Letters to the Editor

Adjunctive Lamotrigine Treatment for Major Depression

TO THE EDITOR: Lamotrigine, which at present has been indicated only for the treatment of epilepsy, has been reported to be possibly useful as an adjunctive treatment for bipolar disorder (1, 2). This letter presents two cases of its successful use as an adjunctive treatment for refractory major depression.

Ms. A was a 45-year-old woman who had been diagnosed with recurrent major depressive disorder; her therapeutic trials of bupropion, phenelzine, venlafaxine, imipramine, and nortriptyline had failed, and she had only been partially responsive to ECT. To her regimen of tranylcypromine, 70 mg/day, lithium carbonate, 1200 mg/day, and clonazepam (0.5 mg/day b.i.d. as needed, used sparingly for anxiety) treatment was added lamotrigine, 25 mg/day, and titrated to 75 mg/day within 3 weeks. Within 8 weeks, Ms. A reported a dramatic improvement in her mood and shortly thereafter returned to work. She continued to do well on this treatment regimen when assessed 6 months later.

Ms. B was a 43-year-old woman with recurrent major depressive disorder whose therapeutic trials of venlafaxine, fluoxetine, and paroxetine had failed. In addition, she could not tolerate a trial of nefazodone treatment. To her regimen of fluoxetine, 50 mg/day, and bupropion, 150 mg/day (sustained-release preparation), was added lamotrigine, 25 mg/day. Within 4 weeks, she, too, reported a dramatic improvement. "I can't remember the last time I felt this good," she commented. She continued to do well when assessed 2 months later.

In both cases, the addition of lamotrigine to the current psychotropic regimen resulted in a significant improvement in mood. The agent was well tolerated, with no additional side effects reported by either patient. In addition, neither had developed a rash of any kind, possibly because of the low doses used. Caution apparently must be taken when adding to a regimen in which selective serotonin reuptake inhibitors are used, because these may increase lamotrigine levels, possibly resulting in toxicity (3). Whereas findings from a study with an N of two are resoundingly underwhelming, it appears that lamotrigine may be effective as an augmentation strategy in treating major depressive disorder, although future studies will be required to bear this out.

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Sublingually Administered Fluoxetine for Major Depression in Medically Compromised Patients

TO THE EDITOR: Fluoxetine, the selective serotonin reuptake inhibitor first introduced for clinical use in the United States in 1988, was discovered in the early 1970s. The long half-life of the drug and its metabolite contribute to a 4-week period to reach steady-state concentrations. As with all available antidepressants, the effects of fluoxetine are seen in the first 1-3 weeks, but the clinician should wait until the patient has been taking the drug for 4-6 weeks before evaluating its antidepressant activity. Fluoxetine is available in 10-mg and 20-mg capsules and as a liquid (20 mg/5 ml) (1–5).

Sublingual delivery gives rapid absorption and good bioavailability for some small permeants, although this type of administration is not well suited to sustained-delivery systems. The sublingual delivery can be predictably used in fasting patients, those having difficulty swallowing, or those who are unable to absorb drugs through the gastrointestinal tract. Furthermore, the sublingual dose is the same as the oral dose. In the following two cases, each patient was diagnosed with major depressive disorder and treated effectively with sublingually administered fluoxetine in a hospital setting.

Mr. A was a 56-year-old, married Caucasian man with four children who was admitted to the hospital after a crush injury. Before the accident, Mr. A was a high-functioning individual with no medical or psychiatric problems. His stay in the hospital was complicated with multiple medical and surgical problems, including a sigmoid resection, a cholecystotomy, and a gastrointestinal fistula. During his recuperation, Mr. A became depressed, so a consultant psychiatrist became involved in his care. He was diagnosed with major depressive disorder, requiring treatment with antidepressant pharmacotherapy. Mr. A was unable to ingest pills orally because of his multiple gastrointestinal problems; therefore, he was given fluoxetine in liquid form sublingually by using a dropper administered by a trained staff member. Treatment was initiated as 10 mg/day sublingually (liquid fluoxetine=20 mg/5 ml), and the dose was gradually increased to 20 mg/day.

