PANDAS Variant and Body Dysmorphic Disorder

TO THE EDITOR: A subgroup of patients with obsessive-compulsive disorder (OCD) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) display symptom exacerbations that are temporally linked to streptococcal infections (1). We report on a patient with severe body dysmorphic disorder and major depression who experienced an exacerbation of symptoms after a streptococcal infection.

Mr. A was a 19-year-old Hispanic man who was admitted to our inpatient unit with the diagnoses of recurrent major depression and body dysmorphic disorder. He reported that he spent up to 8 hours a day checking his face in the mirror and picking at perceived facial blemishes and acne scars. (An examination revealed one or two small, barely visible acne blemishes on his nose.) Mr. A's past history was notable for rheumatic fever at age 8 that had been treated with monthly intramuscular penicillin injections until he was age 12. He and his family reported no childhood symptoms of OCD or tic disorders. He and his family first reported that symptoms of body dysmorphic disorder had appeared at age 14, and by age 16 his symptom profile had been so severe that he had dropped out of school for fear of being scrutinized and talked about by his classmates.

At age 18 he had been admitted to the unit with similar psychiatric symptoms, as well as complaints of a sore throat. The result of a group A streptococcal throat culture had been positive, and he had been given a 10-day course of penicillin. It had been noted that his symptoms of body dysmorphic disorder had improved after penicillin treatment, although he had had little response to low doses of haloperidol up to that point. After the treatment with penicillin, Mr. A had been switched from haloperidol to paroxetine therapy, which had been increased by stages up to 40 mg/day. He had continued to improve after discharge; however, he had been lost to follow-up.

When Mr. A returned 1 year later, his Hamilton Depression Rating Scale score was 33, and his Yale-Brown Obsessive Compulsive Scale score was 26. He again began treatment with paroxetine, which was rapidly increased to 60 mg/day over 3 weeks. By the end of his 4 weeks of hospitalization, his Hamilton depression scale score was 8, and his Yale-Brown Obsessive Compulsive Scale score was 6. He was much improved in mood, and his symptoms of body dysmorphic disorder were better. Before admission, he had had no complaints of a sore throat, and in the hospital, the result of a group A streptococcal throat culture had been negative. As part of a workup for PANDAS, additional serologies were obtained, the results of which revealed an elevated anti-streptolysin O titer of 739 IU/ml (normal: <200 IU/ml) and an elevated DNAase B antibody level of 340 IU/ml(normal: <170 IU/ml). Follow-up antibody titers could not be obtained.

Our patient met some of the criteria for PANDAS. His first admission might have been triggered by his streptococcal infection, which appeared to correlate with worsening symptoms of body dysmorphic disorder. At the second hospitalization, there was serological evidence for remote, but not acute, infection.

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Treatment of Anorexia Nervosa With Tramadol

TO THE EDITOR: Reports of pharmacological treatments of anorexia nervosa have been mixed. Selective serotonin reuptake inhibitors (SSRIs), the treatment of choice, may be helpful after restoration of weight in some patients. However, in underweight patients, SSRIs are generally not helpful and, in some cases, may contribute to further weight loss (1). Endorphins have been implicated in the pathology of eating disorders (2). Moreover, naltrexone has been reported to be useful in the treatment of anorexia nervosa (3). The following is a report of the successful use of tramadol, a selective mu opiate agonist with significant monoamine-reuptake-inhibiting effects (4), in the treatment of anorexia nervosa.

Ms. A was a 19-year-old woman who met DSM-IV criteria for anorexia nervosa, restricting type. At age 15 she had weighed 122 lb and had experienced normal menses. At 16 she had begun to exhibit ritualistic eating behavior. She ate little or nothing during the day. Every night she prepared a specific brand of low-calorie frozen dinner for her evening meal. She ate her meal in her room at precisely 6:00 p.m. and followed each meal with a snack exactly 2 hours later. By age 17 she weighed 101 lb and was amenorrheic.

Initially, she had expressed fear of weight gain. After 2 years of psychotherapy, she appeared to have attained an understanding that she was seriously underweight and her eating rituals were unreasonable. Whether this was true insight is uncertain. She felt ashamed and frustrated but reported no depressed mood, difficulties with sleep, fatigue, or inability to concentrate. Although her symptoms contained an element of obsessive-compulsive disorder, they were entirely linked to food. She did not engage in cleaning or checking behaviors and reported no compulsive slowness or fear of contamination. Roughly 18 months before I saw her, she had started taking fluoxetine. Her dose had been titrated to 60 mg/day. She had remained at that dose for nearly 6 months, but her condition had not improved.

Treatment with tramadol, 50 mg t.i.d., was initiated. Within the first week, Ms. A was more relaxed about food and was able to eat dinner at a restaurant and at a sorority function. Although she mostly kept to her eating schedule, she reported, "I might not have to." Her tramadol dose was increased to 75 mg t.i.d., and in the subsequent 2 weeks she grew less constrained by her eating schedule and increased her food intake in the morning and afternoon. After 7 weeks of tramadol therapy, she reported she was "doing great." She no longer scheduled her eating, she felt free to eat wherever and whatever she chose, and she gained 13 lb. She experienced no adverse effects.

The patient's improvement may have been due to a new therapeutic alliance, to a strong expectancy created by or con-

veyed to the patient, or simply to coincidence. Although the present report suggests that opioid agonists or partial agonists may be useful in the treatment of anorexia nervosa, a placebo-controlled clinical trial is necessary to confirm the efficacy of tramadol.

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Tramadol Dependence With No History of Substance Abuse

TO THE EDITOR: Tramadol is a nonscheduled analgesic drug thought to have minimal potential for abuse. The authors of a recent review of the misuse of tramadol (1) noted infrequent abuse by those without preexisting substance abuse. We report on a woman with no known history of substance abuse who developed tramadol dependence.

Ms. A, a 29-year-old woman, came to the hospital requesting detoxification from tramadol. Tramadol had been initially prescribed for the pain associated with carpal tunnel syndrome. Ms. A's dose of one 50-mg tablet every 4-6 hours as need for pain had been slowly and surreptitiously increased. She had obtained the drug by going to several physicians and different hospitals with self-induced trauma (e.g., a bruised face) in an attempt to obtain increasing amounts of tramadol. After 3 years, she was taking about 30 50-mg tablets a day.

One day before admission, Ms. A had experienced two generalized seizures, and she had stopped taking tramadol. On admission she experienced a severe withdrawal syndrome with blurred vision, dizziness, diarrhea, headache, and insomnia. She reported no history of alcohol or drug abuse. Narcotics had been prescribed previously, but she had had no difficulty taking them. She reported low self-esteem and feelings of guilt, but otherwise she did not meet criteria for any other axis I or II disorders. A family history of alcoholism was noted. A physical examination revealed nothing of significance. Mild hypertension was observed. A CBC indicated slightly elevated white and red blood cell counts and normal differential counts. The results of a screening chemistry profile and urinalysis were within normal limits.

Ms. A was detoxified with tapering doses of tramadol and with celecoxib, metoprolol, and hydroxyzine. She improved gradually and was discharged after 6 days. Several months after discharge, she returned to the emergency room on two occasions with suspected self-inflicted lesions in an effort to obtain tramadol. The emergency room staff were informed of her addiction to tramadol to prevent further abuse. Ms. A did not return to the detoxification unit for follow-up care.

