Letters to the Editor

Psychotic Mania Associated With Fenfluramine and Phentermine Use

TO THE EDITOR: Fenfluramine and phentermine are anorectic agents that are often used in combination, since the activating effect of phentermine tends to counteract fenfluramine-induced sedation. Fenfluramine exerts its anorectic effect through serotonergic mechanisms, specifically by causing presynaptic serotonin release and reuptake blockade. Phentermine, like amphetamine, appears to cause weight loss through presynaptic norepinephrine and dopamine release and by reuptake blockade of these catecholamines (1). Unlike amphetamine, however, phentermine has only mild stimulant effects. Fenfluramine, although chemically related to amphetamine, is not a psychostimulant.

Psychiatric side effects have been associated with fenfluramine treatment. Targum and Marshall (2) found that patients with panic disorder demonstrated significant increases in anxiety when given fenfluramine. Obese patients who discontinue fenfluramine treatment appear to be at risk for developing depressive symptoms (3). We believe this is the first report of psychotic mania after treatment with fenfluramine and phentermine.

Ms. A was a white, 45-year-old woman with severe anergic major depression. There was a history of alcohol abuse, but she had been sober for 13 years. She reported having never experienced major depression before the current episode began 3 years earlier. It was at this time that she experienced severe fatigue, a 60-pound weight gain, depressed mood with loss of reactivity, reduced concentration, and a need to sleep 16 hours a day. Approximately 18 months after her symptoms began, she failed brief treatment trials with fluoxetine and paroxetine. She was eventually stabilized on a regimen of sertraline, 100 mg/day. Ms. A's mood and energy level improved, but she did not return to work or to her premorbid level of functioning.

One year after the initation of the sertraline regimen, Ms. A began taking fenfluramine, 60 mg/day, and phentermine, 15 mg/day, for treatment of morbid obesity. After 2 weeks, she experienced a sudden onset of auditory hallucinations, pressured speech, markedly reduced sleep, grandiose delusions that "God was explaining the universe to her," and combative behavior that required four-point restraints upon hospital admission. She received a 5-mg intramuscular dose of haloperidol, and her symptoms resolved within 24 hours. She was discharged with instructions to stop taking fenfluramine and phentermine and to continue the sertraline treatment. However, after approximately 2 months, during which time her depressive symptoms had worsened, she resumed taking fenfluramine and phentermine on her own. Again, Ms. A experienced an episode of psychotic mania within 2 weeks. She was admitted to the medical service after receiving haloperidol in the emergency room. She was discharged the next morning when her symptoms again appeared to have remitted. However, despite the fact that she had stopped taking fenfluramine and phentermine, Ms. A became increasingly psychotic and agitated over the next 7 days. She was hospitalized and treated with haloperidol (a 5-mg intramuscular dose upon admission, then 2 mg b.i.d.). Within 24 hours her psychosis had resolved, but she remained hypomanic at discharge 2 days later.

On two separate occasions, this patient experienced psychotic mania within 2 weeks of initiating fenfluramine and phentermine treatment, which makes it likely that these anorectic agents were responsible for her symptoms. Since phentermine is a mild sympathomimetic agent, it is possible that her manic symptoms represented an organic psychosis. However, this possibility seems unlikely given phentermine's weak stimulant effects and generally benign side effect profile.

Long-term treatment with fenfluramine has been shown to be superior to placebo in reducing depressive symptoms for patients with bipolar disorder (4). Our patient suffered from anergic depression with reversed neurovegetative symptoms, which is a classic condition of bipolar affective disorder. Thus, it is possible that treatment with fenfluramine induced mania because the patient was predisposed to develop these symptoms. In a longitudinal study, Altshuler et al. (5) found that 35% of patients with bipolar disorder had manic episodes that were induced by treatment with antidepressants. Once initiated, many of these manic episodes persisted even after antidepressant withdrawal, as was seen in our patient, who at one point remained psychotic for 2 weeks even after fenfluramine and phentermine were withdrawn. Our experience suggests that fenfluramine and phentermine should be used with caution in patients with bipolar disorder and also adds to the evidence that fenfluramine, as gauged by its ability to induce mania, may be a clinically significant antidepressant.

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Treatment of Irritable Bowel Syndrome With Fluvoxamine

TO THE EDITOR: Irritable bowel syndrome is a clinical condition in which symptoms of stomach cramps and altered bowel movements occur in the absence of any structural

changes. It is a common condition, with a population lifetime prevalence of up to 22% (1). There is evidence that irritable bowel syndrome is associated with a higher lifetime prevalence of psychiatric disorders, including major depression, social phobia, and panic disorder (2). Treatment is generally nonspecific and includes bulk laxatives, antidepressants, benzodiazepines, anticholinergic agents, and smooth muscle relaxants (3). We wish to report the efficacy of fluvoxamine in the treatment of irritable bowel syndrome.

Ms. A was a white, 33-year-old, divorced woman with symptoms of stomach cramps, bloating, and altered bowel movements that had been present since she was 22. She reported that the constipation that she experienced two to three times a week would alternate with episodes of loose stools, which would occur up to five times a day and were associated with cramps. She was forced to adjust her lifestyle to make sure a bathroom was always available. Results of a rectosigmoidal endoscopic evaluation revealed no abnormality.

Results of a structured clinical interview revealed no comorbid psychiatric disorder and no family history of either irritable bowel syndrome or psychiatric illness. The diagnosis of irritable bowel syndrome was made according to ICD-9 criteria. Ms. A was seen every 2 weeks. At each visit, the frequency and severity of the irritable bowel syndrome was assessed, and the 7-point Clinical Global Impression (CGI) scale was administered.

Ms. A was prescribed a regimen of fluvoxamine, 50 mg/day; the dose was increased in 50-mg increments. A substantial improvement was noted 2 months later at a dose level of 150 mg/day. Ms. A stated that her stools were normal and that there was a marked decrease in symptoms of urgency, stomach cramps, loose stools, and constipation. In addition, she no longer needed to plan her day around the bathroom. She stated that this was the first medication that had helped with her symptoms. Improvement was seen in social and occupational performance, and there was a reduction in symptom severity (CGI rating was 2). She suffered a return of her symptoms after she had moved away because she had allowed her prescription to lapse.

To our knowledge, this is the first report of a case of irritable bowel syndrome that responded to treatment with fluvoxamine, a selective serotonin reuptake inhibitor. Whether the action was enteric or central is unclear at this point, but both are possible. Improvement in the symptoms of irritable bowel syndrome could not be explained by changes in a comorbid axis I disorder, since no such disorder was present. The patient reported substantial improvement in her symptoms after 2 months of treatment, which suggests that a placebo response was unlikely. Further studies are warranted.