Mr. A responded to sublingually administered fluoxetine, and his depressive symptoms resolved within 4 weeks; he had improvements in mood, affect, and the activities of daily living as well as social interactions. Four weeks after the treatment was initiated, his plasma fluoxetine and norfluoxetine levels were measured and found to be in the lower end of the therapeutic range (fluoxetine=47 ng/ml and norfluoxetine=52 ng/ml). Mr. A was maintained with sublingual fluoxetine treatment for 9 weeks, but he was switched to oral administration of the medication as a result of improvement in his medical condition. Mr. A remained psychiatrically stable during the rest of his hospital stay, and he was eventually discharged while receiving oral fluoxetine treatment with outpatient instructions.

Mr. B was a 52-year-old, married Caucasian man with one child who was admitted to the hospital surgical floor

after a motor vehicle accident. In the operating room, surgeons performed abdominal decompression with the placement of a J-tube, surgical repair of the mesenteric system, and a splenectomy. Mr. B's hospital stay was complicated by the formation of an enterovesicular fistula. Shortly after his admission to the hospital, Mr. B became clinically depressed and had psychomotor retardation and feelings of hopelessness. He was diagnosed with major depressive and generalized anxiety disorders by a psychiatrist. Because of his gastrointestinal problems, Mr. B was unable to take any medications orally. Sublingual fluoxetine treatment was initiated with a dose of 10 mg/day, and the dose was gradually increased to 20 mg/day. Within 4 weeks, Mr. B became more verbal and interactive, with improved sleep and appetite. His serum fluoxetine and norfluoxetine levels were within a therapeutic range after 4 weeks of treatment (fluoxetine=62 ng/ml and norfluoxetine=78 ng/ml). Fluoxetine was eventually switched to the tablet form as a result of improvement in Mr. B's medical condition. He was discharged to a rehabilitation facility while receiving oral fluoxetine treatment.

Depression is a common problem in medically compromised patients in hospital settings. Many of these patients have conditions such as difficulty swallowing or being unable to absorb drugs through the gastrointestinal tract. In this letter, we presented two cases of patients with severe depression who were treated with sublingual delivery of a commonly prescribed antidepressant—fluoxetine. Plasma drug levels of fluoxetine and its metabolite, norfluoxetine, were in the therapeutic range in each case. To provide more effective treatment for these patients, psychiatrists need to begin using alternative ways of delivering drugs when necessary.

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Pramipexole Treatment for Cocaine Cravings

TO THE EDITOR: Mr. A was a 34-year-old, single, successful businessman who was referred for evaluation of a possible bipolar disorder. He was currently depressed because he had in the previous year brought financial ruin on himself with cocaine freebasing and sexual and other extravagances that had cost him nearly $1 million.

Along with current major depression, persistent cocaine cravings but rare use, and a questionable past history of primary or secondary (to substance abuse) mania, he manifested an extraordinary movement disorder with constant restlessness and thrashing of the legs that left his inner knees and thighs bruised and discolored with hematomas in various stages of evolution and resolution. For the restless legs, he had consulted a neurologist who diagnosed preparkinsonism, which is presumed to be secondary to neurological damage from cocaine. The disfiguring movements limited his ability to return to and conduct business.

Previously, Mr. A had not responded to or tolerated most of the new generation of antidepressants. Treatment was begun with lamotrigine, up to 200 mg/day, and his mood improved modestly. Because of his severe restless legs and persistent depression, pramipexole treatment was begun, and the dose was titrated to 1.5 mg/day in divided doses.

Mr. A's leg movements quieted substantially, his mood brightened, and he reported the first days in a year in which he awoke without craving cocaine, a benefit sustained for 1 year with pramipexole treatment, combined with 75 mg/day of lamotrigine. During the subsequent year, Mr. A. reported 1 day of noncompliance with his medication regimen when he was out of town overnight without his medication. That night, for the first time, he dreamt about cocaine, and the next day he experienced a renewed craving upon awakening, which disappeared when treatment was restored.

Although Mr. A faces an array of financial and business challenges, his mood is nearly euthymic, his leg movements at worst resemble mild restlessness, and his cocaine cravings are abolished.

We recognize the risks of attributing efficacy of a treatment on the basis of a single anecdote, but the possibility of treating cocaine cravings with this dopamine agonist on the basis of this observation is of potential importance, given the current lack of effective strategies.

Bromocriptine, a dopamine agonist with D_2 selectivity, has been investigated as a treatment for cocaine withdrawal. Recent data do not, however, corroborate its efficacy for cocaine cravings (1). Pramipexole, a dopamine agonist with relative D_3 receptor selectivity, and also D_4 and D_2 effects, may be a treatment option for patients with cocaine cravings, particularly those with comorbid refractory depression. Studies have shown that pramipexole decreases the self-administration of cocaine in rats (2).