This is the case of a woman with no reported prior psychiatric or substance dependence history who became dependent on tramadol. Tramadol is a centrally acting analgesic that is neither opiate derived nor a nonsteroidal anti-inflammatory drug but binds to the mu opioid receptor. Tramadol is thought to have low potential for abuse. A postmarketing surveillance program to monitor tramadol abuse in the United States (1) indicated that the reported rate of abuse has been low, less than one case per 100,000 during the 2-year period before June 1998. However, unlike this case, the majority of cases of tramadol dependence have been found to occur among patients with a history of opioid dependence.

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Mania and Tramadol-Fluoxetine Combination

TO THE EDITOR: Tramadol is a centrally acting analgesic that actives the mu opioid receptor and enhances the action of serotonin and noradrenaline by interference with their uptake and release mechanisms. It has been suggested (1) that tramadol could be useful in the treatment of obsessive-compulsive disorder associated with the use of selective serotonin reuptake inhibitors (SSRIs). Discussion has included possible pharmacological interaction, leading to side effects such as serotonin syndrome. Also, tramadol-induced mania in a patient with bipolar disorder has been reported (2), but to our knowledge, there are no reports of tramadol-induced mania in patients with unipolar disorder. We present a report of a patient with serotonin syndrome and mania who had no previous history of manic episodes and was being treated with fluoxetine and tramadol.

Ms. A was a 72-year-old woman who had been treated with fluoxetine, 20 mg/day, for the last 10 years. She had had no cognitive deficits, had never been hospitalized, and had had only one previous major depressive episode, occurring 10 years before. She had been taking acetaminophen for the last year for articular pain. She was planning to take a trip, so her doctor prescribed tramadol to relieve the pain. After 18 days of taking tramadol, 150 mg/day, and fluoxetine, 20 mg/day, Ms. A began to feel nervous, had a temperature of 37.2°C, piloerection, and muscular contractions.

She stopped taking tramadol, and her physical symptoms disappeared by day 21. Nevertheless, she was agitated, euphoric, and hyperactive, slept less than 3 hours a day, and demonstrated rapid speech and paranoid ideation. She was conscious and oriented at all times. Ms. A was hospitalized for 3 days and stopped taking fluoxetine; haloperidol treatment was initiated at 5 mg/day. The results of a physical examination were normal. After discharge, her symptoms continued, so by day 31 she was hospitalized again. She then began treatment with olanzapine, 10 mg/day. Two weeks later she was euthymic and was discharged from the hospital while taking olanzapine, 10 mg/day.

This case of serotonin syndrome and mania in the same patient could be due to the fluoxetine-tramadol treatment combination. Tramadol contains a mono-*O*-desmethyl metabolite that has less serotonergic activity than tramadol. The rate of production of this metabolite is influenced by the CYP2D6 system. Fluoxetine could previously have inhibited CYP2D6 production, and, consequently, tramadol would have accumulated in serum, conveying a greater risk of adverse effects.

Also, preclinical reports have suggested an antidepressant effect with tramadol therapy (3). If this is the case, tramadol could induce mania itself in a manner similar to that of antidepressants, although the present episode probably was precipitated by coadministration of two compounds with similar mechanisms of action. In conclusion, it is important to consider the potential risk of inducing mania and serotonergic syndrome when using tramadol combined with SSRIs.

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Gabapentin for Behavioral Dyscontrol With Mental Retardation

TO THE EDITOR: Gabapentin is an anticonvulsant drug that has a structure similar to that of γ-aminobytyric acid (GABA) but does not bind to GABA receptors. It increases nonsynaptic GABA release from the glia, and it is a substrate and a competitive inhibitor of the large neutral amino acid carrier system. Furthermore, gabapentin modulates (but does not directly block) sodium channels and increases human whole-blood serotonin concentrations. Finally, the drug may subtly modulate calcium channels by binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels, reducing monoamine release (1). Its favorable safety profile and lack of drug interactions make it an alternative for use in treating a variety of neurologic and psychiatric conditions (2).

Because gabapentin has a potential effect in the management of dementia-associated agitation, it has been suggested as an addition to haloperidol (3) or donepezil (4) treatment. Gabapentin also has been successfully used to treat behavioral dyscontrol in a 13-year-old boy with diagnoses of intermittent explosive disorder, attention deficit hyperactivity disorder, organic mood disorder, simple partial seizure disorder, and closed head injury (5). We report on an agitated woman with profound mental retardation due to Cornelia de Lange syndrome who was treated with gabapentin.

Ms. A was a 23-year-old woman who suffered from profound mental retardation due to Cornelia de Lange syndrome. She had severely limited motor and communication skills (speaking few and isolated words), difficulties adapting to environmental changes, and inadequate sphincter control.

Maladaptive behavior had appeared for the first time when she was 18 years old. She had been treated as an outpatient and given oral risperidone, 1 mg/day, and diazepam, 5 mg/day, resulting in significant remission of her symptoms. Three years later, agitation, hostility, self-destructive behavior, and screaming had reemerged and had been unsuccessfully treated on an outpatient basis with increases in her medication doses (up to 4 mg/day of risperidone and 30 mg/day of diazepam). Finally, 4 months later, Ms. A was admitted to our psychiatric clinic, but despite the alteration of her medications, her condition remained unchanged. Her last drug regimen included 5 mg t.i.d. of orally administrated haloperidol drops, 25 mg t.i.d. of chlorpromazine, and 4 mg b.i.d. of extended-release biperidin; lorazepam, 2 mg given intramuscularly, was used on an as-needed basis.

Oral gabapentin, 400 mg/day, was added, and after a few days it was increased to 800 mg b.i.d. As a result, a remarkable improvement was noticed. All drugs were gradually tapered, and Ms. A's medications were adjusted to 5 mg/day of haloperidol, 400 mg/day of gabapentin, and 4 mg/day of extended-release biperiden without any aggravation of her symptoms. When gabapentin was withdrawn, Ms. A's behavioral dyscontrol reemerged within 48 hours. Gabapentin, 400 mg/day, was reintroduced, resulting again in improvement. Haloperidol was further tapered to a dose of 3 mg/day, and biperidin was completely withdrawn. No further changes were made in Ms. A's drug regimen, because her condition was considered satisfactory. Four months after discharge, Ms. A's clinical condition has remained stable.

This case report supports the effectiveness of gabapentin, parallel to its other uses in psychiatry, as an adjunctive agent in the management of behavior dyscontol related to mental retardation. The addition of gabapentin to our patient's medication regimen resulted not only in improvement in previously resistant maladaptive behaviors but also in a radical decrease in her doses of coadministrated neuroleptics. This is extremely interesting, given that people with mental retardation may be at a greater risk for serious adverse reactions to medicines, including antipsychotic drugs, than their counterparts without mental retardation (6).

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Cataracts and Quetiapine

TO THE EDITOR: Quetiapine is a novel antipsychotic that has been associated with cataract formation in beagle dogs at high doses (1). The manufacturer recommends eye examinations to detect cataracts at baseline and at 6-month intervals in patients treated with quetiapine (1). To our knowledge, no reports of cataract formation in humans during quetiapine use have been published. We report on an inpatient who developed cataracts during quetiapine therapy.