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Exacerbation of Respiratory Symptoms in Patients With Panic Disorder

TO THE EDITOR: According to DSM-IV, panic disorder may involve respiratory symptoms such as hyperventilation, dyspnea, and choking sensations. Similar symptoms have been reported after treatment with angiotensin converting enzyme inhibitors (1). We report the occurrence of persistent respiratory symptoms despite partial response to antipanic treatment in two patients with panic disorder who were taking angiotensin converting enzyme inhibitors.

Mr. A was a 49-year-old man who exhibited the cardiac, respiratory, neurological, and cognitive symptoms of panic disorder. He had had at least four spontaneous panic attacks per week and had experienced prominent phobic avoidance for 9 years. Results of a physical examination revealed no abnormality.

Mr. A was treated with a regimen of sertraline, 100 mg/day. After 8 weeks, he was panic free and experienced minimal phobic avoidance. The rating of symptom severity, from the Clinical Global Impression (CGI) scale, fell from 6 to 2. However, coughing, shortness of breath, and choking sensations persisted. He had denied taking any concomitant medications, but consultation with his family practitioner revealed that for 12 years Mr. A had been taking captopril, 25 mg b.i.d., for treatment of hypertension. The regimen of captopril was replaced with a thiazide diuretic. After 10 days, all respiratory symptoms had resolved.

Ms. B was a 54-year-old woman with an 8-year history of panic disorder and agoraphobia. She exhibited the cardiac, respiratory, gastrointestinal, and neurological symptoms of panic disorder, and for 2 years she had been taking cilazapril, 2.5 mg/day, for treatment of hypertension.

Her panic disorder was treated for 10 weeks with the selective serotonin reuptake inhibitor (SSRI) citalopram, 30 mg/day, after which the CGI symptom severity rating fell from 5 to 2. She still complained of a persistent cough, shortness of breath, and choking sensations. The regimen of cilazapril was replaced with a thiazide diuretic and atenolol, 50 mg/day. After 6 days she was symptom free.

One possible explanation for this phenomenon is that SSRIs may inhibit the metabolism of angiotensin converting enzyme inhibitors. The observed respiratory symptoms thus could have been an expression of the resulting toxicity. However, a MEDLINE search found no reference to any such metabolic interaction. Another possibility is that angiotensin converting enzyme inhibitors may raise the levels of cholecystokinin (CCK), a peptide produced in the small intestine and known to be panicogenic (2). Dubreuil et al. (3) demonstrated that metabolism of CCK_8 was inhibited by the angiotensin converting enzyme inhibitors captopril and EDTA but not by other enzyme inhibitors.

While the mechanism of any possible interaction remains speculative, we would like to draw clinicians' attention to the possibility that in patients with panic disorder, treatment of comorbid cardiovascular disease with angiotensin converting enzyme inhibitors may cause treatment-resistant respiratory symptoms. These symptoms could be misinterpreted as residual limited-symptom panic attacks, which may result in unnecessary changes in antipanic medication.

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Unusual Flashbacks in a Vietnam Veteran

TO THE EDITOR: Recurrent and intrusive images of reliving a traumatic event, often called "flashbacks," are among the characteristic symptoms of posttraumatic stress disorder (PTSD). However, as the following case suggests, even patients with clear PTSD may have flashbacks of events that never occurred.

Mr. A was a 52-year-old man with chronic PTSD; there was no history of psychosis or substance abuse. Mr. A served in the Marines throughout the Vietnam War and saw frequent combat. For years he had suffered flashbacks of seeing soldiers and civilians killed, engaging in hand-to-hand combat, and ripping rats off his clothing while in a bunker. His right leg, injured in combat, had little range of motion, which forced him to walk with a cane.

Eight months earlier, Mr. A had moved from the city to an isolated rural house. This move seemed to trigger a new wave of flashbacks that were related to his leg injury. In these experiences, he would be on the battlefield. He would be shot in the right leg and taken to an army hospital. "It's all chaos," he stated; he would see dead soldiers mingled with wounded ones and would hear others moaning and himself screaming. He reported that he could vividly smell vomitus, pus, urine, and feces. The army doctor would then appear with his aides, all dressed in white smocks. As four men held Mr. A down, the doctor would take out a miter box saw and wipe it on a dirty cloth. Mr. A would smell alcohol on the doctor's breath and pass out.

The flashback remained precisely consistent from one repetition to another; Mr. A was profoundly distressed. He said, "It's as real as me talking to you now," and asked, "Is it possible that this really happened?"

But several details belied the historical accuracy of the flashback. First, Mr. A clearly remembered that his real-life leg injury occurred quite differently: from a "fluke shot" into a helicopter. Second, as an amateur war historian, Mr. A recognized that the uniforms in the flashback (blue pants with a yellow stripe, gold buttons, and epaulets) and the weapons, including his own bayonet rifle, dated from the Civil War. Third, for several months, Mr. A had also experienced another intrusive image of being shot in the leg at point-blank range—this time by a German soldier in a World War I kaiser helmet.

This case suggests several points. First, intrusive and distressing images of a traumatic event, however compelling and consistent they may be, should not be assumed to represent fact. This caveat is especially important in cases with forensic implications, such as when patients report childhood sexual abuse. A corollary implication is that PTSD should not be diagnosed purely on the basis of traumatic events inferred from flashbacks; some independent evidence of the trauma is necessary. An earlier report described three patients with obsessive-compulsive disorder who were misdiagnosed as having PTSD because their intrusive obsessional images were presumed to represent flashbacks of actual trauma (1). Our case illustrates that in patients with bona fide PTSD, flashbacks of nonexistent events can also occur and can intermingle with flashbacks of real experiences.

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Pemoline and Hepatotoxicity

TO THE EDITOR: Pemoline is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and in children over the age of 6. Reports of hepatic injury associated with pemoline therapy have been prevalent in the gastroenterology literature (1–4). The psychiatry literature contains only one report of two deaths associated with pemoline administration (5). We describe a patient who experienced reversible hepatitis after treatment with pemoline.

Ms. A was a 19-year-old woman whose ADHD had been diagnosed at the age of 8. She had been treated with methylphenidate from ages 8 to 16. She was medication free for 2 years, then resumed taking methylphenidate, up to 30 mg/day, for 5 months. At that time, she complained that after methylphenidate administration she would have difficulty concentrating, greater mood lability, and anxiety. Her morning methylphenidate dose was discontinued and was replaced with a regimen of pemoline, 18.75 mg every morning. Results of baseline liver function tests revealed no abnormality. After 1 month, pemoline therapy was increased to 37.5 mg/day with a 15-mg dose of methylphenidate at lunch. Seven weeks later, the methylphenidate treatment was discontinued, and the regimen of pemoline remained at 37.5 mg/day. Six weeks later, she complained of episodic darkened urine and intermittent vomiting.