On the basis of our single observation, we strongly urge that clinical studies follow up on this report.

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Effectiveness of Olanzapine Treatment for Severe Obsessive-Compulsive Disorder

TO THE EDITOR: Although haloperidol and pimozide are commonly employed in treatment augmentation strategies

for severe obsessive-compulsive disorder (OCD), the role of atypical neuroleptics is still unclear (1). Some reports suggest that risperidone and clozapine may induce OCD symptoms (2, 3); a patient with schizophrenia was written about recently whose obsessive-compulsive symptoms worsened with olanzapine treatment. However, we report on two severe cases of patients with OCD who dramatically improved after olanzapine was added to treatment with selective serotonin reuptake inhibitors for 3 months.

Mr. A, a 21-year-old man, had been suffering from OCD for 4 years, and his mother suffered from type II bipolar disorder. His main obsession was contamination, and his compulsions (washing rituals) occupied 8 hours a day, rendering him unfit for college or employment. Various treatments and augmentation strategies at appropriate doses had been ineffective. His Yale-Brown Obsessive Compulsive Scale total score at his first psychiatric interview was 40. He was taking sertraline, haloperidol, risperidone, and diazepam, but all psychiatric drugs were discontinued except sertraline (150 mg/day), and olanzapine (5 mg/day) titrated up to 10 mg/day over a week. After 15 days, Mr. A reported significantly lessened anxiety and, after 1 month, significantly lessened obsessive-compulsive symptoms. By the third month, his symptoms were occurring for only minutes each week (Yale-Brown Obsessive Compulsive Scale total score of 6). At this point, he decided to work and to attend evening school.

Ms. B, a 29-year-old woman, suffered from OCD (with postpartum onset 4 years previously) and had a father who suffered from OCD and alcohol abuse and a mother with type II bipolar disorder. She had order and symmetry obsessions and compulsions that consisted of repeated checking, counting rituals, and washing objects in her room, where she spent 7 hours a day. She became anxious when anyone entered her room and interfered with her rituals. Ms. B was unable to work; her familial and social relationships were severely impaired. Of the various treatments, only fluvoxamine (300 mg/day) led to temporary improvement. Ms. B was given an added 5 mg/day of olanzapine, titrated up to 15 mg over 2 weeks. After 20 days, the dysphoria and irritability that were associated with her compulsions had lessened notably, and over 3 months, her Yale-Brown Obsessive Compulsive Scale total score had decreased progressively from 40 to 8. Her compulsions then occupied only 10 minutes a day. She was undergoing cognitive behavioral therapy and intended to work.

These case reports suggest that olanzapine may help severe, otherwise untreatable patients with OCD and might help resolve frequent diagnostic dilemmas regarding patients with schizophrenia with obsessive-compulsive symptoms and patients with psychotic features with OCD. It is interesting that both patients' mothers were suffering from type II bipolar disorder: this observation, supported by similar findings in other patients, suggests that having a family history of bipolar disorder might predict a good response to olanzapine. Further assessment of the potential benefits of olanzapine treatment in a defined subgroup of treatment-resistant patients with OCD is warranted.

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Body Mass Index Increase of 58% Associated With Olanzapine

TO THE EDITOR: To our knowledge, extreme weight gain in adolescents treated with olanzapine has not been documented. Olanzapine-associated weight gain averaging up to 26.4 lb has been reported (1). We describe a case of an 85-lb weight gain in an adolescent receiving olanzapine treatment.

At age 15.3 years, Mr. A, an African Canadian adolescent with no past medical problems and no personal or family history of obesity or eating disorders met the DSM-IV criteria for undifferentiated type schizophrenia. He was treated briefly with perphenazine and benztropine but was noncompliant with his drug regimen. At age 17.3 years, he was rehospitalized, and olanzapine treatment, 5 mg/day, was initiated (weight=150 lb; body mass index=20.9 kg/m^2). Results of baseline laboratory tests, including thyroid indices and a computerized tomography scan of the head, were within normal limits, and positive psychotic symptoms were resolved. A third admission occurred at age 17.8 years, and Mr. A's olanzapine dose was increased to 10 mg/day.