Mr. A was a 44-year-old Latin American man with a 20-year history of schizophrenia and minimal response to fluphenazine, haloperidol, thioridazine, chlorpromazine, loxapine, and olanzapine. Clozapine treatment had resulted in agranulocytosis, necessitating discontinuation. Partial response had been achieved with risperidone, up to 10 mg/day; however, hostility and anxiety had persisted. Marked improvement in mood with decreased anxiety and hostility had been noted after the addition of quetiapine to risperidone therapy. The results of eye examinations at baseline, 6 months, and 12 months were unremarkable. Fifteen months after the addition of quetiapine, an optometry examination revealed lenticular changes in the left eye and grade I cortical spoking in the interior aspect of the lens (2). Quetiapine was tapered off over 9 days, and an eye examination conducted 1 month later showed no progression of cataract formation.

Soon after he stopped taking quetiapine, Mr. A became more anxious and had less behavioral control, requiring more use of anxiolytics. He and the treatment team evaluated the risks versus the benefits and decided that the combination of quetiapine and risperidone had provided the best response. Quetiapine was reintroduced at 700 mg/day, resulting in decreased hostility and anxiety and only occasional irritability. An eye examination then revealed water vacuoles in both lenses, suggesting cataract formation (3). Despite these lenticular changes, therapy with quetiapine, 700 mg/day, and risperidone, up to 10 mg/day, was maintained, which continued to control Mr. A's symptoms. A later eye examination revealed no changes in the previous findings.

In a recent poster presentation, Nasrallah et al. (1999) reported lens opacities in 15 patients taking quetiapine. The majority of these patients had risk factors for cataracts, including heavy smoking, diabetes, hypertension, and advanced age. Four of the patients had not had a baseline eye examination, and four had a history of cataracts before taking quetiapine. The authors concluded that these findings did not demonstrate a strong association between the development of lens opacities with quetiapine therapy.

Although the possibility of coincidence cannot be excluded, our patient had a normal baseline eye examination and no history of cataracts before quetiapine treatment, and his only known risk factor for cataract formation was cigarette smoking. A MEDLINE search of articles on the patient's other medications revealed no association with cataracts.

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SSRI Discontinuation and Buspirone

TO THE EDITOR: Recently, there has been a greater awareness of selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome, which can appear with both somatic and psychological symptoms (1). Symptoms appear within 1–3 days after the last dose and are usually mild and transient, although they can be more severely distressing. We report on a patient who developed SSRI discontinuation syndrome and experienced an intensification of the symptoms after an attempt to relieve them with buspirone.

Ms. A, a 62-year-old woman, initially came to our clinic with a 3-year history of depression and associated features of anxiety. She had previously been treated with amitriptyline and had experienced only partial response; she had also taken buspirone for anxiety. She began taking sertraline, 50 mg/day, and subsequently increased the dose to 100 mg/day. At 6 weeks, she had a partial response to sertraline and mild side effects of dizziness and nausea. One month later, she reported additional improvement, most notably in decreased sadness and pessimism. Her side effects had disappeared. At the 5-month follow-up, her depression was in full remission, and she was experiencing no side effects.

Six weeks later, she came to the clinic on an emergency basis with intense nausea, anxiety, dizziness, and vertigo. Four days before, she had abruptly stopped taking sertraline because of problems with refilling her prescription. On the third day of symptoms, she had decided to treat the anxiety and dizziness with buspirone, 15 mg/day. She experienced an exacerbation of symptoms shortly after this, which led to her coming to the clinic. She was again given sertraline, 100 mg/day; her symptoms disappeared within 24 hours.

During long-term SSRI administration, there is a greater concentration of synaptic serotonin, which causes autoreceptors and postsynaptic receptors to desensitize or down-regulate (2). With abrupt cessation of serotonin blockade, there may be a temporary deficiency of available synaptic serotonin in the face of these down-regulated receptors. It has been proposed that the symptoms observed during discontinuation syndrome are the result of a deficiency in these serotonin pathways (3). Buspirone, a partial agonist, may have exacerbated the patient's symptoms because of some weak or partial net antagonist properties. Furthermore, since one of buspirone's proposed effects is the partial activation of the se-

rotonin 5-HT_{1A} autoreceptor (purportedly resulting in decreased serotonergic transmission), synaptic serotonin concentrations may have been further decreased (4). It is possible that this patient, who decided to treat her discontinuation syndrome with buspirone, may have exacerbated her symptoms by continuing to block serotonergic transmission.

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SSRIs and Mammoplasia

TO THE EDITOR: Mammoplasia (1), nonpuerperal lactation (2), and aggravation of preexisting fibrocystic disease (3) have all been reported in association with the use of selective serotonin reuptake inhibitors (SSRIs). Mammographic changes associated with SSRI use have not been reported previously, to my knowledge. This report is a description of a woman who had mammographic changes during treatment with an SSRI.

Ms. A, a 43-year-old woman with a history of dysthymia and major depression, had a normal baseline mammogram at age 35 and a normal repeat mammogram at age 40. There was no history of fibrocystic disease. Her menstrual periods were regular. She had gained approximately 6 lb and had subjective breast enlargement as a result of fluvoxamine therapy. Approximately 8 months after starting to take fluvoxamine, 50–100 mg/day, she had another routine mammogram.

The mammogram was interpreted as having "bilateral hyperdensities," and Ms. A was referred to a breast surgeon for consultation. No masses were found during palpation, and a 6-month follow-up mammogram was recommended. Ms. A chose to stop taking fluvoxamine because of concern that the mammoplasia and mammographic changes were related. A non-SSRI antidepressant was substituted, and her breasts returned to normal size. A 6-month follow-up mammogram was normal.

Mammoplasia during SSRI therapy was reported in up to 39% of patients in one study (1). The rate of mammoplasia was unrelated to age, menopausal status, or duration of treatment. Mammoplasia was associated with weight gain in 84% of the patients, and weight gain without mammoplasia occurred in 30% of the patients (1). Serotonergic antidepressants are associated with a risk of nonpuerperal lactation approximately eight times as high as the risk with other antidepressants (2).

These effects are probably mediated by indirect inhibition of dopamine transmission by serotonin. As dopamine is inhibited, prolactin release is disinhibited. This report illustrates that SSRIs may cause not only mammoplasia but also mammographic changes. Clinicians should be aware of this possibility, because this effect can result not only in significant anxiety for the patient but also in referral for consultation with breast specialists who may not be aware of this association.

The clinical significance of these effects is not known. Concern has grown about the long-term risks for women of nonpuerperal elevation of prolactin levels, especially for those with a family history of breast cancer. Research is needed to assess if mammographic changes occur regularly along with mammoplasia associated with SSRI use and whether there are long-term risks associated with SSRI-induced mammoplasia.

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Topiramate for Binge-Eating Disorder

TO THE EDITOR: Topiramate is a broad-spectrum neurotherapeutic agent that may have utility in treating some psychiatric disorders. Additionally, a retrospective review of epilepsy patients treated with topiramate (1) has suggested that reduced appetite and weight loss may be associated with this drug. Binge-eating disorder is a novel diagnostic entity that appears in appendix B of DSM-IV as a diagnostic category requiring further study. Binge-eating disorder affects a substantial group of obese patients and could have a negative impact on their treatment (2). To our knowledge, the only publication on the use of topiramate in binge-eating disorder is a case report of 13 patients with comorbid bipolar or major depressive disorder (3). We report on a morbidly obese woman with binge-eating disorder with no neuropsychiatric comorbidity who failed to respond to other agents and was successfully treated with topiramate.

