Letters to the Editor

ECT-Induced Premature Labor: A Case Report

Sir: The pregnant patient with serious mental illness poses a therapeutic challenge. The clinician must weigh the risks of fetal exposure to psychiatric medications against the potential harm posed by untreated psychiatric disease. Alternatively, electroconvulsive therapy (ECT) is generally considered safe and effective for use during pregnancy, and guidelines have been formulated to reduce the risk of adverse effects. Although a number of case reports have described complications in pregnant women receiving ECT, it is not known whether these events were directly related to the treatment. The case of a woman who experienced premature labor immediately following a single ECT treatment is described.

Case report. Ms. A, a 29-year-old white woman, had chronic paranoid schizophrenia and depressive symptoms that had been managed for 2 years with risperidone and paroxetine. In early 1996, she discontinued these medications because she was planning to become pregnant for the first time. She conceived 2 months later and functioned well at home without medications until 5 months after conception, when in week 23 of pregnancy.

Over a 2- to 3-week period, Ms. A became increasingly disorganized, delusional with paranoid themes, and suicidal. She was admitted to the inpatient psychiatric unit and treated with risperidone, 2 mg h.s. She was also given ferrous sulfate, a prenatal vitamin, and a course of trimethoprim for a urinary tract infection.

Ms. A continued to be very disorganized and psychotic despite an increase of risperidone to 3 mg b.i.d. She also became increasingly depressed and suicidal and began showing symptoms of catatonia such as psychomotor slowing, poverty of speech, and profound thought-blocking. Risperidone was discontinued after 19 days, and Ms. A was treated with loxapine, 75 mg b.i.d., lorazepam, 1 mg t.i.d., and nortriptyline, 50 mg h.s. When she continued to be catatonic after 17 more days, the decision was made to start a course of unilateral ECT.

An obstetrical nurse monitored fetal heart tracings before, during, and immediately after the treatments. Ms. A initially received 80 mg of succinylcholine and 240 mg of thiopental during the first ECT treatment. She received an additional 40 mg of thiopental to discontinue that seizure. Immediately after the first ECT treatment (pulse width = 1.2 ms, frequency = 50 Hz, current = 0.6 A, seizure length = 89 s), Ms. A experienced uterine contractions every 2 to 3 minutes. She was transferred to the obstetrics service, where premature labor was diagnosed. Treatment with indomethacin and ritodrine halted labor successfully.

Urinalysis was obtained and a culture grew 10,000–100,000 CFU/mL of enterococcus. Cervical swab also showed the presence of clue cells and white blood cells consistent with trichomoniasis. Ms. A was started on metronidazole and nitrofurantoin.

Ms. A returned to the psychiatric unit after 1 day. The obstetrical consultant recommended discontinuation of ECT. However, because of Ms. A's continued catatonia, disorganization, and suicidal thoughts, the risk to the fetus and patient of her uncontrolled illness outweighed the risk of resuming ECT. Five days after the first ECT treatment, right-sided unilateral ECT was restarted, and nortriptyline discontinued because it was ineffective. Treatments were performed every Monday, Wednesday, and Friday. She was started on terbutaline, 5 mg p.o. every 4 hours, and indomethacin (50 mg per rectum 2 hours before each treatment then 25 mg p.o. 2 hours after each treatment) for preterm labor prophylaxis. She was also given dexamethasone, 12 mg i.m. every Friday and Saturday, to promote fetal lung development.

Although Ms. A had no further episodes of premature labor, her depressive and psychotic symptoms failed to improve. Bilateral ECT began at treatment number 8 and continued on Mondays, Wednesdays, and Fridays. The total course of ECT lasted 3½ weeks. During treatment 12, Ms. A experienced transient but significant bradycardia and hypoxemia. Given her minimal improvement, ECT was discontinued.

Miller's 1994 review of ECT use during pregnancy[1] cited 300 cases reported in the literature from 1942–1991. Of these, complications were reported in only 28 cases. Uterine contractions occurred in 2 cases and premature labor in 4 cases. In the 4 reported cases of premature labor in pregnant patients receiving ECT, the labor did not immediately follow the treatment and was attributed to other factors—for example, administration of an enema prior to a treatment, a history of concurrent insulin shock therapy, and a congenital fetal malformation.[1–4] One of the cases of premature contractions occurred secondary to mild placental abruption.[5]

In our case, the premature labor immediately followed the ECT treatment. The mechanism for ECT-induced premature labor is unknown, but it is thought that transient hypertension occurring during treatments can lead to uterine hyperstimulation.[5] In this case, however, the patient did not become hypertensive (systolic blood pressure range, 116–130 mm Hg).