Mr. A then weighed 170 pounds; his weight had increased 20 lb over 6 months while taking olanzapine, 5 mg/day. Subsequently, his weight was recorded on four occasions over 7 weeks (index=170 lb, week 1=176 lb, week 3=182 lb, week 7=186.5 lb), indicating a gain of 16.5 lb after 7 weeks of treatment with olanzapine, 10 mg/day. Neither his diet, activity levels, nor any intercurrent medical conditions could account for his weight gain. His positive symptoms disappeared. After 14 months of olanzapine therapy (5.5 months at 5 mg/day; 8.5 months at 10 mg/day), his weight was 235 lb, and he had a body mass index of 32.9 kg/m^2 (age=18.5 years). His dose of olanzapine was discontinued, and quetiapine treatment, 400 mg/day, was initiated, but it failed to control his positive symptoms. His symptoms remitted after switching to risperidone treatment, 2 mg/day. At the age of 19.5 years, his weight was 220 lb (body mass index=31 kg/m^2), a decrease of 15 lb since he discontinued olanzapine.

Obesity increases the risk for diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, certain cancers, and overall mortality (2). A recent case series described two cases of new-onset diabetes associated with olanzapine therapy (3). Minimizing the adverse effects of iatrogenic obesity in patients who require long-term treatment requires monitoring weight and body mass index at baseline and throughout treatment. Antagonism at the H_1 and 5-hydroxytryptamine 2 receptors has been implicated in weight gain associated with antipsychotic agents (4).

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Recurrence of Neuroleptic Malignant Syndrome With Olanzapine Treatment

TO THE EDITOR: The atypical antipsychotic medication olanzapine, which has a neuroreceptor affinity similar to that of clozapine (1), was not associated until now with the occurrence of neuroleptic malignant syndrome. We report a case in which olanzapine was given to an elderly patient who had suffered two previous episodes of neuroleptic malignant syndrome after treatment with two typical neuroleptics; these again caused neuroleptic malignant syndrome symptoms. To the best of our knowledge, this is the first report of olanzapine-induced neuroleptic malignant syndrome.

Ms. A, a 70-year-old woman with a history of schizoaffective illness, was admitted to our inpatient unit with an acute psychotic-manic episode. Two years and 1 year before this admission, she had been treated for similar episodes with the antipsychotic medications chlorprothixene and then zuclopenthixol HCl; both times this treatment resulted in the symptoms of neuroleptic malignant syndrome. Ms. A had been free of antipsychotic medication for over 6 months. Therefore, treatment with olanzapine, a new atypical antipsychotic medication that was not known to be connected with neuroleptic malignant syndrome, was initiated, 5 mg/day, concurrent with treatment with carbamazepine and betahistine. Because of Ms. A's extreme restlessness, her dose of olanzapine was increased to 10 mg/day after 2 days. Immediately, a fever of 37.8°C appeared; she had a pulse of 120 bpm and a blood pressure level of 180 mm Hg diastolic and 100 mm Hg systolic. Ms. A's creatine phosphokinase level was extremely elevated—1,573 U/liter. Ms. A's parkinsonian symptoms included cogwheel rigidity. Olanzapine treatment was discontinued; Ms. A had a corresponding resolution of her neuroleptic malignant syndrome symptoms over 3 days. Ms. A's creatine phosphokinase level on the third day was 343 U/liter. Her psychotic symptoms were barely controlled with high doses of benzodiazepines added to her medication regimen.

Neuroleptic malignant syndrome was described in patients who were given the atypical antipsychotics clozapine and risperidone. Recently, Hasan and Buckley (2) reviewed the literature of 19 cases of clozapine-induced neuroleptic malignant syndrome and 13 cases of risperidone-induced neuroleptic malignant syndrome and concluded that these atypical antipsychotics cause neuroleptic malignant syndrome, which resembles classical neuroleptic malignant syndrome. They did not find sufficient evidence for an atypical neuroleptic malignant syndrome with these novel antipsychotics. Three patients with neuroleptic malignant syndrome who were given clozapine (none were given risperidone) had a history of neuroleptic malignant syndrome from typical antipsychotics, as in our case.

Our case demonstrates the occurrence of neuroleptic malignant syndrome after the administration of another atypical antipsychotic medication—olanzapine. Since the symptoms in our case did not include severe body rigidity, further evidence will reveal whether olanzapine-induced neuroleptic malignant syndrome may be classical or atypical neuroleptic malignant syndrome.

