

## Safety of Vagus Nerve Stimulation With ECT

TO THE EDITOR: ECT is a safe and effective treatment for major depression. (1). Vagus nerve stimulation is a treatment approved by the Food and Drug Administration for refractory epilepsy. It has been reported in an open trial (2) to have acute and possibly continuing antidepressant effects on treatment-resistant depression. However, in a pivotal randomized controlled trial (3), vagus nerve stimulation was found not to be efficacious in treating acute depression. Vagus nerve stimulation involves implantation of a pulse generator that delivers intermittent electric stimulation to the left vagus nerve. The cardiac effects of vagus nerve stimulation are thought to be minimal (3).

ECT has been associated with increases in vagal (parasympathetic) tone immediately after stimulation, which can result in arrhythmias and brief periods of asystole (4). Since cardiac arrhythmias are responsible for rare cases of cardiac mortality with ECT, an enhancement of the cardiac effects resulting from combination treatment would be a significant concern. We know of no literature on the safety of vagus nerve stimulation used with ECT for the treatment of depression. We report a case in which we used vagus nerve stimulation in conjunction with short-term ECT to treat major depression.

Ms. A, a 50-year-old woman with a 20-year-history of recurrent major depressive disorder, had had eight previous episodes of severe depression. She had had multiple trials of antidepressants, mood stabilizers, and antipsychotic medications and had achieved inadequate response. Over 16 years she had received seven courses of short-term ECT and had achieved adequate response; she experienced mild cognitive impairment as the only complication. Her improvements were brief, and maintenance ECT was unable to sustain the response.

Ms. A then underwent implantation of a NeuroCybernetic Prosthesis vagus nerve stimulator (Cyberonics, Houston) at our center. She remained stable for the next several months. She then developed a recurrence of severe depression. She received acute bilateral ECT with a stimulus dose (225 millicoulombs) 1.5 times the seizure threshold. The initial four ECT sessions were given with the vagus nerve stimulation generator turned off. Ms. A showed a slower response than with previous ECT treatments; therefore, the latter five treatments were administered with the vagus nerve stimulation operating at 0.75 A. Labetalol, 15 mg/day; methohexital, 100–120 mg/day; and succinylcholine, 100 mg/day, were administered during each treatment. Ms. A's depression improved; her score on the Hamilton Depression Rating Scale (21-item version) decreased from 26 at baseline to 3 by the end of the treatments.

During ECT sessions 1–4 (with the vagus nerve stimulator off), the mean increase in Ms. A's heart rate was 31 bpm, and the increase in her systolic blood pressure was 32.5 mm Hg. During ECT sessions 5–9, the mean increase in heart rate was 26 bpm, and the mean increase in systolic blood pressure was 40.4 mm Hg. Ms. A's score on the Mini-Mental State Examination remained at 29–30 during these treatments.

Other than the slight increase in systolic blood pressure, no untoward autonomic disturbances were observed throughout the course of acute ECT treatment, with or without vagus

nerve stimulation. There were no cognitive impairments when both treatments were combined; ECT did not interfere with the functioning of the vagus nerve stimulation generator. In conclusion, this case suggests that vagus nerve stimulation may be safely administered during the course of ECT, although future trials are needed to assess the safety of combined ECT and vagus nerve stimulation.

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## Modafinil-Associated Clozapine Toxicity

TO THE EDITOR: I read with interest the letter by Edward Teitelman, M.D. (1), describing the successful use of modafinil for sedation accompanying psychotropic medication treatment: it produced mild side effects and no adverse drug interactions. His conclusion that modafinil is safe for treating medication-induced sedation may be premature. This report describes the emergence of clozapine toxicity after modafinil was added to combat sedation associated with treatment.

