in demographic details between these 2 groups. This appears contradictory to the large body of research documenting the differences in social class, financial status, physical and mental health, and educational attainment that can be found across the different ethnic groups in the United States.

Lastly, most concerning of all the possible flaws in this article is that the authors have not included a single caveat that acknowledges their results may be invalidated as a result of the methodological flaws of this study.

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REFERENCE


Preventing Postpartum Complications in the Depressed Pregnant Women

To the Editors:

I would like to comment on a subset of depressed mothers in whom their offspring may have a serious medical problem. The results reported by Wisner et al checking nortriptyline, a tricyclic antidepressant (TCA),
with sertraline, a selective serotonin reuptake inhibitor (SSRI), are in synthesis: the proportion of women who responded and remitted did not differ between drugs at up to 6 months of follow-up. What is more, their psychosocial functioning was improved similarly in both drug-treated groups of mothers, and the total side effects of each drug were similar, although with different profiles between these agents.

Although the scope of the article was the treatment of postpartum depression, sometimes, this treatment needs to be initiated during pregnancy. Being this the case, in the last years, a worrisome complication has been reported that affects the fetus of the depressed pregnant mothers, situation not mentioned by Wisner et al: taking SSRIs (specifically during the second half of pregnancy) may cause pulmonary hypertension in the offspring.2–4 Although it is certain that this risk is low (1 or 2 cases by each 1000 pregnant women taking SSRIs), the problem is serious. By the recent awareness of these complications, there is no information, to the best of my knowledge, showing analogous effects in mothers taking TCA during the pregnancy, although it is noteworthy that the TCA placental passage resulted in considerable fetal exposure.5

Serotonin has vasoconstrictive properties that increase pulmonary vascular resistance; thus, higher circulating levels of serotonin in the fetus and accumulation of serotonin in the fetal lung might result in the proliferation of smooth muscle cells, which is characteristic of persistent pulmonary hypertension.5 So, it is reasonable to speculate that this side effect is probably present in an analogous form with TCAs as with SSRIs. Although the offspring pulmonary hypertension related to SSRI intake in the mother is a serious complication, we should keep in mind the numbers of patients with depressive disease who are clinically symptomatic and need intervention, compared with the numbers of their offspring that can get the complication. Moreover, because the effective treatments for pulmonary hypertension remain problematic, at present, the most important goal should be prevention.

In summary, I suggest that clinicians must evaluate carefully when to prescribe TCAs or SSRIs to pregnant women, that is, individualizing the cases: (a) a prudential reduction of TCA or SSRI treatment when possible, (b) intensified psychotherapy previous to drug reduction, or (c) in patients that cannot avoid or reduce substantially the dose of the antidepressant drugs, the decision about continuing the pharmacologic action should incorporate a clear discussion of the hazards of the treatment. Simply avoiding the prescription of antidepressant drugs in pregnant women is not a solution.

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REFERENCES

Reply to Drs Henderson and Vale

To the Editors:

We appreciate the interest of your readers in our study,1 the first published randomized comparative antidepressant trial for postpartum major depression (PPMD). The writer of the first letter is concerned that pilot studies we cited to suggest that selective serotonin reuptake inhibitors (SSRIs) were more efficacious than tricyclic antidepressants (TCAs) for PPMD lacked adequate power. This is certainly true. Scientific advancement typically evolves from the sequence of clinical observation, open trials, and small randomized studies, which direct more labor-intensive (and expensive) controlled investigations. Although the strength of previous studies provides an interesting discussion, it does not affect the outcome of our investigation.

The writer states that the serotonergic TCA clomipramine (CMI) is efficacious for obsessive-compulsive disorder (OCD). Indeed, CMI was the first drug shown to be efficacious for this disorder; however, we used the SSRI sertraline and nonserotonergic TCA nortriptyline in our study of women with PPMD. We used CMI to openly treat the breast-feeding group of nonresponders to sertraline or nortriptyline in the study under comment.1 We reasoned that the next line of drug treatment would be a serotonin-norepinephrine reuptake inhibitor such as CMI. Three sertraline nonresponders were treated with CMI; 2 achieved full remission. Four nortriptyline nonresponders were treated with CMI; only 1 responded. Our group has studied CMI levels in breast-feeding mother-infant pairs.2

We3 found that women with PPMD had a significantly higher median number of obsessions (n = 7) compared with nonpostpartum depressed women (n = 2, P = 0.00). Women with PPMD had significantly more aggressive obsessional thoughts. Aggressive obsessions also occur more frequently in patients with postpartum OCD than patients with OCD unrelated to childbearing.4 We and others proposed that aggressive obsessions might be particularly responsive to serotonergic treatments on the basis of serotonin deficit in aggression.5,6 We tested this reasonable hypothesis and found no difference in the reduction of obsessional aggressive thoughts in sertraline- versus nortriptyline-treated women with PPMD as well as no difference in the total Yale-Brown Obsessive Compulsive Scale scores after 8 or 24 weeks of treatment.