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Cybersuicide: The Internet and Suicide

TO THE EDITOR: We report on two suicide attempts in which information about the methods used were obtained from the Internet. Both cases illustrate the danger of having access to information by means of the Internet. Such information may prove detrimental to vulnerable psychiatric patients.

Mr. A, a 16-year-old African American adolescent, appeared at the emergency room after attempting suicide. He has no psychiatric history but had borderline mental retardation (IQ=80). He had ingested castor oil beans (from the plant *Ricinus communis*). After ingesting two beans, he confessed to his mother, who brought him to the emergency room. His suicidal ideas followed a worsening of his academic performance, which also led to his being subjected to ridicule by his peers. Mr. A's education involved using the computer, and he had regular access to the Internet. He got the idea for suicide from Web sites, although he refused to disclose them. He subsequently made an uneventful recovery.

Ms. B, a 34-year-old woman with borderline personality disorder and posttraumatic stress disorder, had a history of several suicide attempts by wrist laceration and overdosing resulting in multiple hospitalizations. On this occasion, she attempted suicide by drinking several liters of water. She got the idea from the Internet, as a less painful and more convenient method of committing suicide. Ms. B did not divulge the Web site address but acknowledged that information about suicide is readily available on the Internet. She was hospitalized for observation and recovered without complications.

It is extremely easy to access information about suicide from the Internet. Using the search engines Looksmart and Yahoo, we identified several such sites. One site described using guns, overdosing, slashing one's wrists, and hanging as

the "best methods to commit suicide." Other site titles suggested various suicide methods. One site illustrated various methods—lethal doses of poison, their availability, estimated time of death, and degrees of certainty. Another site, by its title, appeared to be about committing suicide; its content, however, was more about repentance.

The Internet is already having a significant influence in medicine and psychiatry. Although, it has a great potential in psychiatric education, clinical care, and research (1), its impact on social issues should not be underestimated. It has not escaped the attention of vulnerable individuals who have been sharing information about suicide. There are examples of interactive notes followed by a suicide fatality (2). Although information from the Internet may be useful for research, these two cases illustrate the potential hazard of its inappropriate use.

Mental health care providers should counsel patients about alternatives to surfing the Web at times of crisis. Help may be available by calling crisis lines, clinicians, friends, or family members.

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Seasonality Associated With the Serotonin Transporter Promoter Repeat Length Polymorphism

TO THE EDITOR: The propensity of people to exhibit changes in mood and behavior with the changing seasons, also known as seasonality, has been found to be heritable (1). Seasonality can be viewed as a continuum ranging from those who show no seasonal changes to those who exhibit extreme changes with the seasons (1). Seasonal changes in serotonin metabolism might be responsible for seasonally dependent behaviors (2).

We previously reported that the short allele of the serotonin transporter promoter repeat length polymorphism is associated with seasonal affective disorder, and in patients with seasonal affective disorder, the short allele is associated with higher levels of seasonality than in those with the long allele (3). We recently explored the association between the serotonin transporter promoter repeat length polymorphism and seasonality in a general population study group. We received written informed consent from all subjects.

We administered the Seasonal Pattern Assessment Questionnaire (4) to 209 Caucasian individuals who were selected from the general population, which is described elsewhere (5). We computed global seasonality scores from the Seasonal Pattern Assessment Questionnaire, which are the sum of the scores on items pertaining to self-reported seasonal changes in mood and behavior and evaluated their serotonin transporter promoter repeat length polymorphism genotypes. Knowing that the short allele has been found to act in a dominant fashion (5), and on the basis of our results in patients with seasonal affective disorder (3), we hypothesized that those individuals who had at least one short allele would have higher global seasonality scores than those who were homozygous for the long allele. Our hypothesis was borne out: the global seasonality mean score for the long-long genotypes was 6.2, SD=3.9, and the mean score for the non-long-long genotypes was 8.9, SD=4.9 ($t=3.65$, $df=207$, $p<0.001$). There was no difference in seasonality mean scores between those who were heterozygous and those who were homozygous for the short allele (short-long=9.2, SD=4.6; short-short=7.9, SD=5.7). Thus, the serotonin transporter promoter repeat length polymorphism appears to influence the development of seasonality; higher seasonality scores occur in those with at least one short allele.

