Fluoxetine for OCD After Brain Injury

TO THE EDITOR: Traumatic brain injury is often associated with psychiatric disorders (1). Impulsivity, affective instability, and disinhibition are the most frequent neuropsychiatric symptoms associated with traumatic brain injury, while depression, mania, and obsessive-compulsive disorder (OCD) are less frequent (2). To our knowledge, there are no reports of successful treatment of posttraumatic OCD.

Mr. A, an 18-year-old man, suffered severe head trauma in a car accident. Ten months after the head trauma, he had normal results on a neurologic examination and seemed to be in a good general state of health, but he reported severe checking compulsions and obsessions and greater impulsivity. Two years after the accident, he was referred to our psychiatric hospital and scored a total of 30 on the Yale-Brown Obsessive Compulsive Scale (3). He had no other psychiatric disorders.

Magnetic resonance imaging showed multiple lesions affecting the right ventral-lateral prefrontal cortex, the orbital-frontal cortex bilaterally, the right anterior temporal lobe, the corpus callosum, and adjacent white matter regions. [^{123}I]β-Carbomethoxy-3-(4-idiophenyl)-tropane ([^{123}I]β-CIT) single photon emission computed tomography (SPECT), which was performed as part of an ongoing study (4), showed lower serotonin transporter density (two standard deviations below that of age-matched comparison subjects) in the midbrain and hypothalamus.

Mr. A was treated with up to 60 mg/day of fluoxetine for 90 days and showed a good clinical response. His compulsions were more dramatically reduced than his obsessions. His score on the Yale-Brown Obsessive Compulsive Scale decreased from 30 to 10, which was associated with great improvement in his quality of life.

OCD has rarely been described after traumatic brain injury (1, 2), and we know of no reports of its successful treatment. The impression to be gotten from case reports and small case series is that the same medications that have been found to be effective in treating primary OCD—namely, selective serotonin reuptake inhibitors (SSRIs) (5)—are effective in treating secondary (organic) OCD (6).

Findings from neuroimaging and neuropsychological studies implicate dysfunctions of the frontal-orbital-striatal circuits in the pathophysiology of idiopathic OCD (7). We suggest that structural damage to the frontal-orbital-striatal circuits is a direct cause of secondary (organic) OCD.

In addition, our patient showed lower serotonin transporter density in [^{123}I]β-CIT SPECT, and his compulsions responded favorably to SSRI treatment. This might be explained by a lower number of serotonin neurons ascending from the raphe nuclei, accompanied by lesions in the orbital-frontal circuits known to be involved in OCD after traumatic brain injury.

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Topiramate for Obstructive Sleep Apnea and Snoring

TO THE EDITOR: Characterized by a symptom profile that includes snoring, excessive daytime somnolence, and reports of respiratory arrests during sleep, obstructive sleep apnea affects approximately 2% of the 30- to 60-year-old male population (1). It is believed that between 7 and 18 million North Americans could be afflicted with the disease. The most studied forms of treatment include surgery on the upper airway, intraoral-mandibular advancement devices, and long-term treatment with nasal continuous-positive-airway pressure (2). These treatments are cumbersome and expensive. Several pharmacologic treatments have been proposed, but we know of no widely used drug of reference.

Topiramate is a broad-spectrum antiepileptic and neurotherapeutic agent that may be used in treating several neurologic, psychiatric, and metabolic conditions, such as migraine and other forms of headache, bipolar disorder, eating disorders, and obesity. Topiramate has shown side effects, such as somnolence, cognitive impairment, and paresthesias. This report concerns a patient who suffered from bipolar disorder and obstructive sleep apnea who was successfully treated with the addition of topiramate to his previous medication regimen.

Mr. A was a 50-year-old married engineer who had been in treatment for bipolar disorder for several years. His initial treatment was with 450 mg b.i.d. of controlled-release lithium carbonate, 75 mg/day of venlafaxine, 30 mg/day of mirtazapine, and 1 mg/day of clonazepam. He had remained on this same regimen until the present. As a result of complaints of snoring and breathing arrests, polysomnography was performed. It indicated obstructive sleep apnea of degree III, severe snoring, and a marked reduction in REM and slow-wave sleep. (Operational definitions for scoring of obstructive sleep apnea were suggested by an American Academy of Sleep Medicine task force [3]. Data to justify a severity index based on event frequency were derived from the Wisconsin Sleep Cohort.) The use of a contin-

uous-positive-airway-pressure device was recommended, but Mr. A refused it because of financial concerns.

He began treatment with topiramate, 25 mg/day; the dose was progressively increased to 100 mg/day. My sole recommendation was the use of this medication. A remarkable reduction in snoring was reported soon thereafter; there remained only slight dorsal-decubitus snoring. A follow-up polysomnography, allowed by Mr. A's health insurance, showed obstructive sleep apnea of degree I, moderate snoring, periodic-movement syndrome of the legs, and fragmented sleep. There was a drastic decrease (approximately 70%) in his episodes of apnea, falling from 20.0/hour to 6.6/hour. There were no changes in body weight.

In view of its excellent tolerability, which leads to high compliance, and its excellent clinical results, topiramate should be seen as a promising pharmacological option for the treatment of obstructive sleep apnea and snoring. More in-depth, controlled studies with a larger number of patients are warranted.