Ms. A, a 22-year-old woman who had been overweight since age 18, was referred to our unit for help in losing weight. She had failed to lose weight by several means, including nutritional counseling, pharmacological treatments with amphetamine-like anorectic agents, and 60 mg/day of fluoxetine. She could not tolerate sibutramine, 15 mg/day, because of the side effects of tachycardia and nervousness. At her first visit she weighed 109 kg and was 1.60 m tall; she had a body mass index of 42.5 kg/m^2 and fulfilled the proposed DSM-IV criteria for binge-eating disorder without psychiatric or neuroendocrine comorbidity. Her eating patterns were characterized by periods of eating regular meals alternating with brief restrictive diets.

During the last 4 years, she had been having binge-eating episodes 3–4 days a week.

After a period of nutritional counseling, Ms. A still experienced a mean of 4 days a week of binge-eating episodes, so we prescribed topiramate. The initial topiramate dose of 25 mg b.i.d. for 2 weeks was followed by an increase of 25 mg every week until she reached the target dose of 75 mg b.i.d. At the end of the first 2 weeks of treatment, she showed a marked reduction from 4 days to 1 day of binge eating per week, and the total number of binge-eating episodes per week dropped from eight to two. From the first until the fourth month of treatment, Ms. A was completely well and had no more binge-eating episodes. Her weight was 98.6 kg (body mass index=38.5 kg/m^2). Somnolence in the beginning of treatment was the only medication side effect.

This report emphasizes that controlled studies are warranted to confirm these preliminary observations that topiramate is useful in the treatment of patients with binge-eating disorder.

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Control of Tourette's Syndrome With Topiramate

TO THE EDITOR: Tourette's syndrome carries the truncated eponym designated after Georges Gilles de la Tourette's original article was published in 1885 (1). Although numerous therapies have been attempted (2), neuroleptics have been found to be the most effective treatment of Tourette's syndrome. Seignot's original success with haloperidol (3) has made Tourette's syndrome a human assay of dopamine-blocking agents. We report on two patients who met DSM-IV criteria for Tourette's syndrome who were successfully treated with topiramate while previous medications were tapered and discontinued during the first 2 weeks of treatment.

Ms. A had no family history of Tourette's syndrome, but she had exhibited facial tics, later accompanied by humming, coprolalia, and palilalia, since age 6. She had tried haloperidol between ages 10 and 19 but developed a stiff tongue and difficulty sleeping. The introduction of risperidone, 1.5 mg/day, had controlled her tics but had caused a weight gain of 37 lb and galactorrhea. Treatment with topiramate, 50–200 mg/day, brought her tics under control within 1 week, but she developed a slight lack of concentration, loss of appetite, and greater thirst. Her weight dropped from 183 to 145 lb in 8 months.

After recovering from pneumonia at age 9, Mr. B had experienced facial tics. The only family history of facial tics was found in his son and maternal uncle. For 15 years he had been treated with clonazepam, 0.5–2.0 mg/day. Risperidone had been prescribed instead, and in 13 months Mr. B had reached his highest weight—228.5 lb. Topiramate was substituted, 200 mg at bedtime, but he felt lethargic. When he took 100 mg at bedtime, his tics were under control, and he experienced few side effects. In a month, Mr. B had a weight loss of 12.5 lb.

Topiramate, a fructopyranose derivative, possesses a structure unlike that of other anticonvulsants. The exact mechanism of action is unknown. It has been shown to potentiate the activity of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter (4), which could control tics. Although Tourette's syndrome is not a convulsive disorder, other GABAergic medications, such as clonazepam, have been effective in controlling tics. Topiramate has advantages over neuroleptic medications in that it carries no risk of tardive dyskinesia. Often, weight loss is highly desired by patients. Topiramate can cause alkaline urine, which may induce kidney stones; acidifying the urine with high doses of ascorbic acid may counteract this risk. A search of scientific literature failed to reveal previous use of topiramate for the treatment of Tourette's syndrome.

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Topiramate for Clozapine-Induced Seizures

TO THE EDITOR: Clozapine is an antipsychotic that is associated with a higher prevalence of seizures than traditional neuroleptics (1). Several anticonvulsants, including phenytoin, carbamazepine, and valproic acid, have been found to be effective in the treatment of these seizures (2), but certain side effects and pharmacokinetic interactions may limit their prescription in combination with clozapine. Topiramate is a relatively new, but well-documented, antiepileptic drug with a lack of significant pharmacokinetic interactions and a benign side effect profile (3). We report on a young woman who experienced a generalized tonic-clonic seizure while taking clozapine and was successfully treated with topiramate.

Ms. A, age 23, was seen for treatment of paranoid schizophrenia of a year's evolution. The results of her laboratory tests and brain imaging studies were normal. Her family history did not include mental illness, and she had no personal history of previous seizures or head trauma. During 10 months of follow-up on an outpatient basis, she had received risperidone, up to 6 mg/day, and then olanzapine, up to 10 mg/day; she had experienced a marked weight increase and an evident negative symptom profile. Because of the presence of depressive symptoms, sertra-

line, 100 mg/day, had also been prescribed. Finally, she had been hospitalized after a suicide attempt.

During hospitalization, without suspension of her treatment with sertraline, treatment with clozapine was initiated instead of olanzapine. The dose was increased by 50 mg every 4 days. During the third week of clozapine treatment, while taking a stable dose of 200 mg/day, which resulted in a favorable clinical response, Ms. A experienced a 4-minute generalized tonic-clonic seizure. An EEG showed bihemispheric epileptiform activity. Since a favorable clinical response had been observed, clozapine treatment was not suspended. Because of the substantial weight gain with previous treatments, it was decided to prescribe topiramate as an anticonvulsive, given that this drug has been reported to reduce weight (3). The initial dose was 50 mg/day and was increased to 200 mg/day. After 6 months of a regimen of clozapine, 200 mg/day, and topiramate, 200 mg/day, Ms. A showed no evidence of recurrent seizures, either clinically or on EEG. Pretreatment and 6-month follow-up body mass indexes were 26.81 and 25.92 kg/m^2, respectively.

We describe a schizophrenic patient who had a generalized tonic-clonic seizure with clozapine therapy who was treated successfully with clozapine and topiramate without showing any recurrence of seizures or side effects. As has recently been suggested with gabapentin (4), topiramate should be considered for prophylaxis in patients taking clozapine who are at a greater risk of seizures and for the treatment of clozapine-induced seizures, particularly in patients who have exhibited a satisfactory clinical response to clozapine.

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Possible Interaction of Clozapine and Lisinopril

TO THE EDITOR: Clozapine levels should be at 350–450 ng/ml for clinical efficacy and minimal side effects (1). Factors affecting its metabolism or excretion can influence clinical efficacy. We report on a patient who possibly experienced an interaction effect of clozapine and lisinopril.

Mr. A, a 39-year-old Asian man with treatment-resistant schizophrenia, was receiving 300 mg/day of clozapine; his blood level of the drug was 490 ng/ml. In addition, he had diabetes that was controlled with glipizide, 10 mg/day. One year later, he developed hypertension, so lisinopril treatment, 5 mg/day, was initiated. Shortly afterward, his blood levels of clozapine and one its metabolites, norclozapine, were 966 ng/ml and 512 ng/ml, respectively. Six months later, his dose of lisinopril was increased to 10 mg/day. His blood levels of clozapine and norclozapine, as measured on two consecutive occasions 1 month apart, were 1092 and 380 ng/ml and 1245 and 392 ng/ml, respectively.