Results of liver function tests done at that time revealed elevated serum levels of aspartate aminotransferase (AST) (471 IU/liter), alanine aminotransferase (ALT) (860 IU/liter), LDH (929 IU/liter), alkaline phosphatase (78 IU/liter), and total bilirubin (1.2 mg/100 ml). Ms. A was taking no other medications, had no medical problems, denied excessive use of nonprescription medications, and denied alcohol or illicit drug use. Pemoline treatment was discontinued, and Ms. A was hospitalized for rehydration after vomiting for 24 hours. She was noted to appear slightly jaundiced at that time. Her symptoms resolved within 24 hours, and her liver function test results returned to normal in 1 month, except for serum level of ALT, which normalized after 2 months. The serum levels had peaked at 11 days (AST=1346 IU/liter, ALT=2449 IU/liter, LDH=398 IU/liter, alkaline phosphatase=206 IU/liter, and total bilirubin=4.5 mg/100 ml). Prothrombin time peaked at 0.5 seconds above normal range. Screening tests revealed no signs of herpes

simplex virus, mononucleosis, cytomegalovirus, *Toxoplasma gondii*, drug use, or hepatitis.

While other reports have described the association between pemoline and hepatotoxicity, this association is not well known to psychiatrists. Our patient may have been predisposed to hepatotoxicity by the combination of methylphenidate and pemoline, although no published evidence exists for this interaction (6). There is no indication for using multiple stimulants to treat ADHD, although combination therapy is sometimes used in clinical practice. More frequent monitoring of liver function tests may be warranted in patients treated with both pemoline and methylphenidate.

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Sequential Use of Naltrexone in the Treatment of Relapsing Alcoholism

TO THE EDITOR: In single, 12-week trials, naltrexone has been shown to increase abstinence and reduce the rate of relapse to heavy drinking in alcoholic patients (1, 2). As naltrexone becomes more widely used, subjects who have had a successful initial trial of naltrexone and subsequently relapse are likely to request retreatment. We wish to report the case of an alcohol-dependent subject who responded to naltrexone treatment on two separate occasions.

Mr. A was a white, divorced, self-employed, 40-year-old man who came to our research clinic. Apart from a 3-year period in his 30s, he had been drinking every day since his mid 20s. Before admission he was consuming one pint of vodka a day. There had been a history of moderate cocaine abuse when he was in his 30s, and there was a clinically significant family history of alcohol problems.

Results of a physical examination revealed no abnormality. Blood test results revealed an elevated serum level of alanine aminotransferase (ALT) (61 IU/liter, normal=0–48) and normal levels of aspartate aminotransferase (AST), γ-glutamyltransferase, and mean cell volume. Mr. A was treated with naltrexone, 50 mg/day, for 10 weeks. Compliance with the regimen was confirmed by pill counts and self-reports. Some mild side effects were reported. Mr. A was completely abstinent while he was taking naltrexone. He refused to attend Alcoholics Anonymous meetings but did attend weekly psychotherapy sessions for a number of weeks.

After 10 weeks of naltrexone treatment, Mr. A was to be given either naltrexone or placebo, which would be randomly determined. He ascertained that he was being given placebo after presenting his medication to a poison control center. He then became noncompliant and decided to leave the protocol 10 weeks later; he had remained abstinent. By that time his ALT serum level had returned to normal.

Mr. A returned to the treatment clinic 6 months later. He had been drinking heavily for 3 months, consuming one-half of a pint of vodka a day. Liver function test results revealed elevated serum levels of ALT (72 IU/liter, normal=0–48), AST (37 IU/liter, normal=12–32), and γ-glutamyltransferase (54 IU/liter, normal=0–50). He requested and resumed taking naltrexone, 50 mg/day, and he attended the clinic for group psychotherapy. He remained abstinent and compliant with treatment, and 2 months later his liver function test results returned to normal. He reported a reduced craving for alcohol and minimal side effects. After a total of 5 months of naltrexone therapy he withdrew from the clinic. He cited gains made in employment status and reported that he no longer required treatment. There was no evidence of relapse at this point.

This patient was compliant and successfully treated with naltrexone on two separate occasions. During the first episode, he became noncompliant after being given placebo, and he eventually relapsed. He terminated the second treatment after citing his improvement and determining that treatment was no longer necessary. Each episode of treatment appears to have been equally successful. Follow-up of subjects who completed a 12-week trial of naltrexone revealed that the effects of naltrexone on abstinence persisted through the first month of follow-up, while effects on relapse to heavy drinking persisted through 4 months (3). It is thus probable that some subjects who have responded to an initial 12-week trial may eventually relapse and reappear for treatment. Although naltrexone has been studied in the treatment of opiate addiction for up to and over 12 months continuously (4), the ideal duration and pattern of use of naltrexone for alcohol dependence remains to be elucidated.

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Delta Sleep-Inducing Peptide in Opioid Detoxification

TO THE EDITOR: Delta sleep-inducing peptide is a naturally occurring nonapeptide with a molecular weight of 850 daltons that was first isolated in 1975 (1). It has a wide range of modu-

latory effects on the brain mediator systems, and its mechanisms of actions have not been fully determined. Some findings point to an agonistic effect on opioid receptors (2).

Few clinical studies of delta sleep-inducing peptide application to humans have been conducted. Healthy subjects reported a feeling of sleep pressure (3). Delta sleep-inducing peptide appears to cause attenuation of the withdrawal syndrome in alcohol- and substance-dependent patients (4), but this effect has not been studied in a controlled clinical trial. We studied the efficacy of short-term pharmacotherapy with delta sleep-inducing peptide for treatment of acute opioid withdrawal symptoms in a patient diagnosed with DSM-IV opioid dependence.

Ms. A, a white, 21-year-old woman with a 3-year history of opioid dependence, was admitted for inpatient detoxification. No drugs other than opioids were detected in her urine before the study. Results of a physical examination, routine laboratory tests, and an ECG showed that she was in good health. She reported that she had injected an average of 1.0 g of heroin a day for at least 3 months before detoxification. The presence and severity of withdrawal symptoms were measured before and during detoxification by using the Subjective Opiate Withdrawal Scale (5).