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Pulmonary Embolism and Severe Depression

TO THE EDITOR: Despite only a few cases reported in the literature (1–6), psychotic depression may be considered a predisposing factor (5) in thromboembolism, sometimes associated with life-threatening complications (6). We draw your attention to pulmonary embolism as a possible complication in severe depression. Pulmonary embolism is a potentially lethal condition. It may also be a difficult condition to diagnose at the bedside. In terms of mortality in patients with affective disorders, only pulmonary embolism showed an excess of deaths compared to other general causes (7). In one autopsy study (2), 3.3% of sudden deaths of institutionalized mental patients were due to pulmonary embolism; it was the third leading cause of death in persons experiencing catatonic states. We present the clinical details of a case we have recently handled.

Ms. A was a 64-year-old married woman with a past psychiatric history of bipolar mood disorder that met ICD-10 diagnostic criteria. The disease began about 33 years ago with puerperal psychosis. Ms. A had, in all, nine hospital admissions in the next 23 years. At the first six admissions, she came in with psychotic depression and received treatment with major tranquilizers and antidepressants. On four occasions, ECT was administered.

Ms. A's first four hospital admissions led to a complete recovery; after the last two, Ms. A was discharged with some residual depressive symptoms. She was followed up in the community between admissions. She was admitted again on two occasions after being seen for treatment of manic and hypomanic symptoms, respectively. She was then treated with haloperidol and hypnotic medications. After follow-up in the community, she was admitted again. She exhibited features of psychotic depression and was therefore administered lithium and imipramine. Since then, she had had minor relapses managed with adjustment of her dose of imipramine.

When Ms. A was next admitted, she was profoundly depressed and mute, with akinesia associated with negativism and psychomotor retardation. Upon physical examination, she was found to have bilateral pitting edema. She had a history of chronic cardiac failure; otherwise, her past medical history was unremarkable. The results of an ECG and a chest X-ray were normal. There was no evidence of constipation or dehydration (as indicated by her urea, creatinine, and packed cell volume values). Obesity was present. In view of Ms. A's age, lack of response, and potential physical complication, mainly related to side effects, imipramine was switched to citalopram, 20 mg/day, and the citalopram dose was increased to 40 mg/day after 4 weeks.

When Ms. A started to improve to a degree that allowed her to walk around with a walker, shortness of breath upon minimal exertion was noted. A repeat physical examination and another ECG revealed no new features. Ms. A was referred to a medical unit, where she was admitted with a diagnosis of multiple pulmonary emboli, which was confirmed with a ventilation perfusion scan. She was prescribed an anticoagulant and eventually made a good physical and mental recovery.

In this case, bilateral pitting edema, together with immobility and obesity, could be considered predisposing factors for pulmonary embolism. These findings suggest a considerable risk affecting a patient whose mobility was severely impaired because of depression. It has been reported that depressed patients exhibit 41% greater platelet activation and higher procoagulant properties than healthy comparison subjects (8), perhaps because of lower platelet serotonin uptake (9) and greater serotonin receptor expression (10). However, we know of no evidence that citalopram can cause pulmonary embolisms.

Our patient's case indicates the need for further investigation in such patients in order to screen their coagulation system. The availability of a simple blood test as a first-line investigation, such as a D-dimer assay, has been reported to be helpful in the early diagnoses of thromboembolisms. This test is not always available, and we did not have access to it (11).

Attention should also be focused on the prevention of pulmonary emboli. Early walking confers general benefit, and there are theoretical reasons for supporting its use to reduce thromboembolism, along with other measures such as leg elevation, exercises, and the provision of elastic stockings. All these approaches may be useful, but definitive proof of benefit is lacking (12). Most success in this area has been achieved with low-dose subcutaneous heparin (13). It is, therefore, reasonable to consider administrating prophylactic heparin to severely depressed immobile patients (14) in order to prevent thromboembolism, as has been similarly suggested for immobile patients with neuroleptic malignant syndrome (15).

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Antituberculosis Agents and Carbamazepine

TO THE EDITOR: Concomitant carbamazepine and isoniazid therapy, with or without rifampin, has produced increases in carbamazepine serum concentrations (1–4), causing symptoms of toxicity. However, the significance of a potential interaction between rifampin and carbamazepine has received little attention.

Ms. A, a 44-year-old woman, was admitted to the psychiatric ward with symptoms of hypomania. She had a 10-year history of bipolar affective disorder that had been adequately controlled with carbamazepine, 200 mg b.i.d., and trifluoperazine, 5 mg b.i.d. Before admission, because of suspected tuberculosis, Ms. A had been given 600 mg/day of rifampin, 300 mg/day of isoniazid, and 50 mg/day of pyridoxine. Her serum carbamazepine level 2 weeks after admission was 3.1 mg/liter (therapeutic range=4–10); thus, her dose was increased to 200 mg t.i.d. Subsequent serum measurements (1 week apart) provided the following readings: 2.8, 2.5, and 2.3 mg/liter. The results of liver and renal function tests were normal.

Although our literature search retrieved no evidence of a drug interaction involving antituberculosis agents and a decrease in serum carbamazepine levels, the most likely cause of the continued low levels was a combination of carbamazepine auto-induced metabolism and the concomitant antituberculosis agents Ms. A was taking. The antituberculosis drugs were discontinued, and 5 days later, Ms. A's serum carbamazepine level was 4.9 mg/liter. Ms. A was discharged with a carbamazepine dose of 400 mg b.i.d., having fully recovered from her hypomanic episode. Two months after discharge, her carbamazepine level was found to be 4.6 mg/liter, and her mood was euthymic.

Rifampin is a known inducer of many cytochrome P-450 enzymes and has been shown to reduce the plasma concentrations of many drugs used in psychiatry, such as triazolam, zopiclone, zolpidem, and midazolam (5). It has also been reported that both rifampin and carbamazepine are inducers of the same liver isoenzymes (CYP 2C9, CYP 2C19, CYP 3A4) (6). In our review of the literature, not one report was found describing a possible effect of rifampin in further inducing carbamazepine's auto-induced metabolism, leading to progressively low blood concentrations of the mood stabilizer.