Low levels of serum calcium or magnesium can also cause neuromuscular irritability, although our patient's calcium and magnesium levels were within the normal range.[6]

An inadequate dose of succinylcholine hypothetically could have resulted in abdominal muscle contraction and then premature labor. However, the succinylcholine dose was actually decreased after the treatment that was associated with premature labor (from 80 mg to 60 mg). Alternatively, it is possible that our patient had a pseudocholinesterase deficiency worsened by pregnancy that led to her inability to metabolize succinylcholine.[7] This may have resulted in muscle fasciculations during the first treatment. An increase in circulating succinylcholine might also explain why she later became bradycardic and hypoxemic (when the succinylcholine dose was again increased to 80 mg).

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Another hypothesis is that the patient's uterus was hypoperfused during the initial treatment. It is known that the gravid uterus can compress major blood vessels, thus reducing blood pressure and placental perfusion. It also has been suggested that a further impedance to flow in the placental vasculature occurs during ECT.[7] These factors, coupled with the failure to adequately hydrate the patient prior to the first treatment, may have led to uterine irritability.

Although she did not appear to have any other risk factors for premature labor,[8] it is possible that her urinary tract infection and trichomoniasis may have been additional factors contributing to this complication.[9]

In 1978, Remick and Maurice[8] proposed guidelines for the safe use of ECT in pregnant patients. They suggested that every pregnant patient undergoing ECT should receive a thorough physical examination (including a pelvic examination), that an obstetrician be a member of the team managing the ECT, and that external fetal monitoring be used before and for several hours after each treatment.

In 1984, Wise et al.[10] recommended expanding these guidelines. High-risk pregnant patients undergoing ECT should be intubated, and glycopyrrolate used as the anticholinergic of choice. The patient should be adequately hydrated during each treatment, and a pillow placed under the patient's right hip to maintain the left lateral position.[10,11] Both patient and fetus should be closely monitored before, during, and after each treatment.[1,10]

American Psychiatric Association guidelines echo these recommendations and stress that facilities planning to use ECT in pregnant women should have resources available to manage fetal emergencies and other foreseeable events "including the precipitation of labor (though this has not yet been reported with ECT)."[12]

With such a small number of reported cases of premature labor secondary to ECT appearing in the literature, it is difficult to predict which patients may experience this complication as a result of treatment. No relationship can be drawn between patient's age, race, number of pregnancies, number of ECT treatments, or trimester at the time of administration. Although several mechanisms have been postulated to explain ECT-induced premature labor, it is unclear why this complication occurred in this case, and possible mechanisms for uterine hyperstimulation following ECT should be studied further.

Nonetheless, this case raises some important points. It demonstrates that ECT can be continued in the pregnant patient who has experienced uterine contractions or premature labor. Prophylactic management with indomethacin and terbutaline successfully prevented further episodes of premature labor in this patient, although it is possible that adequate hydration or treatment of an underlying infection may have also helped to avoid further complications. Prophylactic management should be considered in patients who are already at high risk for premature labor and being considered for ECT treatment.

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Capitation

Sir: William M. Glazer says that "capitation should bring an end to reviewers as we have known them" (Supplement 2).[1] Since capitation punishes unneeded treating, it does reward the undertreater, and thus unburdens reviewers on watch for overtreatment.

But in a universe fraught with Unintended Consequences, even if reviewers as we have known them become passé while capitation stays constant, less-than-ample treatment will still reward the treater even while it metamorphoses the needful-but-untreated patient into litigant.

Id est: Capitation can foster litigation.

So now reviewers must prevent *over*treatment that makes the corporation pay a capitated treater excessively, but they must also anticipate, discover, and prevent *under*treatment with outcomes that load the cannons of the tort pirates.

Not an enviable task, that.