Ms. A's score on the Subjective Opiate Withdrawal Scale was over 25. The administration of delta sleep-inducing peptide followed a standardized protocol with a fixed schedule. Slow intravenous injections of delta sleep-inducing peptide (35 nmol/kg body weight diluted in 4 ml of 0.9% saline) were given every 4 hours on day 1, every 6 hours on days 2 and 3, every 8 hours on day 4, and every 12 hours on days 5 and 6; a single injection was given on day 7.

Each time that Ms. A was given delta sleep-inducing peptide, she showed a rapid and marked improvement. Her Subjective Opiate Withdrawal Scale scores declined to 9 points or less. The compound was beneficial for both physical and psychic withdrawal symptoms. The onset of action was rapid (10 minutes), and improvement lasted for 3.5 hours, after which the withdrawal symptoms would slowly recur. No other medication was administered except for a single, 25-mg oral dose of doxepin on day 3 to treat insomnia. Ms. A was successfully detoxified according to our regimen. No side effects were observed.

We conclude that delta sleep-inducing peptide for treatment of opioid dependence could be an effective alternative detoxification approach. Tolerance of the drug was good, and, presumably, no dependence resulted from treatment. However, delta sleep-inducing peptide should be studied in more detail in larger study groups that follow a study design with random allocation. It presently can be given only intravenously, but an intranasal manner of administration might be available in the future.

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SPECT Studies of D_2 Occupancy in Low-Dose Haloperidol Treatment

TO THE EDITOR: We commend Shitij Kapur, M.D., F.R.C.P.C., and his colleagues (1) for their PET study. They demonstrated that among patients who responded to low-dose haloperidol treatment, D_2 receptor occupancy ranged from 53% to 74%, a lower range than previously reported (2). We present pilot data, from a study that employed single photon emission computed tomography (SPECT), to supplement Kapur et al.'s findings and lend further support to the notion that treatment-responsive patients with schizophrenia may experience clinical benefit at lower levels of D_2 receptor occupancy.

After obtaining written informed consent, we performed SPECT imaging studies on three normal comparison subjects and two patients with schizophrenia. The two patients were a 31-year-old woman and a 38-year-old man, both with DSM-III-R diagnoses of schizophrenia and minimal prior antipsychotic treatment. SPECT studies for the patients were conducted on three occasions: at baseline (after a 2-week washout period) and a minimum of 2 weeks after separate haloperidol regimens at two different dose levels. After injection of [^{123}I]IBZM, serial brain SPECT imaging studies were performed by using a Medimatic Tomomatic 564 SPECT camera fitted with a high sensitivity collimator. Results were expressed as basal ganglia/cerebellum ratios, from which estimated D_2 receptor occupancies were calculated. Clinical symptoms were monitored weekly by using the Positive and Negative Syndrome Scale and the Modified Simpson Dyskinesia Scale. The patients were followed for 12 months.

For the female patient, haloperidol, 2 mg/day, resulted in 51% D_2 receptor occupancy and was associated with substantial clinical gains: a 70% reduction in positive symptoms, a 30% reduction in negative symtoms, and a 55% reduction in general symptoms. On an exploratory basis, her dose was reduced to 1 mg/day. Two weeks later, the resulting D_2 receptor occupancy of 39% was associated with significant deterioration in symptoms. The 2-mg/day regimen was thus maintained. For the male patient, haloperidol, 4 mg/day, resulted in 72% D_2 receptor occupancy and was associated with marked reductions in positive (70%), negative (30%), and general (46%) symptoms. No additional benefit accrued after the dose was increased to 10 mg/day, which resulted in 93% D_2 receptor blockade. The dose level was thus maintained at 4 mg/day. It is important to note that both patients maintained their clinical gains throughout the 12-month follow-up period; there were no further dose adjustments. No side effects were reported by or observed in the male patient, whereas the female patient experienced mild akathisia, slight diminution in arm swing, and mild upper extremity tremors throughout the entire 12-month study period (equivalent to a score of 1 on the Modified Simpson Dyskinesia Scale).

These pilot data further support the efficacy of low-dose

haloperidol in the treatment of acute schizophrenia, demonstrate that therapeutic efficacy may be associated with lower levels of D_2 receptor occupancy than have been previously reported, and suggest further exploration of the utility of SPECT technology to measure D_2 occupancy.

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Chromosomal Fragile Site 1q21 in Schizophrenic Patients

TO THE EDITOR: A recent study reported that the chromosomal fragile site 1q32 could be related to the etiopathogenesis of type I bipolar disorder (1). A literature review by Bassett (2) found evidence of fragility on chromosomes 3, 9, 17, and 19 in patients with schizophrenia. Soon after, Garofalo et al. (3) reported an increase of chromosome fragility that especially affects chromosomes 9 and 10 in schizophrenic patients. All these studies were carried out by using blood lymphocytes that were cultured in folic acid-free medium as an inductor of fragile site expression.

We carried out cytogenetic investigations in 19 unrelated patients with DSM-III-R schizophrenia from Clinica Mental Santa Coloma (Barcelona). For comparison, 10 normal individuals were studied under the same experimental conditions. The study was granted ethical approval by the local research committee. All subjects provided written informed consent before inclusion in the study. Peripheral blood samples were cultured for 72 hours in RPMI-1640 medium. All patients showed normal karyotype. Chromosome lesions (gaps and breaks) showed a significantly higher presence in metaphases of schizophrenic patients (7.2%) than in comparison subjects (3.1%) (χ^2=9.37, df=1, p=0.0002). This increase in spontaneous chromosome lesions was similar to the finding described by Garofalo et al. (3) under induction of fragility conditions.

Fragile site 1q21 was altered in seven of the patients (two of them showed one deletion), with a 4%–6% mean frequency of metaphases (range=1.5%–13.9%). Six of these seven patients had relatives who were affected by schizophrenia or a schizophrenia spectrum disorder, and five of these seven patients proved to be nonresponsive to the usual neuroleptic treatment. However, the differences from patients who showed no cytogenetic changes at this fragile site were not statistically significant.

The unexpected spontaneous fragility at 1q21 that occurred in our patient group is indicative that this chromosome region could play a role in the pathogenesis of schizophrenia. It is remarkable that the 1q21 region contains the locus of the dopamine receptor (D_5) pseudogene 2 (4). Furthermore, Kosower et al. (5) have recently reported associations between schizophrenia and both alleles of the Duffy blood group and the heterochromatin 1qh band variants, which are both localized to the same 1q21-23 chromosomal site. Our results add interest to this chromosome area and would justify further genetic studies that involve the 1q21 site.