This case highlights the importance of monitoring carbamazepine levels, particularly when carbamazepine is co-administered with drugs known to be either inducers or inhibitors of hepatic enzymes. Because predicting the clinical significance of the interaction is difficult, it is wise to watch not only for signs of carbamazepine toxicity but also for signs of inadequate symptom control. Close monitoring of serum carbamazepine levels after addition or deletion of antituberculosis drugs is highly advisable so that the carbamazepine dose can be adjusted accordingly.

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Cyproheptadine for Drug-Induced Sweating

TO THE EDITOR: Sweating is a common side effect of treatment with selective serotonin reuptake inhibitors (SSRIs) and occurs in 7% to 19% of depressed patients in placebo-controlled

studies (Physician's Desk Reference, 2001). This can lead to discontinuation of treatment. Two case reports have described the use of clonidine for the treatment of sweating induced by amitriptyline (1) and SSRIs (2). Also, there have been two case reports on the use of benztropine in the treatment of venlafaxine-induced sweating (3, 4). The following are the first cases of which we are aware of successfully using cyproheptadine, a serotonin antagonist and antihistamine, for the treatment of SSRI-induced sweating.

Mr. A was a 51-year-old Caucasian man with major depression, dysthymia, and obsessive-compulsive disorder (OCD) who was taking fluoxetine, 40 mg b.i.d. He had been stable for 4 years but had developed sweating, which did not improve over time. A reduction of his fluoxetine dose led to symptom relapse. When fluoxetine was increased to its previous therapeutic dose, Mr. A was given cyproheptadine, 4 mg in the morning and at bedtime, which has eliminated his excessive sweating, with no side effects, for over 1 year.

Ms. B was a 65-year-old Caucasian woman with dysthymia and OCD who had not responded to, or had been intolerant of, 20 mg/day of fluoxetine, 400 mg/day of nefazodone, 100 mg/day of sertraline, and 75 mg clomipramine at bedtime. However, she had maintained remission while taking citalopram, 60 mg at bedtime, for over 2 years. Excessive sweating forced her to place a napkin on her forehead when she went out to dinner with friends. After trying trihexyphenidyl, fexofenadine, chlorpheniramine, terfenadine, and diphenhydramine without success, she responded to cyproheptadine, 4 mg at bedtime, which she called "a miracle." Mild early-morning sedation was the only side effect. She has maintained her response for 1 year.

Mr. C was a 58-year-old Caucasian man with panic disorder with agoraphobia and major depression who was taking paroxetine, 30 mg at bedtime. His dose was slowly reduced and discontinued after a 9-month period of stability; his symptoms returned 3 months after he had stopped taking the drug. Paroxetine, 30 mg at bedtime, was reinstituted; he attained subsequent remission, which was maintained for 3 years. Sweating developed and has been controlled for 9 months with cyproheptadine, 4 mg in the morning and at bedtime, with no side effects.

Mr. D was a 56-year-old Caucasian man who was treated for major depression with extended-release venlafaxine, 375 mg/day. Excessive sweating necessitated discontinuation of the medication. Giving Mr. D sertraline, 200 mg/day, reduced his sweating, but he reported a return of depression. Extended-release venlafaxine was reinstituted, with the addition of cyproheptadine, 4 mg at bedtime. His excessive sweating has been controlled for 5 months without adverse events.

Ms. E was a 32-year-old Caucasian woman with dysthymia who was taking fluoxetine, 40 mg/day, and extended-release venlafaxine, 300 mg/day, and experiencing excessive sweating. A decrease in her doses worsened her depression, and the excessive sweating continued. Giving her cyproheptadine, 4 mg at bedtime, reduced her sweating markedly. Time spent not taking cyproheptadine led to a return of excessive sweating within 2 days. She has remained in improved health for over 7 months while taking cyproheptadine.

These five cases reflect the elimination of excessive sweating in patients who were taking four different SSRIs. The mechanism by which SSRIs increase sweating is unknown but is hypothesized to be through activation of the sympathetic nervous system or by action on the hypothalamus (3). It is likely that cyproheptadine decreases sweating by its serotonin antagonism. None of these patients lost the efficacy gained from SSRI treatment after the addition of cyproheptadine, and all patients maintained their benefit for many months. (It is noteworthy that one of these patients did not respond to trihexyphenidyl, given a literature report of successful use of benztropine, another anticholinergic agent.) It is possible that the sweating spontaneously disappeared, but it is unlikely, given that it had existed for years in some patients. Placebo-controlled studies would be helpful, not only to prove efficacy but also to delineate optimal dose. These observations may assist physicians trying to aid patients with SSRI-induced sweating.

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Light Therapy, Obesity, and Night-Eating Syndrome

TO THE EDITOR: The prevalence of night-eating syndrome (morning anorexia, evening hyperphagia, and insomnia) among obese patients ranges from 9% to 27% (1). A concurrent attenuation of the nocturnal elevation in melatonin and leptin blood levels with nighttime awakening and eating has been characterized in obese subjects with night-eating syndrome (2). An open study (3) has suggested that bright-light therapy may reduce body weight in obese subjects, especially those with carbohydrate craving, with or without seasonal affective disorder. We report the first case of which we are aware regarding an overweight patient suffering from night-eating syndrome and nonseasonal depression, both treated with light therapy.