Regarding the inclusion of women who had depression before birth, the results of statistical analyses with and without this group were unchanged. On page 357 (paragraph 3, second sentence), the phrase should read, “chronic or acute status during the postpartum” (rather than pregnancy). This analysis
...was correctly phrased in the Methods section (page 355, paragraph 6).

Subjects were treated with a fixed-dose strategy that required dose escalation unless the woman had prohibitive side effects or remission. The sentence that stated that “doses were not titrated to response for either drug” should have read, “the doses were not titrated to serum levels.” Because therapeutic serum levels of nortriptyline, but not sertraline, have been established, an advantage would have occurred for nortriptyline. We note that most randomized trials do not provide evidence via serum levels that the drug was taken, which was included in our investigation of PPMD.

We take this opportunity to provide information about the doses required to achieve remission. At 8 weeks, we observed the following doses for the 25 sertraline-treated women who remitted: 1 = less than 100 mg/d, 12 = 100 mg/d, 5 = 125 or 150 mg/d, and 7 = 200 mg/d; for 26 nortriptyline remitters: 15 = less than 100 mg/d, 7 = 100 mg/d, and 4 = 125 or 150 mg/d.

The reader wondered about the adequacy of the blind. The procedures are described in our Methods section (page 355, paragraph 3). We also checked the success of the blind. Neither subjects nor staff members identified the true drug assignment better than chance, with \( \kappa \) values ranging from 0.02 to 0.07.

We had more minority women in the group randomized to sertraline, but that was a consequence of not stratifying randomization by race rather than not concealing the randomization.

The writer is also critical of our subject flow rates. It is expected that many more inquiries about a study will occur along the pathway to identifying women who are eligible and willing to participate. Initially, 420 women called our program, and a brief interview was done. Additional screening and eligibility details about participation were presented, and 206 women agreed to come to our research suite to be interviewed. After these evaluations and laboratory assessments were completed, 109 women met all eligibility criteria and agreed to be randomized. Our ratio of enrolled subjects to inquiries does not differ substantially from other studies that track and report parallel flow numbers. Generally, 5 patients are screened for every patient enrolled in a clinical trial of an antidepressant.

The writer notes that 83 subjects (76%) remained in the study at 8 weeks. In randomized trials of antidepressants, attrition is commonly observed, and a 20% to 40% dropout rate is typical. After the 8-week acute phase, the only women who were eligible to enter the continuation phase were those who responded, which accounts for the reduction in the number of women. The continuation phase was designed to assess durability of response through 24 (not 20) weeks. We disagree that our evaluation of the differences in times to response or remission (page 357, paragraph 4; Figure 2) needed to be performed within an intent-to-treat analysis. This exploratory analysis included only those women who fully participated through week 8 because of the nature of the question. Intent-to-treat analyses are designed to be certain that the drug efficacy analysis includes people who do not take the drug as directed and that reasons for noncompletion are identified.

Our retrospective power calculations used the observed values derived from our study and estimated the probability that the observed numbers were possible with the hypothesized effect sizes that we anticipated (page 357). As suggested in the guidelines of the journal, we included the calculations upon which we based our study and a retrospective evaluation of their relationship to our initial hypotheses.

The writer commented about marked difference in minority representation that occurred in the sertraline-treated group, yet there were no other differences in demographic details between the groups (page 356, paragraph 1). He or she contends that this “appears contradictory to the large body of research documenting the differences in social class, financial status, physical and mental health, and educational attainment that can be found across the different ethnic groups in the US.” We agree with the writer, but we can only report the demographics of the sample we were able to include in our study. We evaluated the demographics extensively and present additional data in Table 1.

None of the concerns that the writer posits threaten the validity of our findings. In the group of women with PPMD randomly assigned to sertraline or nortriptyline, we observed no difference in any of our outcome measures. Similar efficacy and effectiveness of different classes of antidepressants are consistent with the antidepressant literature for more general populations. Our findings do not preclude that women with PPMD might respond differentially to therapies other than antidepressants (eg, estradiol). Postpartum major depression is particularly well suited for tests of estradiol efficacy because of its occurrence in the context of large-scale estrogen withdrawal immediately after childbirth. Women with PPMD appear differentially sensitive to the mood-disturbing effects of withdrawal from gonadal steroids.

Because of the dearth of studies specific to PPMD, the assumption has been that medications efficacious for major depression are also efficacious for PPMD. The results of our investigation support that assumption. Our population included a range of subjects, unlike most postpartum studies (reviewed by Gaynes et al11). Notably, our sample included 23% minority participants.