Mr. A became more disorganized and had frequent episodes of irritability and angry outbursts. He experienced severe sleep disturbances and frequent nightmares and awakenings. He also salivated excessively. Other known side effects of clozapine, such as anticholinergic toxicity or seizures, were not observed. Laboratory values, including measures of renal functions, were found to be within normal limits.

Mr. A's clozapine dose was decreased to 200 mg/day. His blood levels, measured after 6 weeks, remained high: clozapine, 1335 ng/ml, and norclozapine, 428 ng/ml. When we suspected a drug interaction, his antihypertensive was changed from lisinopril to diltiazem, 240 mg/day. Repetition of laboratory tests after 6 weeks resulted in clozapine and norclozapine levels that had decreased to 693 and 254 ng/ml, respectively. Although Mr. A continued to experience psychotic symptoms and sialorrhea, his sleep disturbances and irritability had improved.

An interaction in which lisinopril raises the level of clozapine or its metabolites has not been reported, to our knowledge. Angiotensin-converting enzyme inhibitors, by dilating efferent arterioles, decrease overall renal vascular resistance. This in turn decreases intraglomerular pressure, which reduces effective filtration pressure and slows the glomerular filtration rate, causing reversible renal impairment (2). This impairment may not be reflected by routine tests of renal function. Increased levels of norclozapine suggest impaired excretion.

Lisinopril does not influence the cytochrome systems, and it is excreted unchanged in urine. Clozapine is metabolized by cytochrome 1A2 and 3A4 isoenzymes. It is a well-known phenomenon that excess levels of substrates cause abnormal enzymatic feedback control (3). In our patient, levels of both clozapine and norclozapine were elevated. It is not known whether accumulation of clozapine metabolites can cause negative feedback inhibition in the cytochrome P450 system. If so, it can cause an accumulation of the parent compound. The toxic effects of clozapine are known to cause sleep disturbances, with intensification of dream activity and immediate onset of REM sleep.

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Psychosis After Ultrarapid Opiate Detoxification

TO THE EDITOR: Ultrarapid opiate detoxification is a procedure that uses high doses of opiate antagonists to precipitate rapid opiate withdrawal (1). Although problems have arisen with ultrarapid opiate detoxification, the University of Illinois at Chicago protocol (2) has resulted in few complications. We report a case of ultrarapid opiate detoxification complicated by psychosis that abated within 24 hours.

Ms. A was a 45-year-old woman who was taking 100 mg/day of methadone and 4 mg/day of alprazolam concurrently. She desired detoxification because of a 40-lb weight gain that she attributed to methadone therapy, but she did not wish to undergo conventional detoxification. Ms. A was advised to stop taking alprazolam before ultrarapid opiate detoxification, but she refused and mentioned that she had attempted suicide after a past detoxification.

Twelve days before the ultrarapid opiate detoxification, a toxicology screen was positive for methadone and benzodiazepines but negative for all other drugs of abuse. Ms. A discontinued methadone treatment, and hydrocodone therapy was initiated. One day before the ultrarapid opiate detoxification, a toxicology screen was positive for methadone. Ultrarapid opiate detoxification was conducted according to protocol (2) and included benzodiazepine substitution. During extubation and over the next few hours, Ms. A was intermittently agitated despite being fully oriented. Several hours after ultrarapid opiate detoxification, Ms. A was observed ingesting pills not supplied by staff. When staff confronted her, she admitted ingesting alprazolam for anxiety.

Subsequently, Ms. A reported feeling as if the previous few hours had been a bad dream or "bad trip." She reported believing staff were trying to kill her and that during extubation the anesthesiologist was attempting to choke her. She also reported auditory but neither visual nor tactile hallucinations. These symptoms completely disappeared in 24 hours. At her 3-month follow-up, Ms. A was still in treatment for addiction, but toxicology screens were negative for methadone and other opiates.

To our knowledge, this is the first report of psychosis in a patient undergoing ultrarapid opiate detoxification. Many of the medications involved (methadone, alprazolam, naloxone, clonidine, propofol, and midazolam) have been associated with the occurrence of delirium, psychosis, or hallucinosis. However, psychosis in the absence of disorientation has not been encountered in the more than 125 patients who have undergone ultrarapid opiate detoxification at our facility.

Psychosis in the presence of a clear sensorium is unusual in alprazolam withdrawal. Although methadone's long half-life could account for its detection 12 days after discontinuation, surreptitious use must be considered. Ms. A's methadone/alprazolam combined doses, which have not been encountered among our patients undergoing ultrarapid opiate detoxification, may be responsible for the unusual reaction that she experienced. This combination is reported to be common in methadone clinics and has been implicated in some fatalities (3). Although no definitive conclusions can be drawn from this case report, extreme caution is advisable when treating methadone-maintained patients who use alprazolam and are undergoing ultrarapid opiate detoxification.

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Modafinil for Narcolepsy

TO THE EDITOR: Modafinil, a wakefulness-promoting oral agent, is approved for the treatment of the excessive daytime sleepiness associated with narcolepsy. It is thought to work by means of the hypocretin-orexin system in the hypothalamus (1). A class IV drug, it is only minimally stimulating in the traditional manner. These facts suggested that it might be useful in treating the excessive daytime sleepiness often seen as a side effect of the neuroleptic treatment of psychosis or depression and in closed-head brain injury (dementia due to head trauma). In both cases the somnolence can be severely disabling and the use of traditional psychostimulants is cumbersome and may be risky or impractical.

I report the successful open-label clinical use of modafinil in 10 outpatients with closed-head brain injury and excessive daytime sleepiness and in two patients with somnolence due to sedating psychiatric drugs. In these instances, it either replaced a schedule II agent or was used as the initial treatment for excessive daytime sleepiness.

The patients ranged in age from 42 to 72 years. All were outpatients whose excessive daytime sleepiness limited their activity and quality of life. The patients were informed that the drug had been approved for other uses, but it seemed to have benefits that might serve their needs. They were informed of possible side effects, including overstimulation. In these individuals, modafinil was well tolerated at doses of 100–400 mg taken once every morning; effectiveness lasted all day and resulted in an apparently normal nighttime sleep. With proper titration, excessive daytime sleepiness was markedly decreased in nine patients and moderately decreased in three; all changes were felt to be beneficial by the patients.

At prescribed doses, there was increased wakefulness and feelings of normality. Some patients noticed a greater sense of attention and other cognitive benefits. The results have often been rapid (within 1–2 hours of taking modafinil) and dramatic and have frequently led to a sense of relief and increased well-being. It is not clear if there is a direct effect on affect or if the patients simply responded to their increased quality of life and function—or both.

To date, my patients have used modafinil between 5 and 13 months, and there has been no evidence of tolerance or decreased effectiveness and no apparent adverse interactions with concurrent medications. Side effects, when present, have usually been mild and transient, primarily complaints of stimulation or gastrointestinal upset. It should be noted, however, that outside of this group, two middle-aged brain-

injured women with multiple other complications and medications could not tolerate modafinil. This was due to strong feelings of emotional instability brought on soon after taking the first dose of 100 mg. Both reported similar reactions to many other medications and felt they were generally hypersensitive to drugs. No further trials were made at a lower dose.