Ms. A, a 51-year-old overweight woman (body mass index=31.2) was seen as an outpatient for the worsening of depressive symptoms over 1 month, despite 2 years of maintenance treatment with paroxetine at a constant dose (40 mg/day). A thorough psychiatric examination by a senior psychiatrist and a record of food consumption (energy and macronutriment content) revealed the following:

1. Nonseasonal major depressive disorder, recurrent episode, moderate, with partial remission between episodes (DSM-IV criteria). Severity was assessed with the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (4) (the usual 21 items of the Hamilton Depression Rating Scale plus eight items assessing atypical symptoms) and with the Beck Depression Inventory (13-item version). Initial scores on the Hamilton scale were 18 on the depression scale and 12 on

the scale for atypical symptoms. Ms. A's Beck Depression Inventory score was 12.

2. Night-eating syndrome, according to the provisional criteria for night-eating syndrome (2): morning anorexia and evening hyperphagia, in which at least 50% of daily energy intake is consumed after the last evening meal (62% after 8:00 p.m.); awakenings at least once a night (at midnight and 3:00 a.m. nightly); and consumption of snacks during awakenings (these snacks were 67.8% carbohydrate and had a carbohydrate-to-protein ratio of 6:1) in order to restore disrupted sleep. These criteria persisted for at least 3 months and were not considered to be side effects of paroxetine treatment.

Bright-light therapy was added to ongoing treatment (paroxetine, 40 mg/day). After 14 daily morning sessions of 10,000-lux white light for 30 minutes, Ms. A no longer fulfilled the DSM-IV criteria for depression, and her scores were significantly lower on the Hamilton scale (depression score=7, atypical symptom score=5) and Beck Depression Inventory (score=5). She no long met the criteria for night-eating syndrome.

One month later, all of Ms. A's previous night-eating symptoms had returned. She was not depressed (DSM-IV criteria), and her severity scores remained low: depression score=6, atypical symptom score=4, Beck Depression Inventory score=5. Another 12 morning sessions with light therapy completely suppressed her night-eating symptoms.

Exposure to light improved the symptoms of night-eating syndrome in an obese subject, irrespective of comorbid depressive symptoms. These findings should be further tested in controlled studies to establish the possible role of light therapy for obese subjects who suffer from night-eating syndrome, with or without affective disorder.

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Clozapine and Venous Thromboembolism

TO THE EDITOR: Thomas Ihde-Scholl, M.D., et al. (1) reported a case of pulmonary embolism associated with clozapine, an atypical antipsychotic. They cited a recent publication by Hägg et al. (2), which described the Swedish experience of venous thromboembolism associated with clozapine. Dr. Ihde-Scholl et al. stated that they knew of only two published case reports of pulmonary embolism in clozapine patients. We call to your attention our published letter (3), which summarized the U.S. experience of suspected venous thromboembolism in association with clozapine based on spontaneous reports submitted to the U.S. Food and Drug Administration's (FDA's) Adverse Event Reporting System database between February 1990 and December 1999. Of 99 unduplicated domestic reports of venous thromboembolism that we received, 83 mentioned pulmonary embolism with or without deep-vein thrombosis, and 16 mentioned deep-vein thrombosis alone. Objective evidence of pulmonary embolism or deep-vein thrombosis was described in 39 cases, and death was reported in 63 cases.

Current U.S. labeling for clozapine describes pulmonary embolism under "Precautions" in the following manner:

> The possibility of pulmonary embolism should be considered in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993, there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 10–54 years of age. Based upon the extent of use observed in the Clozapine National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3,450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% confidence interval=17.1–42.2). Deep vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptom profile should suggest its presence.

Pulmonary embolism and deep-vein thrombosis are also mentioned under "Postmarketing Clinical Experience," in the "Adverse Reactions" section of the label. As for the other atypical antipsychotics, the "Adverse Reactions" section lists pulmonary embolism/embolus for risperidone and olanzapine, deep thrombophlebitis for quetiapine, and pulmonary embolus and deep thrombophlebitis for ziprasidone. Although the adverse events for these atypical antipsychotics were reported with premarketing or postmarketing clinical experience, a causal relationship has not been established nor excluded.

Physicians should maintain a high index of suspicion for the possibility of venous thromboembolism in patients taking antipsychotics, and, as with all medical products, health care professionals are strongly encouraged to report serious adverse events to the FDA's MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), at the MedWatch web site (http://www.fda.gov/medwatch), or by mail (MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857-9787).

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Posttermination Boundary Issues

TO THE EDITOR: While refraining from calling for a repeal of APA's ethical proscription against sex with former patients, Carl P. Malmquist, M.D., M.S., and Malkah T. Notman, M.D. (1), argued in their article on posttermination boundary issues that legal misapplications of imprecise and unproven concepts of transference and countertransference have created an unfair legal liability for therapists who enter posttermination sexual liaisons with their patients. Although their article focused primarily on the legal aspects of this issue, their failure to reference literature describing the destructiveness of posttermination sexual boundary violations (2–4) gave readers a one-sided presentation regarding the reasons that courts and medical licensing boards generally take such a harsh view toward mental health professionals who violate the posttermination standard. Whether the issue of misuse of transference is cited in a final legal order or not, the bottom-line responsibility of courts and licensing boards is to protect the public safety.

From years of study about the problem of human error (5), it has become clear that expert performance of potentially dangerous tasks becomes subject to numerous failure points on the basis of lapses in skill, improper adherence to empirically derived safety guidelines, or lack of an adequate knowledge base upon which to initiate crucial interventions. Skills-based performance, in particular, is formed through repetitive training that results in overlearned behavior and cognitions that enable experts to enter an "auto-pilot" mode, during which they undertake complex cognitive and behavioral operations in a smooth and rapid fashion, without having to rely on more labor-intensive and inefficient conscious mentation. Such automatic cognition or action relies primarily on material encoded in the procedural, as opposed to the episodic, memory system (6).