Mr. A was a 42-year-old man with schizophrenia who, because of persistent psychosis and aggressiveness, was felt to be good candidate for treatment with clozapine. Results of pretreatment laboratory tests and an ECG were normal. At the time clozapine was started, Mr. A was taking haloperidol, quetiapine, divalproex, gabapentin, benztropine, and lorazepam. His nonpsychotropic medications included levothyroxine sodium, furosemide, potassium, and docusate sodium. Clozapine treatment was begun at 25 mg at bedtime and titrated to 400 mg/day over 13 days. After it reached a therapeutic dose, all other psychotropic medications were tapered and discontinued (by day 69). On day 70 Mr. A's serum clozapine level (norclozapine and clozapine) was 761 ng/ml. Because of persistent psychotic symptoms, his clozapine dose was increased to 450 mg/day on day 77. Clozapine monotherapy produced sedation that interfered with his ability to function. To improve sedation, modafinil, 100 mg/day, was administered, starting on clozapine day 82, and titrated to 300 mg/day by day 101; it produced a mild improvement in sedation.

On clozapine day 116, Mr. A complained of dizziness, had an unsteady gait, and fell twice. He was afebrile and tachycardic but had normal blood pressure; his blood oxygen saturation was 86%. Results of physical and neuro-

logical examinations were unremarkable; an ECG demonstrated sinus tachycardia. Results of a lung ventilation-perfusion scan and routine laboratory tests were noncontributory. A repeat measurement of his clozapine serum level on day 112 showed 1400 ng/ml, substantially higher than Mr. A's level on day 70. Clozapine and modafinil were discontinued on day 119.

Mr. A's gait disturbance and hypoxemia resolved without sequelae. Clozapine was restarted at 100 mg/day on day 121 and increased to 300 mg/day by day 122. A repeat clozapine level 21 days after it was restarted (and modafinil discontinued) was 1236 ng/ml; 5 weeks later it was 960 ng/ml. It is noteworthy that all measurements were of trough levels determined 10–12 hours after the bedtime dose.

The patient's clozapine level while he was taking a dose of 400 mg/day was measured after sufficient time at a stable dose that it represented a steady-state level; there was no evidence of covert nonadherence. If linear pharmacokinetics are assumed (2), increasing the clozapine dose from 400 to 450 mg/day should increase the serum level to ~856 ng/ml. The level determined after cotherapy with modafinil (1400 ng/ml) suggests a metabolic interaction between clozapine and modafinil. Alternative explanations for the elevated serum levels of clozapine after the addition of modafinil include laboratory error producing an artificially low measurement at the initial determination of serum level or persistent alteration of the hepatic-metabolizing ability of clozapine produced by the addition of modafinil. However, if the former had been the case, the patient would have manifested signs of toxicity long before starting to take modafinil.

Modafinil and clozapine have a complicated hepatic metabolism involving several isoenzyme systems. Clozapine is primarily metabolized by P-450 2C19 and 3A4, with lesser involvement of 2C9, 2D6, and 1A2 (3). Modafinil metabolism involves P-450 1A2, 2B6, 3A4/5, 2C9, and 2C19 isoenzymes; it has been shown to inhibit P-450 2C19 activity (4). It is possible that inhibition of P-450 2C19 by modafinil interfered with clozapine clearance, elevating serum clozapine levels and thereby producing signs of toxicity. Despite modafinil's potential for reversing clozapine-associated sedation, caution is required when prescribing this drug combination. Close monitoring of serum clozapine levels is recommended.

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## Galantamine for Treatment-Resistant Schizophrenia

TO THE EDITOR: Abnormal neurotransmission at nicotinic cholinergic receptors may contribute to the pathophysiology of

schizophrenia (1). Clozapine may favorably affect these abnormal nicotinic mechanisms (2). We report here on two treatment-resistant patients with schizophrenia whose successful treatment with clozapine had been discontinued because of agranulocytosis. Both fared poorly while taking other antipsychotics. Both showed therapeutic benefit when galantamine, a noncompetitive agonist/allosteric modulator at nicotinic cholinergic receptors (3), was added to their treatment with risperidone.

Mr. A was a 28-year-old man with persistent auditory hallucinations and persecutory delusions who had been given repeated placement in the community, but these efforts had failed because of frequent episodes of agitation, threatening behavior, and destruction of property that seemed to be driven by paranoia and his hearing "voices." Galantamine was introduced and brought to an oral dose of 8 mg b.i.d. over 2 weeks. The episodes of agitation disappeared, and Mr. A became more capable of sustained routine conversation in which he could rationally evaluate his psychopathology. After an additional 2 weeks of treatment, he was successfully placed in a group home, where he has continued to do well for 2 months.