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Rapid Cycling in Bipolar Disorder

TO THE EDITOR: The article by Leonardo Tondo, M.D., and Ross J. Baldessarini, M.D. (1), contains an obvious mistake. The authors report that we, Maj et al. (2), and Bauer et al. (3) found a rapid-cycling course of illness in 33.3% and 50.2%, respectively, of our patients with bipolar disorder. We found that pattern instead in 13.6% of the patients with bipolar disorder who were referred to our center (as clearly stated in the Results section of our article), and we recruited for our comparative study two patients with nonrapid cycling for each patient with rapid cycling. Similarly, Bauer et al., in their multisite study, did not find an unusually high proportion of patients with rapid cycling but simply asked each site to provide an equal number of patients with rapid cycling and patients with nonrapid cycling (as specified in the Method section of their article).

As a consequence of this misunderstanding, Drs. Tondo and Baldessarini calculate an average prevalence of 24.2% for the rapid cycling pattern, which is totally erroneous, as are the risk of rapid cycling of 29.6% in women and 16.5% in men that they mention in the article, the abstract, and table 1. These erroneous data may mislead the reader and should be rectified.

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Drs. Tondo and Baldessarini Reply

TO THE EDITOR: Regarding the comments of Dr. Maj, we stipulated in our article that the prevalence of rapid cycling in patients with bipolar patients on the basis of data from case control or other nonrandom subject selection is invalid: "A rapid-cycling course was found in 24.2% of the patients, but this rate was probably inflated by selection of rapid-cycling cases in some studies…that had unusually high proportions of such cases (40.5%–55.8%)" (p. 1435). This rate averaged to a mean of 16.3% (SD=2.82) in unselected samples versus an obviously inflated mean of 46.1% (SD=9.03) in selected groups (F=49.4, df=1, 8, p=0.0001). In addition, in Dr. Maj's cited study, whereas the prevalence of rapid cycling among all patients with bipolar disorder was 13.6%, in those with data regarding cycling status and sex, it was 33.3% (37 out of 111), as stated (table 1). However, estimating the prevalence of rapid cycling among patients with bipolar disorder, or even absolute, sex-based, rapid-cycling rates (also highly variable and possibly unreliable), was not the purpose of our report.

The aim of our meta-analysis, again, was to compare sex-based, rapid-cycling rates with rates from studies that provided data for women and men with bipolar disorder with and without rapid cycling to test the hypothesis that rapid cycling is more prevalent in women. This hypothesis arose from reports of extraordinarily high proportions of women among patients with rapid cycling (71.7% women versus 28.3% men). Such findings pertain to excesses of women in clinical study groups but not necessarily to the rates of rapid cycling among women. In contrast, sex-based, rapid-cycling risk ratios indicated a much smaller sex difference. Since these risk ratios did not differ significantly between studies involving unselected or selected samples, data were pooled from the 10 studies that were analyzed. The prevalence of rapid cycling averaged 29.6% among women and 16.5% among men—a modest 1.79-fold difference—with an average within-study rate ratio of 1.94 (SD=1.06). The results indicate that the prevalence of rapid cycling is evidently much less excessive among women with bipolar disorder than is widely believed.

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Posttraumatic Stress Disorder in the Adult Offspring of Holocaust Survivors

TO THE EDITOR: I thank Rachel Yehuda, M.D., and colleagues for their excellent structured clinical assessment of trauma exposure, posttraumatic stress disorder (PTSD), and other psychiatric disorders in a group of adult offspring of Holocaust survivors and demographically matched comparison subjects (1). The methodological soundness of their study, which addresses the selection bias criticism of previous studies (2), supports the validity of their finding that there are adverse effects in the offspring of Holocaust survivors compared to a comparison group.

How might their data generate further research? How might it begin to inform our clinical work and health care policy? We need to further progress from the belief that PTSD only occurs as a natural response to horrendous events. We need to further research why some individuals develop PTSD and others do not (3).

As Dr. Yehuda and colleagues emphasize, defining groups at high risk for PTSD furthers this research because the subsequent study of these high-risk groups "permits more effective identification of vulnerability factors." Likewise, studying low- or nonrisk groups—i.e., those who are exposed to a traumatic event but do not develop PTSD or thrive regardless or because of the experience—would be enlightening. The data presented in Dr. Yehuda and colleagues' article are hypothesis generating and beg further research.