Psychiatrists who permit themselves to justify that a sexual relationship with a particular patient after termination would ever be acceptable are likely to engage in preparatory planning to "groom" a patient for a future liaison. Since psychiatric practice is fraught with many opportunities for committing serious error even before a so-called "termination" ever occurs, a psychiatrist's self-granted permission for posttermination sex exposes the patient to biased and dangerous treatment. Harboring the idea during treatment to engage in a romance with a patient at some future time after treatment has ended causes the psychiatrist to consciously or unconsciously be motivated to avoid interventions during the treatment that might serve to "pour cold water" on the eagerly expected posttermination liaison. Such inappropriate, goal-directed bias interrupts vital skills-based procedural memories acquired in training through repetitive drilling and proper role modeling—namely, that lust, need for control, or inappropriate anger must never be allowed to interfere with the physician's prime directive of acting primarily for the patient's well-being. This ingrained "memory" does not occur simply as an intellectual piece of knowledge to be tucked away in books or journal articles. Of more importance, it is a fundamental attitude that should assume the function of a learned but exceedingly valuable character trait, imbued through years of anguished repetition experienced while caring for vulnerable patients (7).

In the debate over posttermination sexual relationships, arguing over the scientific validity of the constructs of transference and countertransference or whether the posttermination prohibition should apply to psychiatrists who claim not to rely on these theories in their treatment methods can be seen as a form of sophistry that is dangerously divorced from clinical reality. From the standpoint of psychiatry's quest to reduce medical error, the transference and countertransference constructs serve a useful purpose, mainly because they conveniently summarize a mode of thinking in which the psychiatrist closely attends to the subliminal, automatic, stereotypical behaviors and cognitions (i.e., procedural memories) that arise during the interpersonal process between the patient and psychiatrist. Transference and countertransference can be seen as convenient ways of labeling the mixture of moment-to-moment overt and covert cognitive and behavioral processes that occur between psychiatrist and patient. Anything that tends to weaken serious attention to these processes increases the risk for medical error. These constructs help to organize and summarize the cognitive and behavioral traps a psychiatrist can get into with patients—something that is as applicable to cognitive behavior treatment as to psychoanalysis. Devaluing attentiveness to transference and countertransference processes invites a "dumbing-down" of the practice of psychiatry and is a ticket for disaster, because it permissively encourages clinicians to harbor the illusion that they are immune to bad judgment or to being blindsided.

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TO THE EDITOR: The excellent article by Drs. Malmquist and Notman provided a needed critical examination of the legal system's use and misuse of the clinical concept of transference. As an expert witness in more than 250 cases of boundary violations/sexual misconduct, I have also been impressed with the curious tendency of both courts and boards of registration to treat transference as tantamount to a finding of incompetence, although I profess that an undue-influence model is plausible and often accurate (1). The latter model is at least more respectful of patient autonomy.

The article seemed to omit a central issue, however—economics. To have sex with a past or present patient is an intentional act, hence, an intentional tort, which precludes coverage by malpractice insurance. Plaintiffs' attorneys have had two choices in making such cases triable: 1) stressing the other negligences commonly found in such cases (2) or 2) "creating" a negligent (insurable) tort by claiming mismanagement of the transference, a form of (insurable) negligence. Legal precedent has then enshrined the centrality of a transference analysis, even when it does not fit, as Drs. Malmquist and Notman so effectively pointed out.

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Drs. Malmquist and Notman Reply

TO THE EDITOR: We appreciate Dr. Epstein's calling our attention to some publications from the early 1990s, although they do not seem centered on the specific area we wrote about—namely, the need to clarify posttermination situations outside of the treatment context. The need to define "termination" is crucial. Dr. Epstein seems to belong to the group that believes that there really never is termination because of transference. In contrast, we argue that such a vague and undefined standard after termination of treatment gives rise to many difficulties for society in general and certainly for the judicial system. This holds not only for psychiatry but for the remainder of medicine as well. More specifically, even if transference continues (although we acknowledge that many psychiatrists and mental health professionals do not work within that framework), it does not mean that a person has lost his or her capacity to make decisions involving his or her future.

Dr. Epstein paints a picture of psychiatrists "grooming" their patients for a future liaison. While this situation undoubtedly happens in some cases, we see that as a situation in which treatment has not actually ended (Brown et al., 1992). However, we certainly expect that evidence about such grooming would be forthcoming in adjudication of a particular case, rather than attributing such a situation retrospectively to transference, in which the psychiatrist is said to have been harboring the idea during treatment.

Finally, we do not view arguments about the scientific validity of constructs, such as transference and countertransference, as "sophistry." We prefer to view such arguments as *essential* if psychiatry is to progress beyond the level of making assertions and expecting our colleagues, and those in other fields, such as law or regulatory bodies, to give us any credibility. Only in this manner can we truly reduce the risk for medical error and promote a milieu of public confidence.

Dr. Gutheil rightfully points out how such reliance on a psychoanalytic concept became enshrined in the courts by way of plaintiffs' attorneys needing some basis for their claim if they were to collect damages. It is a good insight into the contemporary scene. We can only wonder if there may not have been other ways to accomplish this end, although we stress a need to distinguish ongoing treatment situations from posttermination events.

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The Mind-Body Problem

We appreciate the thoughtful and clever piece on the mind-body problem by Kenneth Kendler, M.D. (1). Too little attention has been paid in psychiatric education and training to the philosophical underpinnings of our field, and we believe that many problems with the way in which psychiatry is both perceived from the outside and practiced from the inside are attributable to a lack of clarity—or simply an absence of thought—on this topic.