Mr. B was a 53-year-old man with profoundly disorganized thoughts and poor self-care, including wearing multiple layers of clothing inside out and backward. He repeatedly wandered away from the group home where he had been placed. Galantamine treatment was initiated and brought to an oral dose of 12 mg b.i.d. Mr. B's thoughts became more organized. He wore his clothes correctly and was more social with staff and other patients. Staff at the group home report that since returning there, he no longer wanders away and, in fact, signs out when taking local walks. He remains more social and has maintained clearly improved dressing and hygiene.

The active components of risperidone and galantamine exhibit no change in their bioavailabilities when co-administered (4). Galantamine alters the structure of nicotinic receptors, making them more receptive to nicotinic agonists, in addition to inhibiting the breakdown of acetylcholine by its cholinesterase (5).

Controlled double-blind trials of galantamine as an adjunctive treatment for schizophrenia are currently underway. These two patients were both very heavy smokers and had shown a favorable therapeutic response to clozapine that could not be matched by treatment with any other currently available antipsychotic. Both of these attributes (smoking and clozapine response) may signal that nicotinic pathophysiology contributed to their illnesses and that an agent such as galantamine that can augment nicotinic function may be a useful treatment (6).

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## Narcolepsy Presenting as Schizophrenia

TO THE EDITOR: Patients with narcolepsy have a clinical tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. We report on a patient with a diagnosis of schizophrenia who was resistant to antipsychotic treatment. He was subsequently diagnosed with narcolepsy and responded to treatment with psychostimulants.

Mr. A, a 48-year-old white man, had been admitted to a state psychiatric facility with an acute onset of bizarre behavior and persecutory delusions. Since then he had exhibited frequent episodes of bizarre and agitated behavior, including slamming doors, throwing furniture around, and stealing food from other patients. This necessitated almost daily seclusion or restraint. His behavior and thought disorder did not respond to treatment with antipsychotics, including risperidone, olanzapine, quetiapine, and clozapine. Although Mr. A exhibited hypersomnia, this was initially attributed to neuroleptic therapy. A diagnosis of narcolepsy was considered when a sudden buckling of the knees was observed. This was consistent with cataplexy; Mr. A was therefore referred for a sleep study after tapering of neuroleptics. The sleep study was suggestive of narcolepsy; Mr. A had a mean sleep latency time of 1.7 minutes and onset of REM sleep at under 20 minutes. A human leukocyte antigen (HLA) typing revealed the presence of an HLA DR2 phenotype, which occurs in 85%–100% of white subjects with narcolepsy and cataplexy (1, pp. 669–671).

Mr. A was diagnosed with narcolepsy and was given nortriptyline and methylphenidate. His episodes of violent and agitated behavior ceased completely, and there was no thought disorder noted upon serial mental status examinations. He has sustained this improvement at least until the time of this writing, more than 6 months since treatment with the stimulant was first begun.

The clinical picture, the results of the sleep study, the HLA phenotyping, and the patient's significant response to nortriptyline and methylphenidate therapy confirm the diagnosis of narcolepsy rather than schizophrenia. When hallucinations and delusions are prominent, cases of narcolepsy can simulate schizophrenia (2). Hallucinations in narcolepsy are common and are usually visual or auditory (1, p. 677). Thought disorder is less common but can develop as a secondary delusional elaboration of narcoleptic hallucinations (2). Purposeful but inappropriate behavior, sometimes accompanied by hallucinations, can occur in narcolepsy, probably secondary to "microsleeps" (1, p. 531). A survey of 69 patients with schizophrenia (2) indicated that up to 7% of all

patients with a diagnosis of schizophrenia may have a psychotic variant of narcolepsy. Larger studies are necessary to clarify this since, as illustrated by this case, the correct identification of this variant of narcolepsy and subsequent treatment can result in a remarkable reversal of symptoms.