Modafinil appears to be useful in the treatment of excessive daytime sleepiness associated with closed-head brain injury and with sedating psychiatric drugs, facilitating rehabilitation and enhancing quality of life. However, adequately controlled clinical trials will be needed to fully determine the role of modafinil in the treatment of excessive daytime sleepiness associated with these and other medical conditions apart from narcolepsy.

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Cognitive Behavior Therapy for Weight Gain

TO THE EDITOR: Some evidence has suggested that atypical antipsychotics offer a more comprehensive treatment for schizophrenia than typical antipsychotics. However, these drugs often lead to considerable weight gain (1, 2), resulting in poor compliance and a greater risk of cardiovascular morbidity and mortality. To our knowledge, effective treatments of this side effect have not been identified. Here we report on the successful treatment of weight gain due to atypical antipsychotics with an approach that included elements of behavior therapy and counseling.

Six patients with chronic schizophrenia and a patient with bipolar disorder were referred to a treatment group for medication-associated weight gain. Three additional schizophrenic patients signed up for individual treatment. In both group and individual sessions, a therapist trained as a psychologist and a dietician provided a treatment that included detailed counseling and a cognitive behavior approach. Treatment sessions focused on causes of weight gain, healthy low-calorie nutrition, specific recommendations for weight loss, and instructions about physical exercise and relaxation. In addition, problems with weight reduction were discussed, and behavioral and cognitive remedies were explored. Individual treatment spanned seven to nine sessions; in the group setting, 10 biweekly sessions focused on weight reduction, followed by six sessions focusing on weight maintenance.

We evaluated the outcome of the treatment with a retrospective analysis of the weight data recorded in the charts of the patients and the notes of the dietician. Three patients dropped out of group treatment within two sessions. No data were recorded for these patients. For one patient who completed treatment, no data were available retrospectively. Thus, data were analyzed for six patients, all with a diagnosis of schizophrenia (two men and four women; age: mean=37.3 years, SD=14.7). Four patients were treated with clozapine (dose range: 25–250 mg/day) and two with 10 mg/day of olanzapine. Before treatment the mean body mass index was 29.6 kg/m^2 (SD=2.5, range=26.6–34.0). After treatment, the body mass indexes ranged from 22.28 to 30.12 kg/m^2 with a mean of 25.1 (SD=3.0); the difference between pre-and posttreatment was significant according to a paired t test ($t=3.97$, $df=5$, $p<0.02$). Actual weight loss ranged from 0 to 21 kg. Five of these six patients showed a posttreatment body mass index of less than 25 kg/m^2, the upper limit of the recommended range.

Our results suggest that cognitive behavior treatment may be a successful approach to control of an important side effect of atypical antipsychotics. Prospective controlled trials should be conducted to confirm these encouraging results.

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Dopamine D_2 Receptor Blockade in Schizophrenia

TO THE EDITOR: We read with interest the results of a recent study making use of [^{123}I]iodobenzamide single photon emission computed tomography ([^{123}I]IBZM SPECT) with schizophrenic patients (1). The authors demonstrated a significant correlation between striatal dopamine D_2 receptor occupancy by olanzapine and risperidone in the presence of depressive symptoms, negative symptoms, and negative subjective experiences as measured by the Subjective Well-Being Under Neuroleptic Treatment Scale.

We attained similar results in a study of 18 schizophrenic patients treated with typical antipsychotics who were scanned with[^{123}I]IBZM SPECT (2). We reanalyzed this data using three items from the Brief Psychiatric Rating Scale (BPRS) that were specific to depression (depressive mood, guilt feelings, and suicidality) as a measure of depressive symptoms that shows little overlap with measures of negative and extrapyramidal symptoms. We found a significant correlation between striatal D_2 receptor occupancy by typical antipsychotic drugs and scores on BPRS depression items (3). This association remained significant after control for total BPRS scores. There was no correlation between BPRS total scores and either BPRS depression item scores or striatal D_2 receptor occupancy (3).

The most significant association with D_2 occupancy in the study by Lieuwe de Haan, M.D., et al. was negative subjective experience. In our study, high D_2 occupancy was associated with mild rather than severe depressive symptoms. Patients frequently complain about taking antipsychotic medications, even in the absence of overt motor side effects. It is possible that this behavior reflects the emergence of the mild depres-

sive symptoms identified in both of these studies. This phenomenon might have important implications for drug choice, dosing, and treatment-adherence strategies. Although our findings are consistent with those of Dr. de Haan et al., both are preliminary, and full elucidation is awaited in larger prospective studies.

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Dr. de Haan and Colleagues Reply

TO THE EDITOR: Dr. Bressan and colleagues present findings that are consistent with our findings of a correlation between D_2 receptor occupancy and depression, but their findings resemble ours even more than they suggest. The highest significant correlation with striatal D_2 receptor occupancy we found was with the total score on the Montgomery-Åsberg Depression Rating Scale (r_s=0.46, N=22, p=0.02) (p. 1020). This resembles the correlation they found between striatal D_2 receptor occupancy and BPRS depression item scores (r=0.52, p=0.03) (Bressan et al., 2000). Like Dr. Bressan et al., we also found no correlation between total psychopathology scale scores and striatal D_2 receptor occupancy (Pilowsky et al., 1993). Actually, this leads to the main conclusion of their original study: poor clinical response does not appear to be accounted for by differential blockade or inadequate occupancy of striatal D_2 receptors by antipsychotic medication (Pilowsky et al., 1993).

However, we think it is important to also stress the differences between their study and ours. The patients they studied had a mean illness duration of about 8.5 years; the group included responders and nonresponders who used a variety of typical antipsychotics in a wide dosing range (mean=687.9 mg/day of chlorpromazine equivalents, range=150–2000). However, all of our patients (mean age=22 years) had recent-onset schizophrenia (mainly first episode) and were stabilized with moderate doses of olanzapine or risperidone. These differences probably have important implications. The inclusion of patients with chronic illness and nonresponders might introduce a confounding association of psychosis and depression. The range of striatal D_2 receptor occupancy in their study was much larger than in ours, making it more likely that if there was an association between striatal D_2 receptor occupancy and aspects of mood, it could be found in their population. That we found a comparable association is taken to imply that small differences in D_2 receptor occupancy may have consequences for the subjective experiences of patients. We think that the comparable finding of a relationship between aspects of negative mood and striatal D_2 receptor occupancy in such different groups of patients with schizophrenia supports the notion that more (antipsychotics) could be less (a favorable result).

Contrary to what Dr. Bressan and colleagues have suggested (Bressan et al., 2000), we suppose that typical antipsychotic drugs in doses that lead to the same range of D_2 receptor occupancy as that of atypical antipsychotics lead to comparable subjective experiences in patients. The findings of Dr. Bressan and colleagues and those of our group may have important implications for dosing and treatment-adherence strategies. Our study supports the notion that subjective experiences of patients are important in these strategies (1). We agree that both findings are preliminary.

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5-HT_{1D} Function and Repetitive Behaviors

TO THE EDITOR: In a recent article, Emanuela Mundo, M.D., et al. (1) reported a significant linkage disequilibrium between the G861C variant of the serotonin $5\text{-HT}_{1D\beta}$ receptor gene and obsessive-compulsive disorder (OCD). This is of interest given reports that the 5-HT_{1D} agonist sumatriptan may improve the symptoms of OCD (2). However, although the effect of the presence of the G variant of the $5\text{-HT}_{1D\beta}$ receptor gene increases the risk of developing OCD by 5.26-fold, the authors acknowledged that OCD is complex and more than one gene is expected to contribute to its etiology. Each gene has only a relatively small effect in increasing the risk for the disorder.