As the second writer recognizes, our study was specifically focused on the treatment of PPMD, and medication was initiated only after parturition. For treatment during pregnancy, we agree that the risks and benefits of antidepressant use must be focused on an individual patient. The writer notes that Chambers et al13 reported that the risk of persistent pulmonary hypertension of the newborn (PPHN) was 6 to 12/1000 versus 1 to 2/1000 in infants with gestational exposure to SSRIs versus no exposure to SSRIs, respectively, in the final 20 weeks of gestation. This is a 6.1 relative risk, but a small absolute risk. No fatalities occurred in the infants with PPHN. Exposure to TCA at any point in pregnancy was not a risk factor for PPHN. These findings, as well as neonatal syndrome (reviewed by Moses-Kolko et al14), are additional risks to bring to the decision-making process, which must be balanced against untreated depression.

Postpartum major depression exacts a heavy toll on women’s functioning and the health and well-being of...
TABLE 1. Demographics of Consented Subjects Across Drug Groups

<table>
<thead>
<tr>
<th></th>
<th>Sertraline (n = 55)</th>
<th>Nortriptyline (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33 60.0</td>
<td>44 81.5</td>
</tr>
<tr>
<td>Black</td>
<td>20 36.4</td>
<td>8 14.8</td>
</tr>
<tr>
<td>Other</td>
<td>2 3.6</td>
<td>2 3.7</td>
</tr>
<tr>
<td><strong>Living Arrangement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spouse or</td>
<td>38 70.4</td>
<td>40 74.1</td>
</tr>
<tr>
<td>significant other</td>
<td>FE, P = 0.485</td>
<td></td>
</tr>
<tr>
<td>With family of origin</td>
<td>7 13.0</td>
<td>9 16.7</td>
</tr>
<tr>
<td>With no other adults</td>
<td>9 16.7</td>
<td>5 9.3</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>10 19.6</td>
<td>9 18.8</td>
</tr>
<tr>
<td>Completed high school</td>
<td>7 13.7</td>
<td>5 10.4</td>
</tr>
<tr>
<td>Some college or trade</td>
<td>21 41.2</td>
<td>18 37.5</td>
</tr>
<tr>
<td>Completed college</td>
<td>13 25.5</td>
<td>16 33.3</td>
</tr>
<tr>
<td><strong>Employment Status</strong></td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>22 44.9</td>
<td>20 41.7</td>
</tr>
<tr>
<td>Not employed</td>
<td>27 55.1</td>
<td>28 58.3</td>
</tr>
<tr>
<td><strong>Acute or Chronic Postpartum Depression</strong></td>
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<td></td>
</tr>
<tr>
<td>Chronic*</td>
<td>15 27.8</td>
<td>22 40.7</td>
</tr>
<tr>
<td>Acute onset†</td>
<td>39 72.2</td>
<td>32 59.3</td>
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<tr>
<td><strong>Parity</strong></td>
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<td>1 Child</td>
<td>22 40.0</td>
<td>25 46.3</td>
</tr>
<tr>
<td>2 Children</td>
<td>16 29.1</td>
<td>14 25.9</td>
</tr>
<tr>
<td>&gt;2 Children</td>
<td>13 22.6</td>
<td>12 22.2</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.54</td>
<td>28.15</td>
</tr>
<tr>
<td>Range</td>
<td>16–39</td>
<td>15–42</td>
</tr>
<tr>
<td>SD</td>
<td>5.99</td>
<td>6.72</td>
</tr>
<tr>
<td><strong>Initial CGI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mildly ill</td>
<td>6 11.2</td>
<td>8 15.1</td>
</tr>
<tr>
<td>4 moderately ill</td>
<td>36 66.7</td>
<td>35 66.0</td>
</tr>
<tr>
<td>&gt;4 severely ill</td>
<td>12 22.2</td>
<td>10 18.9</td>
</tr>
<tr>
<td><strong>Initial HRS-D</strong></td>
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<tr>
<td>Mean</td>
<td>24.9</td>
<td>23.61</td>
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<tr>
<td>Range</td>
<td>13–40</td>
<td>11–36</td>
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<tr>
<td>SD</td>
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<td>5.42</td>
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<tr>
<td><strong>Initial GAS</strong></td>
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<td>Mean</td>
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<tr>
<td>Range</td>
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<td>48–82</td>
</tr>
<tr>
<td>SD</td>
<td>6.7</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>No. Social Problems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 16.7</td>
<td>7 13.7</td>
</tr>
<tr>
<td>1 or 2</td>
<td>20 41.7</td>
<td>23 45.1</td>
</tr>
<tr>
<td>&gt;2</td>
<td>20 41.7</td>
<td>21 41.2</td>
</tr>
</tbody>
</table>

*Depressed during pregnancy. †Not depressed during pregnancy.