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Dr. Glazer Replies

Sir: Dr. Sheeley's logic is consistent with my comment that "capitation should bring an end to reviewers as we have known them." But it is unfortunate that he imagines the new reviewer to be the litigious patient and chooses to consider the "unintended consequences" rather than the intended ones! *My* intention is for physicians to perform *our own* utilization review rather than remain "victim" to external intrusions that we have attracted out of our failure to monitor our practices in the first place. If we align with our patients in an honest and accurate ef-

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fort to protect quality of care, the "tort pirates" will become very bored with us. Such an alignment will require some reengineering of the way we have related to patients traditionally.

A final point: We must develop methods to facilitate patient-level treatment decisions that are free of financial incentives that stem from the reimbursement method. Psychiatrists' decisions have been driven as much by the terms of the patient's benefits as they have by the clinical dimensions of the disorder treated. Also . . . not an enviable task.

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Risperidone Augmentation of Paroxetine in a Case of Severe, Treatment-Refractory Obsessive-Compulsive Disorder Without Comorbid Psychopathology

Sir: Risperidone is an atypical antipsychotic drug distinguished from conventional neuroleptics by its antagonism of serotonin receptors of the 5-HT_{2A} and 5-HT_1 subtypes while having a similar affinity for dopamine D_2 receptors.[1,2] The novel pharmacologic profile of risperidone suggests the possibility of other therapeutic applications, particularly in disorders putatively associated with abnormal central serotonergic function.[3] Obsessive-compulsive disorder (OCD) is such a disorder, and recent reports suggest that risperidone may be an effective adjunct to treatment of OCD with selective serotonin reuptake inhibitors (SSRIs).[4–8] Classical dopamine antagonists have been shown to be effective when added to SSRIs in OCD patients with concomitant tic disorder[9] and have also been reported to improve OCD symptoms in patients with concurrent psychotic spectrum disorders.[10] Risperidone addition to an SSRI may be effective in OCD patients without comorbid illness.[6] In line with this suggestion, we report a case of severe, treatment-refractory OCD, without comorbid psychiatric disorder, which responded to the addition of risperidone to ongoing paroxetine treatment.

Case report. Mr. A, a 25-year-old white male Orthodox Jew, had been diagnosed as having OCD 10 years previously. His obsessions and compulsions began toward the end of the eighth grade and included fears of disease, particularly AIDS, concerns about food being spoiled, thoughts about cursing God, and worries about being stupid. These concerns resulted in periods of excessive hand washing and refusal to eat. In addition, Mr. A found himself in constant need to pray in a certain way and to repeat certain prayers over and over. He also needed to touch certain objects repeatedly. His symptoms resulted in significant functional impairment and social difficulties. The obsessions and compulsions were ego dystonic; Mr. A was never in a psychotic state and always had good insight into his mental problem.

Mr. A's early development had been unremarkable. He was a bright student who did well both academically and athletically. His peer relationships during school were considered good. His physical health was and is still excellent. On examination, he fulfilled DSM-IV criteria for OCD and had no additional diagnosis on Axis I or Axis II. His father had been treated in our clinic for recurrent major depression with anxiety (but no obsessional components) and responded well to sertraline.

Mr. A had been treated with a variety of medications as well as with behavioral therapy, psychodynamic psychotherapy, and family therapy. The medications he received included fluoxetine, up to 80 mg/day; imipramine, up to 150 mg/day; clomipramine, up to 175 mg/day; fluvoxamine, up to 250 mg/day; sertraline, up to 200 mg/day; and paroxetine, up to 60 mg/day, all with and without clonazepam, 2–10 mg/day. All of the above drugs had been administered for at least 8 weeks. Various additions to the above antidepressants were used: lithium (with blood levels in the range of 0.8–1.0 mEq/L) was added to fluoxetine, imipramine, clomipramine, and fluvoxamine. Pindolol, up to 7.5 mg/day, was added to paroxetine. Our treatment of Mr. A began with dextroamphetamine, up to 10 mg/day, as well as methylphenidate, up to 10 mg/day, added to paroxetine.

None of the above medications was of help to Mr. A, although he reported that pindolol addition to paroxetine was the best combination. (However, it resulted in only a minor change in the Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score from 14 to 10 on the obsessions scale and from 20 to 18 on the compulsions scale.) Dextroamphetamine addition to paroxetine had a dramatic effect in the first 24 hours after the drug was taken—the Y-BOCS obsessions score decreased from 14 to 4 and the compulsions score decreased from 20 to 2—but this effect was not maintained.