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## Pedophilia Treated With Carbamazepine and Clonazepam

TO THE EDITOR: Compulsive sexual behavior involves excessive or uncontrolled behavior and sexual cognitions that lead to subjective distress, social or occupational impairment, or legal and financial entanglements (1). Compulsive sexual behavior can involve both conventional sexual practices and deviant patterns of arousal, including pedophilia. Few treatments have been described, although Kafka (2) reported the use of serotonin reuptake inhibitors and antiandrogen drugs. We report the case of a patient with pedophilia who responded to combination treatment with carbamazepine and clonazepam.

Mr. A, a 56-year-old married man, was referred for treatment of pedophilia. He had been preoccupied with sexual fantasies about children since his teen years, but only in the last 10 years had his preoccupation led him to seek out sporadic contact with prepubescent boys and girls (usually between ages 3 and 14 years). His behavior with older children (boys and girls) involved penile penetration, although with younger children, he mostly rubbed against them to the point of orgasm. He reported that his fantasies were repetitive, and while he experienced a sense of shame, he felt unable to control his fantasies: "I've become a monster." Despite his impulsive behaviors, he had never been arrested, and he reported no other paraphilic behaviors, such as exhibitionism. The behavior led to considerable dysphoria and guilty ruminations, accompanied by panic attacks. In addition to these contacts, he usually masturbated two to three times each week.

Mr. A's only complaint was occasional headaches, which were treated with analgesic medication. He had no history of other psychiatric symptoms or impulsive behaviors, such as trichotillomania, compulsive buying, kleptomania, pathological gambling, or intermittent explosive disorder. There was no history of drug or alcohol abuse. He was gainfully employed and active in his church. Married 30 years, Mr. A reported normal sexual relations with his wife until his disturbing thoughts about children eventually led him to distance himself emotionally and sexually from her.

Because of Mr. A's dysphoria and anxiety relating to his sexual behavior, he was given carbamazepine, 300 mg/day, and clonazepam, 2 mg/day. His only side effects were transient sedation and headache. He reported significant improvement over the course of a month, with near-com-

plete resolution of inappropriate sexual cognitions and behavior. His doses were gradually lowered to 0.5–1.0 mg/day of clonazepam and 200 mg/day of carbamazepine for long-term maintenance. The improvement has now persisted for over 1 year.

Kafka (2) has written extensively on the use of serotonin reuptake inhibitors and antiandrogens in patients with compulsive sexual behaviors to reduce sexual preoccupation and decrease hypersexuality, but to our knowledge, this is the first report of a patient with pedophilia responding to the combination of carbamazepine and clonazepam. This particular combination was selected to pharmacologically target the patient's impulsivity and mixed anxiety and depression. We cannot, of course, exclude the possibility that the patient experienced a placebo response. Nonetheless, our experience suggests that this medication combination may be beneficial to other patients as well.

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### Metyrapone for Cushing's Syndrome

TO THE EDITOR: Cushing's syndrome secondary to olfactory neuroblastoma is rare (1). We report a case of psychiatric manifestations caused by Cushing's syndrome secondary to ectopic ACTH secretion from an olfactory neuroblastoma. This is the first report of which we are aware of psychiatric manifestations caused by Cushing's syndrome that have been controlled for more than 1 year by metyrapone, an 11 $\beta$ -hydroxylase inhibitor. In addition, abnormal regulation of ACTH secretion was suspected; this abnormality may have brought about the dramatic effectiveness of metyrapone.

Mr. A was a 33-year-old man who underwent resection of a nasal olfactory neuroblastoma at 26 years of age. Seven years later, metastases were diagnosed in the retropharyngeal lymph nodes, and chemotherapy, consisting of cisplatin and etoposide plus decadrone, was administered. After that, Mr. A experienced numbness in his lower extremities, dysgeusia, adynamia, stomatitis, facial and extremity edema, diarrhea, and thrombocytopenia; unexplained hypokalemia was found. These symptoms were believed to be adverse effects from chemotherapy. Mr. A then developed anxiety, irritability, insomnia, and psychomotor excitement and was referred to the psychiatry division.