It is for that reason that we are troubled by the misunderstanding of the doctrine of eliminative materialism that this dialogue is likely to engender. "Teacher" states that, according to eliminative materialism, "Mental experiences are all epiphenomenal or, as some say, inert" (p. 992). Eliminative materialism, put forth by the philosopher Richard Rorty (2), carries no such implication. Rather, it likens the concept of "mental" events to obsolete ideas, such as Zeus's thunderbolts. Instead of asserting that Zeus's thunderbolts are identical to discharges of electricity (lightning), we say that what were once considered Zeus's thunderbolts are now thought of as electrical discharges. In our current discourse, there are no such things as Zeus's thunderbolts; they have been eliminated. Similarly, for the eliminative materialist, mind can be seen as nothing more than body (i.e., neural events). Thus, rather than being identified with or reduced to body, mind can be eliminated—at least as far as scientific discourse is concerned. However, just as what used to be seen as Zeus's thunderbolts can still be lethal, what is currently referred to as mind can certainly be—and clearly is—causally efficacious.

Of more obvious direct import for psychiatry, "Teacher" opines that acceptance of eliminative materialism would imply that "Any psychiatric interventions that are purely mental in nature, like psychotherapy, could not possibly work" (1, p. 998). Attempting to adopt the perspective of eliminative materialism while invoking the Cartesian category "purely mental" is what cannot possibly work. An eliminative materialist would not describe psychotherapy as an intervention that is "purely mental" for the simple reason that the concept of the

"purely mental" makes no sense. An eliminative materialist would have no difficulty conceiving of the techniques of psychotherapy as being effective—to whatever extent they may actually be effective—because they are methods of changing the function of the brain. Moreover, there is absolutely no need (and certainly no reason!) to posit the existence of a mental intermediary that transduces the techniques of psychotherapy into changes in brain function.

Nonetheless, Dr. Kendler has done us all a great service by writing this piece, and we applaud him for it.

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TO THE EDITOR: Eliminative materialism is a philosophical theory developed by Paul M. Churchland (1) that argues that neuroscience has restricted, and will eventually eliminate, any need for psychology. In his article, Dr. Kendler addressed whether it is appropriate for psychiatrists to accept the theory that "The sufficient cause for all material events is other material events" (p. 992). In opposition to eliminative materialism, Dr. Kendler presented conventional arguments that focus on ordinary (folk) psychology, which explains nonpathological human action by means of propositional attitudes, e.g., beliefs and desires. He also alluded to arguments against eliminative materialism, based on irreducibility of subjective states ("qualia"), multiple realizability of mental states, and human autonomy. These arguments, which presume normal action and absence of brain disease, have flaws that Churchland has addressed (2). The gist of Churchland's response was that even if neuroscience cannot yet eliminate folk psychology or qualia, future advances will make this possible and desirable.

The preceding arguments are not very effective because eliminative materialism seems farfetched in dealing with actions of individuals without brain dysfunction but plausible in those with brain diseases that may causally explain their deviant behaviors. Churchland (1) recognized that mental illness associated with brain disease provides the strongest argument for eliminative materialism. "So long as one sticks to normal brains," he wrote, "the poverty of folk psychology is perhaps not strikingly evident." But he noted that the poverty of psychological explanation, and the rationale for eliminative materialism, becomes clear "as soon as one examines the many perplexing behavioral and cognitive deficits suffered by people with damaged brains" (1).

A fair and effective critique of eliminative materialism should occur in a domain in which the theory is plausible and strong. Thus, rather than examining normal patients, we should examine ones marked by neurological dysfunction. If psychological explanations are useful, even for disorders associated with well-defined and causally relevant brain dysfunction, then eliminative materialism would be undermined where it seems most plausible. Implicitly, then, it would also be undermined in ordinary behavior. If eliminative materialism could be weakened where it is strongest (i.e., in neuropsychiatric illness), then the general case against it would be bolstered as well.

This theoretical argument is developed and supported by case material in an article in which I reviewed the relationship between causal, neuroscientific explanation and meaningful, psychological explanation in psychiatry (3). There is growing evidence that psychiatric disorders have many causes spanning the biopsychosocial spectrum and thus necessitating multifactorial explanatory models (4, 5). Such empirical findings support arguments against eliminative materialism, which are based not on folk psychology, in which Churchland's theory is already weak, but on clinical neuropsychiatry, in which biological dysfunction is causal; so his theory seems plausible. While Dr. Kendler accurately depicted traditional philosophical arguments against eliminative materialism, alternative arguments make a stronger case for an ongoing need for psychology and multifactorial explanations in contemporary psychiatry.

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TO THE EDITOR: Dr. Kendler has performed a highly useful service; in principle, the issue is conceptually central in psychiatry. However, the various traditional dualist and monist "solutions" he describes are untenable, as many centuries of analysis have demonstrated and as is well known (1). The standard available options bristle with internal unresolvable logical contradictions.

I call attention to radical contemporary ontological approaches that begin to offer some hope of progress. These concern three related assumptions: one concerning the nature of inanimate matter, the Cartesian bifurcation into an inner and outer world, and the so-called "referential-instrumental" conception of language. While these assumptions may be acceptable and useful in many contexts and applications, strong arguments have been made to show that they are inadequate when it comes to psychiatric and psychological matters. Typically, these arguments are ignored or brushed aside.