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Subconvulsive Magnetic Brain Stimulation No Replacement for ECT

TO THE EDITOR: Recently, magnetic brain stimulation without seizure induction has been mentioned in medical journals and newspapers, and there are expectations that this method will replace ECT in the treatment of depression (1, 2). Clinical applicability has not been established, and several experiences have suggested that nonconvulsive brain stimulation will not treat the conditions that ECT helps, e.g., melancholia, mania, catatonia, and schizophrenia. These experiences include both absent and weakly developed seizure activity, which have no substantial clinical benefit.

At the same time, the robust generalized tetanic contraction that accompanies the ECT stimulus, whether or not seizure activity follows, reflects brain stimulation broadly distributed over the motor strip and presumably elsewhere. Its intensity is emphasized by its strength, which had a notorious tendency to cause compression fractures and joint dislocations when anesthesia was not given.

Yet, ECT's clinical benefit depends on the quality of the seizure, and not on the stimulus alone, i.e., not solely on externally induced electrical currents in the brain. Electrical stimuli without consequent seizure activity are inadequate (3). Indeed, even electrical stimulation that produces mild convulsions can be ineffectual, and efficacy typically requires still larger stimuli (4, 5). Accordingly, when the seizure threshold rises along the ECT course, the stimulus is increased to maintain efficacy (6); this approach and other pharmaceutical and anesthetic maneuvers to counteract these changes (7) presumably reflect a clinically appreciated relationship between benefit and the achievement of seizure. The efficacy of pharmaceutical-induced (e.g., flurothyl) seizure also clarifies the seizure as the therapeutic essence of ECT (8), as does diminution of seizure propagation and ECT efficacy from lidocaine (9) or benzodiazepines (10).

Magnetic brain stimulation induces electrical currents in the brain. There is no justification known to assert that these electrical currents differ therapeutically from the same currents

induced by voltage gradients. In the absence of seizure, magnetically induced currents should be no more therapeutic than ECT stimuli that produce no seizures.

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Rethinking Treatment Terminology

TO THE EDITOR: A recent conversation on a nationally broadcast mental health radio program stimulated these thoughts about the assumptions inherent in some of the common phrases that we use when discussing treatment outcomes of patients with depression. A patient telephoned to inquire about the value of ECT. The host, a psychiatrist, asked if the patient had failed two or more antidepressant treatments. At this point, the guest commentator, not a psychiatrist but a nationally prominent advocate of patients' rights, interjected that it is not the patients but rather the drugs that fail. This brief exchange left me with the impression that the profession of psychiatry was being chided for implying that patients exhibit some type of failure when pharmacotherapy is unsuccessful. This is clearly an issue of semantics but one that deserves some discussion.

To suggest that a drug has the capacity to fail is to suggest that it can also succeed. This personification of chemicals seems inappropriate. The capacity to succeed or fail requires a willingness, or lack thereof, to achieve some goal. Such traits are not inherent in drug molecules. Thus, it seems wrong to state that drugs fail when depression does not improve. However, most patients clearly want to improve, which is implied by the act of ingesting medication. So when a patient exhibits inadequate response from taking antidepressants, where does the blame lie?

In discussing unsuccessful antidepressant therapy with patients, it would be accurate to state that the choice of drugs turned out to be wrong, even though the choice was an informed one that was based on the best available data to predict success. When the outcome of pharmacotherapy is disappointing, it is because of a mismatch between the selected drug and the patient's physiology. By avoiding the issue of failure altogether, we will neither suggest to patients that they have failed somehow if they did not improve satisfactorily nor suggest that drugs can possess a bias in determining who improves. This may aid patients' understanding of the reality of occasionally requiring trials of different medications before finding the most appropriate choice.

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Depression Awareness Training and the Clergy

TO THE EDITOR: We read with interest the article by Michael W. O'Hara, Ph.D., and colleagues (1) in which they report the positive outcomes of providing information and training regarding the identification and treatment of depression to health, mental health, and social service professionals in Iowa. We want to make a suggestion that future programs to educate community helpers about depression should consider including an often overlooked group: the clergy. The more than 312,000 rabbis, priests, pastors, and chaplains in the United States constitute a major group of frontline mental health workers that, according to the National Institute of Mental Health Epidemiological Catchment Area Surveys, are as likely to see a person with an affective disorder as is a mental health professional and more likely if the person is over 65 years of age (2).

In rural areas of states like Iowa there is often little separation among church, community, and family. In a study of midwestern older adults who attended church regularly, the majority reported that 80% or more of their closest friends came from their church (3). In a survey in Iowa, 67% of elderly men and 79% of elderly women who live in rural areas reported attending church once a month or more despite limitations of mobility due to health (4).

Clergy are often in long-term relationships with individuals and their families, which enable them to observe changes in behavior that may indicate early signs of depression. Furthermore, clergy are frequently sought for counseling in crisis situations that are associated with depressive reactions, such as personal illness or injury, change in health of a family member, and death of spouse, family member, or close friend. Given the high levels of depression in our society, it is not surprising that urban and rural clergy report that depression is among the most frequent problems brought to them by those seeking help (5). These same studies find that clergy see themselves as inadequately trained to meet the mental health needs of the persons they serve, and they are interested in continuing education programs in mental health, including those that feature depression awareness. We believe that inviting clergy to future depression awareness training sessions could increase the positive impact of the programs.

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Progression of Viral Illness

TO THE EDITOR: In their meta-analytic synthesis of the associations between depressive symptoms and the clinical progression of viral infections, Eric P. Zorrilla, M.A., and colleagues (1) reported a number of important findings. However, with reference to depression and the progression of HIV infection, it was surprising and unfortunate that Zorrilla et al. paid little attention to the significant overlap between patient reports of HIV symptoms and symptoms of depression. The majority of studies of HIV infection included in Zorrilla et al.'s review assessed depression by using psychometric scales with somatic depression items that correspond to symptoms of HIV infection. Fatigue, muscle aches, insomnia, suppressed appetite, weight loss, night sweats, poor concentration, and memory lapses are symptoms of both depression and HIV disease (2). Seven of 21 items on the Beck Depression Inventory and five of 20 items on the Center for Epidemiological Studies Depression Scale overlap completely with HIV-related symptoms. Because a majority of the studies of HIV infection reported by Zorrilla et al. rely on these and other psychometric measures of depression, their results must be considered confounded; the overlapping symptoms can account for the magnitude of effects reported in the meta-analysis. The lack of significant associations between depression and either immunological markers or clinical progression of HIV further supports the interpretation of the associations among symptoms of HIV and depression as being artificial. Overlapping symptoms of depression and HIV infection result in inflated scores on depression scales (3) and spurious correlations between symptoms of HIV disease and depression (4). Understanding the relationship between depression and HIV infection requires removing the overlapping symptoms, done by using subscales of depression instruments or nonsomatic correlates of depression such as hopelessness or by statistically removing the overlapping symptoms from the association. Thus, Zorrilla et al.'s conclusions that "even if depressive symptoms do not accelerate clinical progression of HIV, they are clearly associated with increased reporting, and possibly the experience, of HIV-related symptoms . . . . increased reporting of HIV-related symptoms could reflect higher levels of distress about the illness" do not move us closer to understanding the complex emotional reactions of people living with HIV infection.