Mr. A gradually began to exhibit a depressed mood and suicidal ideation. At first these symptoms were diagnosed as an adjustment disorder with mixed anxiety and depressed mood. Psychotropic medication was effective in treating the psychomotor excitement. After the completion of chemotherapy, however, the anxiety, irritability, insomnia, and depressed mood persisted. Because of these long-lasting psychiatric manifestations and the hypokalemia, Mr. A was tested for a hormonal abnormality and was found to have elevated plasma levels of ACTH (837 pg/ml; normal range=9–520 pg/ml) and cortisol (103  $\mu$ g/dl; nor-

mal range=5–15  $\mu$ g/dl). In addition, an abdominal magnetic resonance imaging (MRI) examination revealed bilateral adrenal hypertrophy; an MRI of the head was negative for pituitary tumors or hypertrophy. Cushing's syndrome secondary to an ectopic ACTH-secreting tumor was diagnosed, and metyrapone treatment was begun.

Mr. A's cortisol level became normal (7.4  $\mu$ g/dl), and his anxiety, irritability, insomnia, and depressed mood improved 6 days later. His Cushing's syndrome and psychiatric manifestations have been controlled with metyrapone, 750 mg/day, for more than 24 months. His cortisol level has been maintained within the normal range, and his ACTH level has been stabilized around 200 pg/ml for more than a year.

After administration of metyrapone, the patient's Cushing's syndrome and psychiatric manifestations immediately resolved; his cortisol levels and ACTH levels immediately became normal. Metyrapone can inhibit production of cortisol but not ACTH directly. Therefore, in this case, there may have been positive feedback regulation between cortisol and ACTH in the tumor. After reduction of the cortisol level with metyrapone, the effect of the positive feedback regulation of cortisol on ACTH secretion might have decreased. In this case, decadrone, a glucocorticoid used with chemotherapy, may have triggered ACTH secretion by means of positive feedback regulation. Physicians should be aware that the potential abnormal regulation of cortisol secretion in a tumor can cause psychiatric manifestations.

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### Topiramate for Bulimia Nervosa With Bipolar II Disorder

TO THE EDITOR: The novel anticonvulsant topiramate is under investigation regarding its mood-stabilizing properties. Topiramate promotes weight loss and effects satiety. It reportedly assists in treating eating disorders, especially binge eating disorder (1, 2). We are aware of only two cases relating topiramate to bulimia nervosa. The first involves the abuse of topiramate for its weight-loss effect (3)—a valid consideration when using this drug with any population. The second case describes topiramate as useful in treating bulimic symptoms in a patient with epilepsy (4). In this case topiramate did not induce significant weight loss but produced cognitive changes in the patient, leading to the cessation of her bulimia.

Ms. A, a 27-year-old professional with a body mass index of 26, was treated with topiramate for bipolar II disorder. After 3 months of taking 75 mg/day, her mood stabilized, and she noticed life-changing differences in her eating disorder. In her teens, Ms. A had struggled with body-image concerns and began purging to lose weight at 18 years of age. She binged and purged from three to 10

times per week, occasionally refraining from this behavior for 3–4 weeks. She tried group therapy and treatment with a selective serotonin reuptake inhibitor with little improvement. When depressed, she binged for comfort and distraction from her negative self-image. When hypomanic, she binged for the “rush” of purging, making her feel powerful. When euthymic, she binged and purged out of boredom.

Ms. A began topiramate therapy when she was bingeing and purging three to four times a week but soon found her eating behavior had returned to normal. Although she lost minimal weight while taking topiramate (2–4 lb), she gained a sense of satiety. She noticed reduced anxiety, minimizing her need to binge for comfort. The most interesting change was in her self-image. She still felt overweight, but it no longer bothered her. She felt better about herself and kept her weight in perspective. Ms. A has been taking topiramate for 7 months and has not binged or purged and reports no desire to do so.

Of the patients described in previous case reports, only the patient with epilepsy and bulimia reported cognitive changes similar to those in our patient, saying she was “less concerned” about her weight (4). Changes in cognition are important in recovery from bulimia nervosa, as evidenced by the success of cognitive behavior therapy. It is unclear why these cognitive changes might occur with topiramate treatment. However, they have been noted in more than one patient and have had dramatic effects on the individuals’ behavior. Therefore, the effect of topiramate on cognition in patients with eating disorders warrants further investigation.