After dextroamphetamine was stopped, risperidone, 1.5 mg/day, was added to paroxetine, 60 mg/day. Within 1 week, Mr. A reported a marked reduction in his obsessions and compulsions. His Y-BOCS obsessions score decreased from 14 to 4, and his score on the compulsions scale decreased from 20 to 2. This effect was maintained for 2 months. Mr. A started to teach in a yeshiva, returned to his studies for ordination as a rabbi, and was able to function consistently and interact socially for the first time in many years.

During the third month of treatment with these drugs, there was a dramatic change in Mr. A's mood. Without any apparent trigger, he started complaining about being depressed most of the day, having markedly diminished interest in most activities, loss of appetite, diminished ability to concentrate, and difficulty falling asleep. These symptoms caused impairment in his occupational and social functioning. The total score of the 21-item Hamilton Rating Scale for Depression (HAM-D) was 23. Before starting risperidone, Mr. A had received a score of less than 6 on this scale. The improvement in his OCD symptoms was maintained (Y-BOCS total score = 6).

Mr. A was advised to take an additional antidepressant drug (a tricyclic antidepressant with adrenergic effects such as desipramine), but he refused. He said he was receiving too many drugs and was despondent about pharmacotherapy. A short time afterward, Mr. A stopped taking all medications, and 2 weeks later he felt an improvement in his mood. He scored 6 on the 21-item HAM-D, but at the same time, his obsessive and compulsive symptoms worsened. His Y-BOCS obsessions scale score was 14, and his compulsions scale score was 20.

After 1 month, Mr. A agreed to start taking medications again. This time he was given paroxetine at the same dose as before (60 mg/day) and risperidone at a dose of only 0.5 mg/day. Within 2 weeks, there was an improvement in his obsessive and compulsive symptoms, although the improvement was not as dramatic as it was the first time he received risperidone (at a dose of 1.5 mg/day). His Y-BOCS obsessions scale score was 6, and his compulsions scale score was 4. Mr. A felt slightly depressed with mild diurnal variations, reported slight sleep disturbances, and fatigue; his score on the 21-item HAM-D was 9. Thus, augmentation with risperidone at a dose of 0.5 mg/day improved the patient's obsessive and compulsive symptoms less than a dose of 1.5 mg/day, but caused fewer depressive symptoms. This clinical state has been maintained for 9 months.

Although SSRIs are widely used for the treatment of OCD, 40% to 60% of patients are resistant to these drugs or have a therapeutically inadequate response.[11] Together with previous reports,[4–8] this single case suggests that risperidone could be a useful supplement in such instances and that a therapeutic effect may be achieved in patients with good insight and in the absence of comorbid psychopathology. Thus, controlled studies of risperidone augmentation in refractory OCD are indicated.

We speculate that an antiobsessional effect of risperidone in conjunction with an SSRI could be due to blockade of dopamine receptors or of 5-HT_{2A} (and/or 5-HT_7) receptors or to both. Dopamine blockade is less likely to be the pivotal factor, since dopamine blockers, combined with an SSRI, would appear to be preferentially effective in OCD patients with concurrent tic disorder or psychotic states.[9,10] Moreover, risperidone given as monotherapy has been anecdotally reported to exacerbate obsessive-compulsive symptoms.[12,13] Blockade of 5-HT_{2A} (and/or 5-HT_7) receptors by risperidone may alter the balance between the various postsynaptic serotonergic receptors acted upon by serotonin released into the synapse as a consequence of reuptake inhibition by the SSRI. If so, a 5-HT_{2A}/5-HT_7 receptor blocker lacking antidopaminergic properties could be effective as an adjuvant treatment for OCD.

The appearance of depression in this patient while receiving paroxetine plus risperidone and the apparent dose-relatedness of this effect is interesting but difficult to explain. In this regard, it is interesting to note the report by Stein et al.[8] of 2 patients, 1 who met DSM-IV criteria for trichotillomania and 1 for Tourette's syndrome, who had comorbid OCD symptoms. These patients received augmentation of an SSRI with risperidone and reported significant clinical improvement. However, after 3 and 2 months of treatment, respectively, they noted dramatic worsening of mood.