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Dr. Zorrilla and Colleagues Reply

TO THE EDITOR: Dr. Kalichman suggests that the relationship observed between depressive symptoms and HIV-related symptoms in our recent meta-analysis is an artifact of psychometric nonspecificity. We agree that future studies should employ methods that better discriminate somatic symptoms of depression from symptoms specific to HIV-related illnesses. Dr. Kalichman, however, may overstate the case that the observed correlation is spurious. A large, community-based study that was included in the meta-analysis found that removing depressive symptoms from a measure of HIV-related symptoms did not attenuate its relation to an affect-based index of depression (1). Physical symptoms that are endorsed more often by HIV-positive individuals who report greater levels of depressed *affect* include persistent fever, diarrhea, weakness or numbing in arms or legs, and "chills so bad you shook" (1)—symptoms that are not hallmarks of depression. Still, we concur that the relationship between depressive symptoms and HIV-related symptoms likely reflects something other than disease progression, since prospective, objective measures of clinical outcome do not show similar effect sizes, and depressed HIV-negative homosexual men who are unaware of their serostatus also score higher on HIV-related symptom scales (2, 3). Possible explanations for these findings include somatization, greater attention to or perception of physical symptoms, greater help-seeking behavior, higher prevalence of non-HIV-related physical illnesses secondary to depression, and demoralization secondary to worsening health.

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Psychotropic Treatment During Pregnancy

TO THE EDITOR: The recent article by Lori L. Altshuler, M.D., and colleagues (1) on psychotropic treatment during pregnancy is an important analysis in a much-needed area. Several aspects of this study lend themselves to comment.

The authors present an investigation of neuroleptic safety by

combining the results of prior studies. A degree of bias is introduced in an early stage by only including studies with similar odds ratios. An additional complication is that the studies used for this analysis often did not control for significant variables (i.e., dose, concomitant medications, illicit drug use, tobacco use, alcohol use, maternal age, or timing of exposure).

Edlund and Craig (2) published a reanalysis of a previous study and discovered an apparent neuroleptic-sensitive teratogenicity between gestation weeks 6 and 10. This period initially had been obscured because of the analysis protocol. Similarly, Altshuler et al.'s technique of combining data may artifactually obscure the possible dangers posed by neuroleptic use.

The studies employed in their analysis contained a database of heterogeneous populations, including nonpsychotic mothers who received neuroleptics to treat hyperemesis gravidarum at doses that were typically less than those employed for psychosis. As pointed out by Altshuler et al., schizophrenic mothers appear to experience a significantly higher rate of perinatal complications. This may reflect a different susceptibility for fetal insult and questions the validity of using nonpsychotic mothers in evaluating the risks posed by treating schizophrenic mothers during pregnancy.

The authors also note a case report of clozapine use during pregnancy. Although the Food and Drug Administration (FDA) has placed clozapine in category B (no evidence of risk in humans) in its use-in-pregnancy ratings, certain pharmacologic properties suggest questions regarding its use during pregnancy (3, 4). These concerns include the greater risk for seizures, hypotension, deficiency in knowledge regarding the prenatal/neonatal risks for clozapine-induced agranulocytosis, and lack of fetal white cell measurements during pregnancy.

Furthermore, in the discussion of benzodiazepine use, there was no comment on the possible differential risk among benzodiazepines. FDA guidelines have assigned pregnancy-related ratings of C (risk cannot be ruled out), D (positive evidence of risk), and X (medication contraindicated in pregnancy) (4, 5) to various benzodiazepines (although the X rating is generally associated with those benzodiazepines that are used for insomnia).

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Psychotic Depression

TO THE EDITOR: In the article that compared neuropsychological test results of patients with psychotic depression to those of patients with nonpsychotic depression and schizophrenia, Dilip V. Jeste, M.D., and colleagues (1) argued that their data support a separate diagnostic category for psychotic depression. This article was discussed at a monthly journal club for students, residents, and faculty at the Louisville Veterans Administration Medical Center. Several questions emerged from that discussion that we hope the authors will address.

The authors report that the age at onset of depression in patients with psychotic depression preceded the age at onset of psychosis by 6 years. This observation would seem to be consistent with the current conceptualization of psychotic depression as a form of severe major depression. The onset of depressive symptoms among patients with nonpsychotic depression occurred nearly a decade earlier than that of patients with psychotic depression, which might support the authors' belief that psychotic depression should be considered a separate diagnostic category. Yet, how would the depression that the patients with psychotic depression had for 6 years before the onset of psychosis be classified?

In their introduction the authors allude to a report that emphasized the distinctiveness of delusional depression (2). However, Jeste et al. did not distinguish in their patients with psychotic depression those who had only delusions from those with delusions and hallucinations. Do patients with psychotic depression whose only psychotic symptoms were delusions have the same gap between onset of depression and onset of psychosis? If not, perhaps the diagnostically distinct category is not psychotic depression but rather delusional disorder with depressed mood.

Finally, my colleagues and I wondered how the large population of schizophrenic patients affected the statistical significance achieved by the authors. Would the results of the analyses and multivariate analyses of variance be different had the authors used only 30 schizophrenic patients (either selected randomly from their pool of 160 or selected to match the depressed patients demographically)? The title of the article notwithstanding, it is hard to avoid the conclusion that the study was really a comparison of schizophrenia with psychotic and nonpsychotic depression.

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Dr. Jeste and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Strauss's comments on our article and want to compliment the journal club members for raising some excellent points.

The first issue concerned the classification of the depressive episodes that predated psychosis in the patients with psychotic depression. Of these subjects, a large majority had psychotic features either during their first depressive episode or within 2 years of the onset of depression, while a minority had a much longer delay from the onset of depression to the emergence of psychosis. If the latter subjects had been clinically assessed before the onset of their first psychotic episode, they would have been classified as having nonpsychotic depression. Thus, there was a risk of misdiagnosing a proportion of patients with even-

tual (or "latent") psychotic depression as having nonpsychotic depression. However, this possibility would not greatly impact our findings, since the presence of such "false negative" subjects in the group with nonpsychotic depression would only serve to reduce the chances of finding a significant difference between the two groups. Our results seemed to suggest that the cognitive impairment in the patients with psychotic depression was a trait marker rather than a state marker.