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### Gabapentin-Induced Anorgasmia in Women

TO THE EDITOR: Sexual dysfunction is an unfortunate side effect of many medications, including those used to treat common psychiatric and neurologic disorders. Gabapentin, a medication used widely in the treatment of epilepsy, neuropathic pain, and bipolar disorder, is generally well tolerated. To our knowledge, only four definite (1–4) and three possible (5) cases of gabapentin-induced anorgasmia have been reported—and all in men. We report two cases of definite gabapentin-induced anorgasmia in women.

Ms. A, a 28-year-old woman, had been treated for epilepsy for 3 years, after the onset of secondary generalized tonic-clonic seizures. Simple partial limbic seizures had begun at the age of 15, and unresponsive staring was witnessed immediately before the onset of her second convulsive seizure. The results of a neurological examination,

brain magnetic resonance imaging (MRI), and an EEG were normal. After the failure of several antiepileptic medications because of either lack of efficacy or adverse reactions (none of which were sexual in nature), Ms. A was given an escalating-dose regimen of gabapentin monotherapy. At a dose of 1800 mg/day, she complained of profoundly decreased libido and anorgasmia, first noted at a dose of only 900 mg/day. Seizures recurred when the daily dose was reduced to 1500 mg/day. Ms. A was gradually switched to monotherapy with levetiracetam. Her libido and sexual function returned to normal only after the gabapentin was entirely discontinued.

Ms. B, a 41-year-old woman, had a 15-year history of well-controlled complex partial seizures. The results of a neurological examination, brain MRI, and an EEG were normal. Treatment with phenytoin, carbamazepine, and oxcarbazepine had each eventually produced intolerable side effects. Ms. B was given an escalating-dose regimen of gabapentin monotherapy. At 600 mg t.i.d. she was seizure free but complained of anorgasmia. The evening dose was decreased to 300 mg and was moved from bedtime to dinnertime, with continued seizure control and return of sexual function during nocturnal sexual activity.

These two cases indicate that gabapentin-induced sexual dysfunction can occur in women. Furthermore, unlike the cases reported in men (1–4), decreased libido may be a symptom. Gabapentin-induced sexual dysfunction may be dose related and effectively treated by decreasing the dose or adjusting the dose regimen to maximize the time interval between drug ingestion and sexual activity. However, as in the first case, the medication may have to be discontinued for normal sexual function to return.

These cases illustrate that gabapentin can cause decreased libido and anorgasmia in women, even at relatively low doses. Clinicians should be aware of this potential side effect, as it is likely to be disturbing to the patient and can result in non-compliance (3).

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### Solar Eclipse and Suicide

TO THE EDITOR: Solar eclipses have been cloaked with myth and superstition since ancient times (1), but scientific accounts of their psychiatric and public health impact are sparse (2, 3). Specifically, the impact of a solar eclipse on suicide incidence has not yet been investigated, to our knowl-

edge. We report the impact of the total solar eclipse of Aug. 11, 1999, on the incidence of suicide in Austria.

Apart from the turn of the millennium, the eclipse was the single most important media event in Austria in 1999. Extensive media coverage started months before, leading to collective anticipation in the population. With the last total solar eclipse over Austria occurring in 1842 and the next occurring in 2081, it was a once-in-a-lifetime experience for most Austrians. On eclipse day (a Thursday), 40% of the working population was on leave, and an estimated 750,000 of the country's population of 8 million traveled into the narrow strip (110 km in length) of eclipse totality, causing traffic jams and public transportation disruptions.

We compared the incidence of suicide in a 4-week study period before eclipse day with the incidence of suicide during the corresponding 4 weeks in a 15-year comparison period. The latter yielded 2,269 suicides that occurred in Austria during the 4 weeks before August 11 in the years 1984–1998. The standardized incidence ratios, i.e., the observed numbers of suicides in the study period in relation to the expected numbers based on the comparison period, with 95% confidence intervals (CIs) (4), for weeks 4, 3, 2, and 1 before eclipse day were 0.69 (CI=0.46–0.99), 0.68 (CI=0.42–0.97), 0.75 (CI=0.50–1.08), and 0.62 (CI=0.40–0.94), respectively. There was no decrease in suicide incidence on eclipse day (standardized incidence ratio=0.99 (CI=0.36–2.16)). All six suicides on eclipse day were by men and occurred exclusively in the regions crossed by the path of totality, in which unusually large numbers of people gathered. In the weeks after eclipse day, the national suicide incidence did not significantly differ from expected numbers.