The OCD phenotype is heterogeneous, and it is possible that transmission disequilibrium of the 5-HT_{1D} receptor gene may be more closely related to certain behavioral patterns, such as repetitive or compulsive behaviors per se, rather than to a categorical disorder, such as DSM-IV OCD. A neuroscientifically based psychopathology attempted to transcend the boundaries of convenience that permit reliable categorizations because these categories may not have any inherent biological meaning (3). For this reason, it is of interest to explore whether 5-HT_{1D} function is related to the severity of repetitive behaviors across other neuropsychiatric disorders that cross categorical boundaries.

There is a higher rate of OCD in first-degree family members of autistic probands (4), and parents with high levels of repetitive behaviors have higher whole-blood 5-HT levels (5). Recently, we reported that in autistic patients, a high level of severe repetitive behaviors correlated with higher 5-HT_{1D} sensitivity, as manifested by the response of growth hormone to sumatriptan (6). Thus, one component of 5-HT function, 5-HT_{1D} sensitivity, may play a role in mediating one specific behavioral domain within autism—repetitive behaviors—thus influencing heterogeneity in autism.

Future studies might examine the role of 5-HT_{1D} receptor gene function and the repetitive behavior domain, not only within OCD but across other disorders in which this clinical symptom is a key symptom component.

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Dr. Mundo and Colleagues Reply

TO THE EDITOR: Most psychiatric disorders, including OCD and autism, are defined as complex because of the heterogeneity of the phenotype and because of their unclear etiology. For these disorders, is likely that several factors (genetic and nongenetic) interact at the level of pathogenesis.

The involvement of the 5-$HT_{1D\beta}$ receptor in the pathogenesis of both OCD and autism has been suggested by challenge studies involving the acute administration of the selective agonist sumatriptan. This compound has been found to worsen OCD symptoms in OCD patients (1) and repetitive behaviors (rated by means of a compulsion scale) in adult autistic patients (Hollander et al., 2000). In our recent study, we found that the G variant of the G861C polymorphism of the 5-$HT_{1D\beta}$ receptor gene was significantly associated with the diagnosis of OCD and that the estimate of the increased risk conferred by the presence of the G variant was about five.

However, both OCD and autism are likely to be caused by more than one gene and by environmental factors as well, and it is not possible to know the magnitude of the specific genetic contribution to the total risk. Thus, this estimate should be considered suggestive of an effect but not a definitive assessment of the risk, as it would be in the case of noncomplex disorders with Mendelian transmission (2).

Moreover, considering also the heterogeneity of the OCD phenotype, pointed out by epidemiological, biological, clinical, and pharmacological studies as well as the nonspecificity of symptoms in OCD and autism, it appears to be more reasonable in genetic studies of these complex disorders to investigate genes that may be responsible not for a (heterogeneous) diagnostic category but rather for more homogeneous phenotypes.

The hypothesis derived in the article by Hollander and colleagues (Hollander et al., 2000) that serotonin, and particularly the 5-$HT_{1D\beta}$ receptor, plays an important role in repetitive behaviors across disorders may be correct and may represent a valid approach for relating phenotypes to neurobiology beyond the diagnoses. However, evidence that repetitive behaviors have a more homogeneous origin than OCD remains uncertain.

Alternative phenotypes for investigation in genetic studies for psychiatric disorders might include course specifiers, functioning patterns, or response to medication. The new strategies now available for the consideration of quantitative phenotypes that are an alternative to diagnosis in family-based association studies (3) seem the most appropriate procedures for addressing these issues and represent the future of our research in the genetics of OCD and related disorders.

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ECT Failure Rate Among Specific Devices

TO THE EDITOR: In reporting that adequate ECT seizures were not obtained at the maximum electrical stimulus dose in 5% of ECT patients, Andrew D. Krystal, M.D., M.S., et al. (1) did not recognize that this result is limited to the MECTA Corporation ECT device they used. Instead, they suggested that their results apply to all devices: "Approximately one of six patients…required the maximum possible ECT stimulus intensity available on U.S. ECT devices" (p. 965). The result is limited to MECTA devices because the pulse width and frequency of the maximum stimulus they use are specific to MECTA devices, and their values are crucial to the reported study. These values are for a 2.0-msec pulse width and a 90-Hz frequency with a 2.0-sec duration and 0.8 A current. Compared to these values, the combination of a narrower pulse width, lower frequency, and longer duration should produce lower rates of failure for seizure induction (2, 3). The point that a 5% failure rate is needlessly high is indisputable. However, the failure rate should be substantially lower with more efficient electrical stimuli as well as with higher doses.

Dr. Krystal et al. repeatedly noted a "maximum stimulus intensity limitation of 576 millicoulombs (mC) imposed on U.S. ECT devices by the Food and Drug Administration (FDA)" (p. 963). The actual limitation is 100 J of energy at 220 Ω of impedance. For 0.8 A current, as used in MECTA devices, this limitation corresponds to 572 mC. The original source for a

figure of 576 mC is MECTA's commercial literature. I also wish to point out that nowhere in their published article do Dr. Krystal et al. note their relationship with MECTA Corporation.

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Drs. Krystal and Weiner Reply

TO THE EDITOR: We appreciate Dr. Swartz's comments underscoring that the stimulus characteristics used in our study may have affected the results. As he points out, and as we discussed in our article, some reports have suggested that shorter pulse widths and a longer duration of stimuli may be more efficient at eliciting seizures. Such stimulus characteristics might be associated with fewer than 5% of the subjects having ineffective treatments because of short seizures at the maximum available stimulus level. It should be noted, however, that to our knowledge, there have been no published studies that directly address this issue with the use of precise dose-titration methodology, and this possibility therefore remains speculative. Further, other, admittedly flawed, investigations have suggested diminished efficacy with shorter pulse widths.

Nonetheless, both MECTA Corporation, whose device we used, and their competitor, Somatics LLC, now produce ECT devices with shorter pulse widths and longer duration stimuli than we employed in our study. Using the newer device made by MECTA Corporation, we have since analyzed new data from 49 subjects. These subjects received a recent clinical index ECT course administered like those in our study, except that a briefer pulse width (1.0 versus 2.0 msec) and a maximum stimulus of longer duration (6.0 versus 2.0 sec) were employed. Fourteen subjects (29%) required the maximum intensity stimulus, and five (10%) had a short seizure at the maximum stimulus level. These preliminary results do not suggest a "substantially lower" failure rate; however, it remains undetermined whether this might be true with even shorter pulse widths.

Thus, to our knowledge, no data exist suggesting that our results apply only to the MECTA device used in our study. Of more importance, to our knowledge, no studies contradict our conclusion that there is a need for higher maximum stimulus intensities. This conclusion is also supported by recent compelling independent findings by others (1–3).

With respect to the present maximum U.S. stimulus intensity, as we noted, the FDA limited U.S. ECT devices to a maximum intensity before FDA regulation. For MECTA devices, there is a maximum charge of 576 mC versus 504 mC for devices made by Somatics. Since we reported the maximum allowable charge for U.S. devices, the former figure was used. The limitation of 100 J at 220 Ω of impedance referred to by Dr. Swartz reflects a standard once adopted by the International Electrotechnical Commission for ECT devices that has since been withdrawn.