The next issue was whether depression with delusions differs from depression with delusions and hallucinations. In the literature, the terms "delusional depression" and "psychotic depression" have often been used interchangeably (1). Our terminology was consistent with DSM-III-R, which defined "psychotic features" as either delusions or hallucinations. A future study with a larger group of patients with psychotic depression and delusional depression is necessary to compare patients with and without hallucinations. Our patients with psychotic depression, by definition, did not meet the criteria for delusional disorder. As per DSM-III-R, delusional disorder must be excluded in order to diagnose major depression. In delusional disorder, if mood episodes occur concurrently with delusions, their total duration is brief relative to the duration of the delusional periods.

The final question concerned the effect of the unequal cohort sizes for the three patient groups, with there being a much larger number of patients with schizophrenia. Our groups were similar in age, education, and ethnicity (please see the original article for a discussion of gender), which made it unnecessary to match them on demographic variables. The schizophrenia patient group was larger because of the overall focus of our Clinical Research Center. The focus of this specific study, however, was psychotic depression, and we used patients with nonpsychotic depression and schizophrenia as comparison groups. The goal of a research design is to maximize the power to detect a difference without increasing the chance of a type I error; apparently the latter possibility was the basis of Dr. Strauss's concern. To address this issue, we reanalyzed our results after adjusting the degrees of freedom so as to have similar cohort sizes across the three patient groups. With the exception of one measure (figure learning, which changed from a significance level of $p<0.05$ to $p=0.054$), all the reported findings in terms of significance remained the same. Thus, the degrees of freedom resulting from the larger cohort did not account for the reported findings.

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Dissociation and the Holocaust

TO THE EDITOR: The recent article by Rachel Yehuda, Ph.D., and associates (1) provides an interesting look at the relationship—or lack thereof—between posttraumatic stress disorder (PTSD) and dissociation, and it certainly suggests further study of this topic. Nonetheless, the methods and conclusions of this study deserve comment.

The authors conclude that "Holocaust survivors show lower average scores and infrequent clinically significant dissociation compared to other traumatized groups." However, while most of the Holocaust survivors in this study had never sought mental health treatment, they are compared throughout to studies of psychiatric patients who were typically in ongoing treatment. It is quite possible that the cohort in question experiences milder symptoms than Holocaust survivors with PTSD who are in outpatient or inpatient treatment and hence were not included in this study.

Furthermore, even among the Holocaust survivors studied, failure to detect symptoms of dissociation is possible, given the limitations of self-administered tests such as the Dissociative Experiences Scale. Such tools demonstrate a tendency to register false-negative results for patients who are either unaware of their symptoms or who are unmotivated to disclose or even adverse to disclosing these symptoms (2). A 1990 study of 507 undergraduates given the Dissociative Experiences Scale indicated that this tool does not assess dissociation in its entirety (3). About two-thirds of the test's 28 items deal with nonpathological dissociation, and as Frankel (4) noted, the scale's developers have admitted "to the much smaller number of items that are qualitatively different and probably reflect psychopathology." Cultural differences have been noted as possible factors in the unusually high dissociation scores of Cambodian refugees (5). The same phenomenon may account for the varying levels of dissociation recorded in Holocaust survivors and other groups.

Since the Dissociative Experiences Scale may serve only as a preliminary screening tool, it should be followed up with a diagnostic instrument, such as the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (6). A test such as this is not only more comprehensive and sensitive in its assessment of the severity of specific dissociative symptoms and its diagnosis of the dissociative disorders but has even "shown the capacity to pick up *previously unsuspected* cases of dissociative disorders" (italics mine) that the Dissociative Experiences Scale might miss (7). The SCID-D's ability to identify subtle manifestations of dissociation—as well as the fact that it is administered by trained clinicians rather than by the patients themselves—makes it a much more appropriate tool for this study's global conclusions. In addition, research with the SCID-D among Dutch, Norwegian, and Hispanic patients has found virtually identical symptom profiles among dissociative disorder populations, which demonstrates the test's cross-cultural accuracy and reliability.

I believe, therefore, that the authors cannot rightly conclude that there is a relatively low level of dissociation among Holocaust survivors. To be accurate, they might only claim that there is a low level of dissociation as approximated by the Dissociative Experiences Scale among Holocaust survivors who do not seek treatment.

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Dr. Yehuda and Colleagues Reply

TO THE EDITOR: Dr. Steinberg suggests that subjects in our study showed infrequent clinically significant dissociation because they were less symptomatic than treatment-seeking PTSD patients in whom dissociation is typically studied. Although it is not unreasonable to assume that subjects who do not seek treatment are less symptomatic than those who do, it is well established that a large proportion of trauma survivors with PTSD do not seek treatment for their symptoms. It is therefore important to evaluate both treatment- and nontreatment-seeking trauma survivors with PTSD in order to clarify which sequelae are associated with trauma exposure and PTSD and which reflect other phenomena associated with treatment seeking. Doing so requires a recognition that while subjects who do not seek treatment may register "false negatives" for the reasons stated by Dr. Steinberg, those who do may endorse falsely positive symptoms for reasons relating to disability claims, other secondary gain, or comorbidity (e.g., personality disorders). This can be true regardless of whether self-report or structured interviews are used.

In the case of trauma survivors, it is a mistake to assume that lack of treatment seeking necessarily implies less severe PTSD. Unfortunately, those who are most traumatized and in need of services may also be least able to access mental health services. For Holocaust survivors in particular, numerous reasons may exist for the low use of mental health services, such as financial considerations, the belief that Holocaust experiences cannot be understood by others, or a general distrust of physicians (which may be associated with firsthand knowledge of medical experimentation and of the fate of the mentally incapacitated in concentration camps). Moreover, Holocaust survivors who wanted treatment were not always successful in procuring the appropriate clinical care because health care workers may not have recognized the contribution of their traumas to their symptoms or because of the paucity of specialized trauma-focused programs.