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Donepezil Overdose

Sir: We report the case of a patient who inadvertently ingested an overdose of donepezil, a reversible acetylcholinesterase inhibitor approved for the treatment of Alzheimer's disease.

Case report. Ms. A, a 74-year-old white outpatient with a history of cerebrovascular accidents, myocardial infarction, hypothyroidism, and probable multi-infarct dementia, was begun on treatment with donepezil 5 mg/day for cognitive decline, including marked language impairment, and agitation. Donepezil was administered with the hope of improvement in cognition and/or function due to improved cholinergic neurotransmission. This off-label treatment was selected because Ms. A might have had coincident Alzheimer's disease (not easily diagnosed) and/or functional lesions in the central cholinergic system that might respond to therapy. On donepezil therapy, she demonstrated improved comprehension and increased verbalization. This anecdote, while interesting, is not central to the case report.

Ms. A inadvertently obtained access to the supply of donepezil at home and consumed 9 tablets before her husband discovered her action. Her husband and daughter described onset of nausea approximately 2 hours postingestion. She vomited 3 times with no pill fragments evident at any time. Ms. A then fell asleep for 4 to 5 hours but remained arousable. The family sought assistance from the Poison Control Center and followed recommendations to monitor her arousability every half hour. They were told to call an ambulance if they were unable to awaken her at any time. After 5 hours of sleep, Ms. A was able to maintain wakefulness and ambulate. Approximately 9 hours postingestion, she was observed to be flushed and had 1 episode of a large quantity of diarrhea. No further difficulties were noted the following day. At the recommendation of the local Poison Control Center, donepezil was not administered again until 3 days later. There were no side effects when it was resumed. Ms. A continued to maintain her gains in comprehension and verbalization.

Overdose with a cholinesterase inhibitor can lead to cholinergic crisis, which is characterized by nausea, vomiting, salivation, diaphoresis, bradycardia, hypotension, respiratory collapse, and convulsions. Two oral cholinesterase inhibitors, tacrine and donepezil, are currently approved by the FDA for the treatment of probable Alzheimer's disease. Tacrine is an acridine-based cholinesterase inhibitor that lacks selectivity for acetylcholinesterase in the central nervous system and has peripheral cholinesterase inhibition leading to undesirable side effects. It has an elimination half-life of 2 to 4 hours, therefore requiring multiple daily doses, and it can cause dose-limiting hepatotoxicity.[1,2]

Donepezil may pose advantages with respect to overdose. It is a piperidine-based cholinesterase inhibitor that has a high degree of selectivity for acetylcholinesterase in the central nervous system, lacks peripheral activity, and has an elimination half-life of 70 hours, allowing once-a-day dosing. There is ex-

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tensive documentation of expected adverse events found with normal doses of both agents, most commonly nausea, vomiting, diarrhea, and sedation. The expected rate of these typical cholinergic symptoms is about 20% in patients receiving tacrine,[2] and for donepezil, less than 10% in patients receiving 5 mg/day, up to 20% for patients rapidly titrated to 10 mg/day, and between those percentages for those titrated to 10 mg/day gradually (i.e., over 4 to 6 weeks).[3–5]

To our knowledge, there are no published reports of overdose with tacrine or donepezil. Data on file (1998) from Eisai Inc. and Pfizer Inc include information on an overdose of between 14 to 70 mg (exact dose unknown) of donepezil in a patient enrolled in a prior open-label study. This overdose resulted in mild, transient vomiting, fatigue, and lethargy. Our case report illustrates the outcome of a donepezil overdose 9 times the patient's maintenance dosage, indicating that this single patient tolerated a 45-mg dose without significant difficulty.

Currently, there are no standard overdose guidelines put forth by our regional Poison Control Center. Rather, strategies are adjusted based on the time and the patient's condition since ingestion. If symptoms are severe and/or time of overdose is less than 8 hours, charcoal administration is recommended. Otherwise, since donepezil reaches peak plasma concentration in 3 to 4 hours, supportive care and observation may be suggested. In this case, the recommendation to withhold treatment with donepezil for 3 days was based on the elimination half-life of 70 hours. It may become clear whether different strategies to manage overdose will evolve as the drug becomes more widely used.

This single case illustrates that inadvertent overdose can occur in demented patients who are prescribed medication and indicates what can happen with a donepezil overdose of this magnitude.

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