These data indicate an impact of the collective anticipation of eclipse day on the incidence of suicide in Austria. The lack of a decrease in suicides on eclipse day and the suicides' spatial clustering correspond to the stressful circumstances owing to massive eclipse trekking. While previous research has highlighted the media's role in triggering copycat suicides after suicide reports (5), this finding is indicative of a suicide-preventive effect of media hypercoverage and collective anticipation of a positive event, probably by means of greater social cohesion.

On Aug. 21, 2017, for the first time since Feb. 26, 1979, the continental United States will experience a total solar eclipse. This nationwide event, with a coast-to-coast path of totality from Lincoln City, Ore., to Charleston, S.C., will be an excellent opportunity to examine the replicability of our findings.

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## Role of Antidepressants in Murder and Suicide

TO THE EDITOR: Since the introduction of fluoxetine a decade and a half ago, there has been controversy in the lay media and scientific literature as to whether fluoxetine and other selective serotonin reuptake inhibitor (SSRI) antidepressants cause violence and suicide. Proponents of that position have based their opinions on case reports or large clinical groups in comparing patients taking SSRIs to those taking other types of antidepressants (1, 2). Those finding no association between the use of SSRIs and violence and suicide have compared patients taking SSRIs to those receiving placebo in terms of the incidence of violent and suicidal behaviors (3, 4).

We chose a different strategy to examine this controversial topic. We reviewed all murder-suicides that took place in New York City from 1990 through 1998 using data collected from the files of New York City's chief medical examiner. Blood from murderers who committed suicide is routinely tested for drugs, including antidepressants. There were 127 murder-suicides over the 9-year period. Three of the murderers (2.4%) were taking antidepressants according to results of toxicological testing. A 46-year-old woman who killed her son and then herself with injections of heroin was taking amitriptyline. A 48-year-old man who set fire to rags and paper in a closet and lay on his two young sons and his young daughter was taking amitriptyline. A 77-year-old man who killed his spouse and then himself with a gun was taking sertraline.

The findings in our study lend no support to the position that the use of SSRIs is associated with violence or suicide. The fact that only 2.4% of these persons were taking antidepressants at the time they killed family members and then themselves is less than one would expect in the general population, given that SSRIs were widely prescribed in the 1990s (5). These data do not support an association between the use of SSRIs and violence or suicide. There is no evidence suggesting that clinicians should hesitate in prescribing SSRIs, which have been shown to be safe and effective, for fear of violent and/or suicidal consequences.

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### Change in Criterion for Paraphilias in DSM-IV-TR

TO THE EDITOR: In the introduction to DSM-IV-TR (p. xxix), the following unequivocal statement is made concerning its changes from DSM-IV: “As with the original DSM-IV, all changes proposed for the text had to be supported by empirical data. Furthermore, all proposed changes were limited to the text sections (e.g., Associated Features and Disorders, Prevalence). No substantive changes in the criteria sets were considered.” This claim is misleading. In fact, DSM-IV-TR has made a substantive change to criterion B for paraphilias. The only way the reader would know of this change would be to read all of Appendix D (“Highlights of Changes in DSM-IV Text Revision”) to discover that a change had been made in the paraphilia criteria set (p. 840).

In DSM-IV (p. 523), criterion B for all paraphilias was, “The behavior, sexual urges, or fantasies cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.” The editors of DSM-IV-TR apparently recognized the unintended and clinically absurd consequence of the change in DSM-IV from DSM-III-R criterion B. According to DSM-IV, the diagnosis of pedophilia cannot be made if the individual acts on pedophilic urges but is not distressed by the urges and is not socially or occupationally impaired. In DSM-III-R, however, acting on the urges alone meets criterion B, as is the case again in DSM-IV-TR for pedophilia and all of the other paraphilias that involve a non-consenting person.

This welcome change in the DSM-IV-TR criteria is certainly substantive. Would it not have been better for the DSM-IV-TR editors to acknowledge that they had made a few substantive changes in the criteria and that they had corrected a mistake made in DSM-IV for the paraphilias?