Despite the lack of treatment-seeking behavior, our study group displayed substantial symptom severity for many PTSD symptoms and showed biological alterations similar to those of other trauma survivors. However, whereas some symptoms were clearly present, dissociation was not prominent, which was reflected by the scores on the Dissociative Experiences Scale and by the lack of flashbacks and psychogenic amnesia. Although use of a structured interview like the SCID-D might have been warranted to further investigate the nature of high dissociation scores, we saw no reason to relentlessly search for symptoms that were not endorsed. Rather, the lack of dissociation in Holocaust survivors seemed plausible for the reasons discussed in the article. We chose to conclude that not all PTSD patients suffer from dissociative experiences. Thus, it is appropriate to consider the extent to which results of studies on dissociation in subjects who seek treatment are generalizable to the larger community of trauma survivors and if not, to consider whether the high amounts of dissociation are due to factors other than symptom severity.

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Creativity in Psychodynamic Psychotherapy

TO THE EDITOR: Theodore Nadelson, M.D., provides a truly elegant argument for the role of creativity in psychodynamic psychotherapy (1). However, while expressing concern that his model may be lost in the current emphasis on the bottom line, he fails to propose the necessary steps for preserving it.

Nadelson's beliefs, i.e., his hypotheses, are testable by using available techniques of psychotherapy research. For example, measures of creativity can be devised, one of the manualized psychodynamic psychotherapies can be used (2), and therapy sessions can be rated by therapists, patients, and independent observers. These data can then be related to process and outcome measures.

Psychotherapy research is often difficult to do, but the failure to pose relevant questions will only perpetuate the ambiguous position that psychodynamic psychotherapy has in present-day psychiatry.

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Dr. Nadelson Replies

TO THE EDITOR: It would be very difficult to disagree with Dr. Flegenheimer's well-argued position with regard to the need for psychotherapy research. I did not mean to imply that psychotherapy is to be based solely on sudden and unanalyzed insight, an intuition, always mysterious and absolutely untestable. I did point out that science often receives a spark from a revelation that can be constructed into a question and go on to hypothesis testing. My essay did not pose relevant questions or hypotheses for testing; it had another direction, but it was not meant to be a deterrent to such efforts. Others, such as Dr. Flegenheimer, will do just that, and all of us should welcome it.

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ECT Response in Medication-Resistant Patients

TO THE EDITOR: Joan Prudic, M.D., and colleagues (1) conclude that ECT is less efficacious in depressed patients who are medication resistant and suggest an overlap in mechanisms of actions of ECT and heterocyclic antidepressants. However, there are several flaws in their study that make it difficult to accept their conclusions.

Patients were administered unilateral ECT at a stimulus intensity 50% above the threshold. It has been demonstrated by the same group of authors that the stimulus intensity needs to

be at least 150% above threshold to achieve good results with unilateral ECT (2).

Some patients who did not respond to unilateral ECT were switched to bilateral ECT. However, the authors do not mention whether every patient who did not respond to unilateral ECT was switched. If this was not done, the results could be skewed.

One wonders what prevented the authors from independently measuring the outcome for patients receiving unilateral and bilateral treatments. This would resolve the debate on whether the poor outcome was due to the type of treatment used. The authors chose instead to quote another study that was done on a biased sample (3).

To hypothesize that ECT and heterocyclic antidepressants have similar mechanisms of action is highly speculative, especially after acknowledging in the same article that heterocyclics alone are not an effective treatment for psychotic depression, whereas ECT is!

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3. Prudic J, Sackeim HA, Devanand DP: Medication resistance and clinical response to electroconvulsive therapy. Psychiatry Res 1990; 31:287–296

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Drs. Prudic and Sackeim Reply

TO THE EDITOR: We thank Dr. Chandragiri for commenting on our study. Contrary to his interpretation of our previous work, there is no evidence regarding the efficacy of right unilateral ECT administered with a stimulus intensity 50% above seizure threshold (1). We have only demonstrated that right unilateral ECT is ineffective when administered just above seizure threshold. Nonetheless, only five of the 100 patients in our study received right unilateral ECT at 50% above seizure threshold, and all patients who did not respond to this form of ECT (N=3) were crossed over to bilateral ECT at 150% above seizure threshold. Of the remaining patients in the study who were initially treated with right unilateral ECT, the *minimum* dose was 150% above the initial seizure threshold.

The key finding in this study was the multisite confirmation that resistance to antidepressant medications during the index episode predicted clinical outcome with ECT in primary, unipolar, nonpsychotic patients. In Dr. Chandragiri's second and third points, the issue is raised as to whether the findings were contingent on a large number of patients who were being treated with right unilateral ECT and not bilateral ECT. In our study, 90 of the 100 patients were treated initially with right unilateral ECT. Thirty-two of the 45 patients (71%) who initially did not respond to right unilateral ECT were crossed over to bilateral ECT. Consequently, the bulk of patients who did not respond to right unilateral ECT subsequently received bilateral ECT. In a 1990 study that Dr. Chandragiri cited, we had already shown that medication resistance predicted a lower response rate to bilateral ECT. Our new study indicates that this effect pertains to both right unilateral and bilateral ECT. Indeed, we conducted a new logistic regression that predicted initial ECT response or nonresponse on the basis of categorization as medication resistant and whether the patient was treated with only right unilateral ECT (N=58) or received bilateral ECT as an initial or crossover modality (N=42). Medication resistance was strongly related to ECT short-term outcome (χ^2=7.57, df=1, p=0.006), while ECT modality was not (χ^2=1.07, df=1, p=0.30).

The argument that ECT and antidepressants have independent mechanisms of action had been supported by the previously untested belief that ECT is as effective in patients who are antidepressant resistant as in patients who have not failed an adequate medication trial. This argument is now more tenuous given our findings that antidepressant-resistant patients have a poorer response to ECT. Since we also found that resistance to heterocyclic antidepressants predicted a poorer response to ECT, whereas resistance to selective serotonin reuptake inhibitors (SSRIs) did not, it is reasonable to speculate that there is more overlap in mechanisms among heterocyclics and ECT than for SSRIs and ECT in the treatment of nonpsychotic depression. The efficacy of ECT in the treatment of psychotic depression is not germane.

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Reprints of letters to the Editor are not available.

Corrections

In "Correlation Between Reduced in Vivo Benzodiazepine Receptor Binding and Severity of Psychotic Symptoms in Schizophrenia" by Geraldo F. Busatto, M.D., Ph.D., et al. (January 1997, pp. 56–63), the fourth line of the footnote (page 56) should indicate that the paper is also from the Institute of Nuclear Medicine, University College and Middlesex School of Medicine, London.

In "Posttraumatic Stress Disorder Associated With Peacekeeping Duty in Somalia for U.S. Military Personnel" by Brett T. Litz, Ph.D., et al. (February 1997, pp. 178–184), the sentence beginning on the 10th line of the last paragraph on page 179 should read: "On average, the survey was completed 14.9 weeks (SD=9.2, range=62) after participants had returned to the United States."