Three major unorthodox works have addressed these issues (2–4), and I have sought to integrate their sense into two articles (5, 6). I submit that it would be worth exploring these radical alternative perspectives. It would seem that if one is to obtain any understanding of consciousness beyond the present correlational dual views (those that simply correlate

physical and "mental" events) or monistic reductionist conceptions, then the old options concerning "solutions" to the mind-body problem need to be abandoned.

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TO THE EDITOR: Dr. Kendler's admirable article addressed psychiatry's growing need to revisit the philosophical assumptions underlying current clinical and research practices. His informal presentation of dualism, identity theory, and functionalism was both illuminating and entertaining.

Unfortunately, Dr. Kendler's metaphysical "primer," as he himself warned us from the outset, is incomplete. In particular, his discussion excluded an important pair of epistemological approaches to cognition: hermeneutics and quantum computation. These two domains of discourse (1) complement each other's power to unmask the illusory nature of distinctions between matter and psyche.

When Descartes proclaimed, "*Cogito ergo sum*," he conjured up a chimerical barrier between subject and object. This fictitious boundary was predicated on the mistaken notion that an individual mind's subjective semantic content is coextensive with private, first-person perspectives, while the formal structure of objective facts correlates with a public, third-person viewpoint.

All subsequent forms of dualism as well as derivative eliminativistic monisms have rested on this false distinction between public and private domains. Identity theories have been based on the same flawed foundation in the guise of an explanatory gap between intersubjectively reproducible measurement and subjective qualia. Functionalism, as shown by the Chinese-room argument, demonstrates similar dependencies cast in semantic terms.

Hermeneutics shatters the Cartesian barrier by opening hidden aspects of an individual mind's subjective content to interpretation by third persons; the prime therapeutic example of such an interpretative process is psychoanalysis, although Marxism and Heideggerian existentialism offer alternative methodologies (2). Quantum computation breaches the Cartesian barrier from its opposite end by generating quantitative knowledge, albeit with limited precision, through the quasi-subjective agency of an operator.

Today neither hermeneutics nor quantum computation occupies center stage in academic circles. Hermeneutics has been driven from institutional power in the psychiatric world by the economics of drug research and its positivistic demands. Quantum computational neuroscience (3, 4), plagued by thermodynamically oriented criticisms, sits stalled outside the mainstream of psychobiology.

However, hermeneutics and quantum computation may yet prove to be seminal components of a decisive future breakthrough beyond the conceptual prison wall erected by Descartes. Both are part of the postmodern legacy that "decenters" the human subject. Acceptance of both, therefore, requires stoical endurance of narcissistic blows to our misplaced faith in an imaginary self-omniscience. It is still possible that organized psychiatry will summon the programmatic strength to sustain such blows in the interest of progress.

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Dr. Kendler Replies

TO THE EDITOR: It was with some trepidation that I ventured into the troubled waters of the mind-body problem. Given my lack of formal philosophical education, I anticipated receiving numerous letters from professional philosophers pointing out my egregious misunderstandings of key concepts in this sometimes obscure field. I was, therefore, relieved to review the letters printed here. Comments that the article was "useful," "illuminating," and "entertaining," are particularly gratifying in that that was precisely my goal. These individuals share my conviction that the profound issues surrounding the mind-body problem are given short shrift in psychiatric education and discourse.

Drs. Waterman and Schwartz correctly take me to task for oversimplifying the spectrum of opinions underlying the associated positions of eliminative materialism and epiphenomenalism. I am sure that their characterization of Rorty's position on this is correct, although I have not read his work. Perhaps we are describing the subtle difference between the view of epiphenomenalism that mental experiences are "real" but causally inert versus the eliminative materialism position that mental events do not exist and represent a view of the natural order as mistaken as that of pre-Copernican man thinking that the heavens rotated around the earth. I think that Drs. Waterman and Schwartz would argue that psychotherapy works because sound waves elicited from the mouth of one individual (the therapist) produce adaptive changes in the brain of a second individual (the patient). Would not the eliminative materialism position assert that the subjective sense of the parties involved that "meaning" or "insight" played a causal role in that process was as mistaken as the belief that a thunderstorm indicated that Zeus was angry?

There is nothing with which I disagree in Dr. Brendel's letter. Indeed, I recommend his recent review (Brendel, 2000), which examines the tensions between explanatory and causal models for mind as alternatives to eliminative materialism. In the language of my review, Dr. Brendel compares models of "explanatory dualism" (which assume that humans will always need to make sense of their experiences in mental terms) and nonreductive materialism (in which mental states have top-down causal powers).

I am not as pessimistic as Dr. Berger that radical approaches are needed to reach some greater clarification of the mind-body problem. Although I am not familiar with any of the "unorthodox works" that he cites, I did read his most recent article (Berger, 2001). He is correct that my essay assumed a classic or Newtonian view of the physical world. However, perhaps out of ignorance, I remain unconvinced that any of the issues reviewed are changed dramatically by taking quantum mechanical or relativistic models into account.

Dr. Mender notes, correctly, that the dialogue did not discuss hermeneutics or quantum computation. I fail to discern how the latter would directly affect the mind-body problem. As I understand it, the central "storytelling" element of hermeneutics would be incorporated into the concept of explanatory dualism.

Those interested in the central mind-body questions of reduction and emergence might profitably consult the September–October 2001 issue of the *Journal of Consciousness Studies,* which contains several helpful reviews.