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The authors are the inventors listed on a U.S. patent that Duke University has licensed to MECTA Corporation. Neither receives royalties from this patent.

Antidepressant Use by Race

TO THE EDITOR: We read the recent article by Dan G. Blazer, M.D., Ph.D., et al. (1) with great interest. The article draws important attention to marked differences in antidepressant use by race in an elderly community sample and is a significant contribution to the literature in this area. We certainly agree with the authors that differences in antidepressant use between Caucasian and African American elders could have many causes.

These could include, as the authors noted, practitioners' underdiagnosis of depression in elderly African Americans (in spite of the known similar prevalences of the disorder in these races when assessed in large-scale controlled studies). In fact, there is a growing literature suggesting that this phenomenon occurs in a variety of settings. In two separate studies of patients admitted to geropsychiatric acute inpatient units, Fabrega et al. (2) noted a lower proportion of elderly African Americans diagnosed with mood disorders and higher proportions of elderly African Americans diagnosed with psychotic disorders, and Mulsant et al. (3) found that elderly African American patients were significantly more likely to receive a diagnosis of schizophrenia. Leo et al. (4), in a study examining geropsychiatric consultation, found that African Americans were diagnosed with psychotic disorders and dementia significantly more often and with mood disorders significantly less often than Caucasians. In a large retrospective examination of a group of elderly patients treated within the Veterans Affairs health care system, we found that African Americans were significantly less likely to receive a diagnosis of depression than Caucasians (5); the rate of mood disorder diagnoses in elderly African Americans was less than half that of elderly Caucasians.

Differences in depression diagnoses between races in elderly samples could be due to patient factors (less reporting, different symptom presentation, or less use of formal health care settings for treating depression) or provider factors (mis-

diagnosis or clinician bias). On the basis of these findings, we agree that it is possible that the subjects in the study by Dr. Blazer et al. were much less likely to receive antidepressants because they were much less likely to be given the diagnosis of major depression in the clinical setting. The question remains as to whether elderly patients of different races receive different treatments once a diagnosis of depression is made. Further studies are needed to examine the contribution of both patient and provider factors to racial differences in this area.

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Dr. Blazer and Colleagues Reply

TO THE EDITOR: We appreciate the letter by Dr. Kales and her colleagues commenting on our recent report. They focus on an important factor that should be addressed by both clinicians and clinical investigators—namely, the documented differences in the recognition of depression by race in treatment settings. The studies they note, however, refer exclusively to treatment samples. Three of the samples (Fabrega et al., 1994, Mulsant et al., 1993, Leo et al., 1997) were derived from psychiatric inpatient populations. The use of treatment samples to generalize to the community (from which our sample was drawn) can potentially lead to bias. For example, older African Americans may be admitted differentially to psychiatric facilities because of differences in their seeking of health care, which limits the ability to conclude that these African American elders are less likely to receive a diagnosis of major depression in a clinical setting. African Americans may be just as likely to receive a diagnosis of major depression in an ambulatory setting, but they may be less likely to be hospitalized (thus leading to the higher rates of admission for dementia and schizophrenia reported). Unfortunately, our data and the data from the studies cited by Dr. Kales and colleagues cannot address these questions.

We are in the process of linking our self-report data to ambulatory care data from the Health Care Financing Administration, which will permit us to address this question. We suspect that, as Dr. Kales and her colleagues point out, the diagnosis of major depression will vary by race in the ambulatory setting; however, this will explain only a portion of the variance between Caucasians and African Americans in the use of antidepressant medications. We hypothesize that even given the diagnosis of major depression (or the diagnosis of other depressive disorders), physicians are less likely to prescribe antidepressants to African Americans than Caucasians, especially selective serotonin reuptake inhibitors. We also hypothesize that African Americans are less likely to seek or accept a prescription for antidepressant medications; however, even these new data cannot address this latter hypothesis.

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Dysthymia and Comorbid Disorders

TO THE EDITOR: I read with great interest the serendipitously juxtaposed articles by Daniel N. Klein, Ph.D., et al. (1) and Ernst R. Berndt, Ph.D., et.al. (2). The article by Dr. Klein et al. described an elegantly performed 5-year study of the course and outcome of dysthymic disorder, whereas the article by Dr. Berndt et al. addressed the loss in personal achievement and actualization among patients with chronic depression. Clearly, the cost in human suffering and compromised development as a result of these mood disorders is profound and has heretofore been underappreciated.

From the details of the article by Dr. Klein et al., I was able to glean further differences between their cohort with dysthymic disorder and the group with major depression without dysthymic disorder that may be of significance and warrant further discussion and research. Table 1 shows three comorbid conditions that were present at significantly higher rates in the dysthymic disorder cohort. Dysthymic patients were more likely to have suffered from recurrent major depression (among the dysthymic disorder subjects with a history of discrete episodes of major depression), personality disorder, and substance abuse or dependence (1).

The poorer outcomes in the cohort of patients with dysthymic disorder than in the "pure" cohort of patients with major depression may initially appear to be a somewhat paradoxical finding in that dysthymic disorder seems to be a minor illness compared to major depression. Do the authors believe that the poorer clinical outcomes may relate in part to the comorbid psychiatric illnesses in the cohort with dysthymic disorder? It is common clinical experience to encounter patients with chronic mood symptoms for whom personality disorder or substance use disorder is the primary diagnosis. A study of dysthymic disorder versus major depression in which the study groups did not differ in the prevalence of these potentially complicating comorbid conditions could yield different results in terms of patient outcomes. The report by Dr. Klein et al. highlighted the vexing issue of psychiatric comorbidity in dysthymic disorder.

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Dr. Klein Replies

TO THE EDITOR: Patients with dysthymic disorder differ from patients with episodic major depressive disorder in a number of respects, including experiencing higher rates of axis I and II comorbidity (1, 2). Dr. Bourgeois raises the important question of whether the differences in patients with comorbid personality and substance use disorders explain why patients with dysthymic disorder had a poorer course and outcome than patients with episodic major depressive disorder in our 5-year follow-up study.

To address this question, we conducted hierarchical multiple linear regression analyses to determine whether baseline diagnosis (dysthymic disorder versus episodic major depressive disorder) predicted mean level of depression across the follow-up period (3) and scores on the Modified Hamilton Rating Scale for Depression (4) at the 5-year follow-up evaluation after control for the presence of a personality disorder diagnosis (5) and lifetime alcohol and drug use disorders (few patients were currently abusing substances at entry into the study). Baseline scores on the modified Hamilton scale were included as a covariate in the analysis of 5-year scores on the modified Hamilton scale.

After control for personality disorder and lifetime substance use disorder, a diagnosis of dysthymic disorder (as opposed to episodic major depressive disorder) significantly predicted a greater mean level of depression across the follow-up period (change: R^2=0.18; F=33.73, df=1, 121, p<0.001). Similarly, after control for baseline score on the modified Hamilton scale, personality disorder, and lifetime substance use disorder, dysthymic disorder was found to be significantly associated with a higher score on the modified Hamilton depression scale at follow-up (change: R^2=0.09; F=13.89, df=1, 107, p<0.001). Thus, although differences in patients with comorbid personality and substance use disorders may be a contributing factor, they do not account for the differences in course between patients with dysthymic disorder and patients with episodic major depressive disorder in our study. Nonetheless, the impact of comorbidity on the course of dysthymic disorder is an important issue that we plan to explore in greater detail in future analyses of our data.

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