CGI indicates Clinical Global Impression; HRS-D, Hamilton Rating Scales for Depression (17 item); GAS, Global Assessment of Functioning; FE, Fisher Exact Test.

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REFERENCES

Selective Serotonin Reuptake Inhibitors in Adolescent Depression Still Controversial

To the Editors:

As investigators participating in the study of von Knorring et al., we cannot share all of the conclusions drawn by the authors.

First of all, there is the implicit statement that citalopram, which was more effective than placebo in the restricted group who did not receive psychotherapy, could be a treatment of major depressive disorder in adolescents instead of psychotherapy. As a result, this means that selective serotonin reuptake inhibitors (SSRIs) could replace a specific treatment by specialists such as psychotherapy. Regrettfully, no information is available concerning the suicide attempters regarding their belonging to the group receiving psychotherapy or not. We might assume that suicidal risk is an intrinsic component of depression and cannot be totally excluded. Nevertheless, such a risk would be better evaluated and monitored by trained professionals and in a context of close follow-up as it is during psychotherapy. However, clinical efficacy of psychotherapy for adolescent depression remains controversial.

Actually, the nonsignificance of the active treatment effect on suicide attempts in this placebo-controlled study should be considered with caution. P = 0.06 means that there is only 1-in-17 chance that the observed increase in suicide attempts is caused by hazard. Moreover, if we hypothesize that SSRIs increase the suicide risk, we should consider a univariate analysis, with a significant difference (P = 0.03). Therefore, the statement, that is, consistent indications that the higher frequency of suicide-related events in the citalopram group could be associated with treatment were not identified, appears to be weak, and this study cannot exclude this possibility. This statement relies only on a worsening of single-item scores (Kiddie Schedule for Affective Disorders and Schizophrenia–Present, Montgomery–Asberg Depression Rating Scale) of suicidal thoughts more frequent in the placebo group.

The methodological limitations mentioned that could explain the lack of citalopram efficacy merit further discussion. The severity of depression and history of previous suicide attempts in this study are likely, according to the authors, to explain the nonsuperiority of citalopram and its higher risk profile as such patients were excluded from other placebo-controlled studies. This statement is contradictory to the conclusion of a meta-analysis which found a better efficacy of escitalopram in the severely depressed population. For ethical reasons, investigators could hardly enroll patients who have a severe depression with an obvious suicidal risk in the study. It was difficult to take the risk that such patients receive placebo, especially in an outpatient setting. The recruitment bias mentioned by von Knorring et al results probably not in a more severe and more suicidal sample, although it is in this way we would expect the bias.

We need effective pharmacological treatment for the more severely depressed at higher risk for suicide, rather than for the mild or moderate depressive state that is frequent during adolescence. From our point of view, the main methodological limitation is not the severity of depression in the sample in itself, but the adultomorphic criteria of inclusion, which does not fit a wide range of depressive states occurring during adolescence. Even if the Beck Depression Inventory score was lowered to 16 for boys, adolescents are more likely to express their depressive state in acts and behaviors, rather than in internal feelings, and to fail to reach a sufficient Beck Depression Inventory score to be enrolled.

This study maintains and stimulates the SSRI in adolescent depression controversies. Answers in such controversies need further studies with methodological improvement. In addition, taking into account the specificities of adolescent depression with a redefinition of diagnosis criteria and a refinement of depressed adolescent samples is a prerequisite to answer the debating and passionate question of the efficacy of SSRIs and psychotherapy in adolescents.

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REFERENCES

Reply to Comments by Drs Holzer and Baumann

To the Editors:

We agree with the comments regarding methodological difficulties in designing clinical trials in pediatric depression, including the need to redefine diagnostic criteria.

The high incidence of children that were treated with some form of psychotherapy was a confounder in this trial, and we were unable to show a benefit of citalopram. A post hoc analysis of those children not receiving psychotherapy indicated that citalopram might have been more effective than placebo. We did not conclude that citalopram could be a replacement for psychotherapy.

Unlike the other trial with citalopram in pediatric depression, children at risk for suicidal behavior were not excluded from our study. We wanted to include patients similar to common clinical practice, and to ensure close monitoring of suicidality, psychotherapy was allowed in the study. It has been shown that the response of adults to escitalopram increases as a function of baseline severity, but this was not found for citalopram. The nonsignificance of citalopram treatment is related to suicide-related events, not just suicidal attempts. The trial was not powered to detect a difference in suicide-related events, and we do not consider a post hoc 1-sided test to be valid. We do agree, as stated in the label of all SSRIs, that close monitoring by the treating clinician for suicidal behavior in the patient is required.

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