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Abuse, Dependence, or Withdrawal Associated With Tramadol

TO THE EDITOR: We write to add commentary from the Food and Drug Administration's (FDA's) MedWatch database of adverse-event reports to the case report by William R. Yates, M.D., et al. (1) of tramadol dependence in a patient with no past history of substance abuse. We note an honest but problematic inconsistency in the case report. Specifically, Dr. Yates et al. juxtaposed the statement "Tramadol is thought to have a low potential for abuse" (p. 964) and the results of a study on the frequency of abuse by Cicero et al. (2): "less than one case per 100,000 exposures" (p. 964). Although the absolute incidence of dependence, withdrawal, or abuse associated with tramadol may be "low," this case report highlights the dependence potential of this agent, as written in the approved product label: "[Tramadol] has the potential to cause psychic and physical dependence of the morphine-type (μ-opioid)."

Since tramadol's initial marketing, from March 1995 through June 2001, the FDA has received 912 domestic adverse-event reports classified under the coding terms "drug dependence," "drug withdrawal," or "drug abuse" in association with tramadol. (The use of these terms is not based on DSM-IV criteria but taken from the reports themselves and so will vary by reporting clinician.) The distribution by adverse-event term is as follows: dependence: N=426, withdrawal: N=407, abuse: N=241 (the sum exceeds 912 since a report may have included more than one adverse-event term).

Most of these 912 reports included a history of drug/substance abuse. However, some reports specifically stated no such history, as in the case described by Dr. Yates et al. Additional reports described compelling clinical summaries that suggest, but do not state, that there was no past history of drug/substance abuse. (No percentages are presented because of the multiple possibilities afforded by differential report inclusion/exclusion criteria.)

The FDA receives an unknown fraction of the total true number of reports of adverse events attributed to drug products. In general, interest in the reporting of adverse events is usually highest in the early years of drug marketing (described as the "Weber effect") and declines over time (3). The FDA's data for reports of dependence, withdrawal, or abuse of tramadol, by year of receipt (May 1995 through June 2001) (N=912) are as follows: a total of 30 in 1995, 285 in 1996, 149 in 1997, 28 in 1998, 170 in 1999, 91 in 2000, and 159 in 2001. Although reporting of adverse events associated with tramadol peaked in 1996, reporting continues through the present. Although adverse-event reporting is subject to numerous forces, including total exposed population and publicity of an adverse event, these reports also suggest that clinicians are still interested in (surprised by) cases of tramadol-associated abuse, dependence, or withdrawal, as in the case reported by Dr. Yates et al.

As stated in the current product label, tramadol is not recommended for patients with a history of drug abuse or dependence, as these patients are at high risk for abuse or dependence with tramadol. In addition, and of particular relevance to the issue raised by Dr. Yates et al., the recently revised (August 2001) approved product label for tramadol states that dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain tramadol, are not limited to patients with a prior history of opioid dependence.

(The views expressed herein are those of the authors and do not necessarily represent those of the FDA nor imply its endorsement.)

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Dr. Yates Replies

TO THE EDITOR: The letter by Dr. Brinker et al. provides further insight into the abuse potential of tramadol. The number of reported cases of abuse and dependence reported to the FDA demonstrates the clinical relevance of this issue. The revision of the product label in August 2001 occurred after the *Journal* publication of the case. This revision underscored that the FDA reporting data confirm the experience of abuse and de-

pendence in some patients without a personal history of substance abuse.

Although Dr. Brinker et al. note that this case is not unique or uncommon, the case did have significant implications for psychiatrists. Since many psychiatrists do not routinely prescribe tramadol, they may have limited experience with the clinical pharmacology of this compound. Additionally, psychiatrists working in an emergency room setting or treating patients with comorbid substance abuse may encounter similar cases.

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Residual Depressive Symptoms in Bipolar Depression

TO THE EDITOR: Ramin Mojtabai, M.D., Ph.D. (1), recently reported important data on residual symptoms in major depression in the community. Overall, 34% of respondents whose last major depressive episode had ended had residual depressive symptoms, and 23% had residual symptoms for more than 1 year. Unipolar major depressive disorder has been the main focus of studies of residual depressive symptoms (1, 2). In clinical study groups, residual depressive symptoms were reported to be common in unipolar depression (1, 2).

Bipolar II depression has recently been reported to be much more common in depressed outpatients than has been previously reported, with a frequency ranging from 30% to 55% (3, 4). The study of residual depressive symptoms is, therefore, also very important in this common disorder. In my recent study (5), 44.9% of outpatients with bipolar II disorder who were seen for treatment of a major depressive episode in a private practice (a setting closer to the community than tertiary care settings) (N=138) had residual depressive symptoms for more than 2 years from the index major depressive episode. (In the updated group of patients with bipolar II disorder [N=206], 43.6% had had residual depressive symptoms for more than 2 years.) Persistent residual depressive symptoms in bipolar II depression were significantly ($p<0.001$) and positively associated with illness duration and number of recurrences. These findings have important treatment implications. Prevention of major depressive episodes and treatment of residual depressive symptoms could reduce recurrences and, thus, reduce further residual symptoms and impairment.

However, the use of antidepressants may be a problem for patients with bipolar II depression, because antidepressants may induce hypomania, mixed states, and rapid cycling, and aggressive antidepressant treatments are more likely in patients with long-lasting depression (3). Consequently, antidepressants may induce mood instability when used in the treatment of residual depressive symptoms in bipolar II patients and may require concurrent treatment with mood stabilizers to prevent or reduce mood instability. Clinicians should know that residual depressive symptoms are common also in bipolar II depression (frequently in depressed outpatients) and that treatment of residual depressive symptoms in bipolar II patients may be more complicated than in patients with unipolar depression. Skillful, structured questioning by clinicians about past hypomania during a depression assessment, supplemented by information from family members and/or close friends, is required to increase the bipolar II case findings (3, 4) and to prevent the possible negative effects of antidepressants on bipolar II depression that is misdiagnosed as unipolar depression.

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