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### The Beef With Atypical Antipsychotics

TO THE EDITOR: We recently approached the manufacturers of atypical antipsychotics in the United Kingdom in order to identify a product free from animal materials. All of the atypical antipsychotics contain animal-derived lactose, and risperidone and quetiapine contain bovine-derived magnesium stearate.

Magnesium stearate contains organic acids derived from beef tallow, but it can also be extracted from vegetable sources and be synthetically produced. Lactose is the carbohydrate component of milk and is widely used in the production of capsules or tablets (1).

The use of these materials as excipients is widespread in tablet manufacturing. The World Health Organization recom-

mends that in situations in which products from animals at risk for encephalopathies are not essential, alternatives should be used (2).

Concerns related to the use of animal-derived materials in medications are not restricted to the hypothetical risk of infection with new-variant Creutzfeldt-Jacob disease. Awareness of patient ethnicity, religion, and dietary habits plays a part in drug choice. For example, a Hindu patient may prefer a medication free of bovine-derived products. People with lactose intolerance, of which there are 50 million in the United States (3), should be offered medication free of lactose. Although information about drug constituents can be found from different sources, it is not readily available to prescribers, and patients do not always have access to this information. We acknowledge that in many clinical situations it might be impractical to consider drug constituents. As long as products continue to be produced that contain animal derivatives, physicians have an ethical obligation to inform patients of their presence.

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### Pregnancy in Women With Eating Disorders

TO THE EDITOR: Although the study by Debra L. Franko, Ph.D., et al. (1) aimed to contribute to the current knowledge of mental health disorders in relation to pregnancy outcomes, it was severely limited because of research design and methods. While this longitudinal study provided much-needed groundwork for an open-ended study of eating disorders and their impact on pregnancy, it did so without a comparison group, thus limiting its generalizability. Most significant, the inferences regarding the prevalence of postpartum depression are difficult to meaningfully interpret because of the methods used and the measurement of postpartum depression. Because of the research design, it is difficult to ascertain how many women were depressed before the study and how many became depressed for other reasons. While the correlation between depression and eating disorders is certainly worthy of exploration, it is important to note that clinical depression may have been already established before the pregnancy.

Although the women diagnosed with depression in this study were classified as experiencing “postpartum depression,” it is unclear whether this was preexistent or actually developed during the postpartum period. The measures used by the authors are specific to the detection of depression but may be less sensitive in detecting postpartum depression or subclinical symptoms suggestive of “postpartum blues.” The use of an instrument specific to the postpartum period, such

as the Edinburgh Postnatal Depression Scale, has been demonstrated in the literature to be sensitive to the detection of postpartum depression as distinct from other forms of clinical depression (2) and has demonstrated reliability and positive predictive value in the detection of depression specific to the postpartum period (3–6).

While DSM-IV does not currently differentiate postpartum depression as a separate diagnosis, this distinction is a significant issue in current research surrounding women's mental health during and around pregnancy. Perhaps this added specificity and the use of a comparison group in future studies could add salient research understanding to the unique epidemiology of postpartum depression.

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#### Dr. Franko and Colleagues Reply

TO THE EDITOR: We agree that the lack of a comparison group is a limitation of our study and acknowledged this in the arti-

cle. With regard to postpartum depression, we also noted that all of the women with postpartum depression had a lifetime history of affective disorder. Earlier work with this cohort found that 66% of the anorexic subjects, 50% of the bulimic subjects, and 76% of the mixed anorexic-bulimic subjects had at least one affective disorder at the time of intake and that depression was common in the group over the course of the study (1, 2).

Depression was measured every 6 months—before, during, and after pregnancy—by structured clinical interview. Depression in the 6 months before pregnancy was not predictive of postpartum depression, suggesting that those who had postpartum depression, in fact, were not depressed just before pregnancy. In addition, because medical records corroborated the subjects' reports of depression in the clinical interview, we feel confident that our assessment identified those with postpartum depression. However, we agree that the use of an instrument specifically designed to assess postpartum depression would have been optimal and that including a more explicit assessment than we provided would strengthen future studies. We hope that our study will lay the groundwork for additional research on postpartum depression and eating disorders.

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