On one hand, the children of Holocaust survivors, versus the comparison subjects, have a significantly higher current and lifetime prevalence of PTSD and other psychiatric disorders. What would explain this difference? There was no significant difference of lifetime traumatic events between the offspring and comparison groups. The findings of this study demonstrate a higher vulnerability in the adult children of Holocaust survivors. What would cause this vulnerability? What degree of the variance might be genetic versus nongenetic? What is the mechanism of the nongenetic intergenerational transmission that might produce this vulnerability? Future studies could test various hypotheses. Although in this study, "all subjects were born at least 1 year after the end of World War II," and seven offspring had only a father who was a survivor, are there intrauterine effects of maternal exposure to a traumatic event and its aftermath during gestation that sensitize the fetus? Do these parents lack the ability to sufficiently nurture their children because of the effects of the Holocaust on themselves? To explore these questions, we need to have data on the characteristics of the parents (4). Is the transmission effected through learned behavior? Are the children traumatized by hearing parental stories of the Holocaust and witnessing the chronic suffering of their parents? In this study, there was no comparison group consisting of offspring raised apart from their Holocaust survivor parents by individuals who were not Holocaust survivors.

On the other hand, why do 69% of the offspring (a high-risk group) not develop PTSD? What is different about this subset of the offspring group compared to the subset that develops PTSD? What is protective for them? Furthermore, that there are "those for whom a non-life-threatening event was the most distressing although there was a life-threatening event" (comparison group and offspring group 2) is fascinating. Why would someone who experienced a life-threatening event endorse a non-life-threatening event as being more distressful? What might we learn from this group about subjectivity and cognitive appraisal of the experience of both stressful and traumatic life events?

Regarding clinical implications, this study underscores the importance of screening questions during initial psychiatric assessments that not only ascertain whether a patient has experienced trauma but also whether a patient's parents have experienced trauma. Undoubtedly, we must consider intergenerational factors in understanding and treating our patients.

Finally, Dr. Yehuda et al.'s study and studies like it remind us about the importance of allocating health care dollars and developing prevention and treatment programs for high-risk groups vulnerable to developing PTSD.

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JOSEPH C. NAPOLI, M.D.
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Dr. Yehuda Replies

TO THE EDITOR: In his letter, Dr. Napoli raises a series of very important questions regarding the putative etiology of vulnerability factors for PTSD. Each of the questions raised is empirical and can be addressed with systematic research. Ongoing work in our laboratory aims to elucidate differences between vulnerable and less vulnerable children of Holocaust survivors by exploring psychological and biological characteristics of the offspring as well as their parents. Dr. Napoli is correct in underscoring the importance of adoption studies, which, although difficult to perform, would shed light on the nature as opposed to nurture aspects of the intergenerational transmission of PTSD.

This exciting area of research is in its infancy, and we look forward to future findings.

RACHEL YEHUDA, PH.D.
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Length of Therapy for Depression Treatment

TO THE EDITOR: I read with interest the recent article by Frederick W. Reimherr, M.D., and colleagues (1) and congratulate the authors for studying the clinically important topic of optimal length of therapy for the treatment of depression.

The value of this contribution is lessened, however, by their failure to address the risks associated with continuation therapy. Other reports of antidepressant continuation therapy (2–5) have included an assessment of adverse experiences, often with comparisons of adverse experiences occurring during acute therapy and long-term treatment. Data regarding adverse experiences are as helpful to the clinician as are descriptions of efficacy parameters.

As the authors mention in their introductory remarks, patients may be reluctant to participate in long-term medication therapy out of concern for side effects. I question how the authors can adequately determine the optimal length of therapy without an assessment of treatment risks and the hope that future studies balance education about the risks involved with information regarding benefits.

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JOHN TRAVERS, M.D., M.P.H.
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Dr. Reimherr Replies

TO THE EDITOR: The focus of our article was on the optimal length of therapy required to reduce the risk of relapse, which, as Dr. Travers points out, is not the same as the optimal length of therapy, more broadly defined. I strongly agree that determining the optimal length of treatment for depression involves balancing risks and benefits. Indeed, because the issue of safety and tolerability during long-term fluoxetine administration is so important, we have addressed these issues in great detail at several scientific meetings (unpublished presentations by Michelsen, 1997, and Beasley, 1998) and in publications (1–3).

Additionally, Eli Lilly and Company made the complete data set available to each of the five principal investigators (J.Z., J.D.A., F.M.Q., F.W.R., and J.F.R.) for further analysis. The data set could be used for whatever analysis they decided to pursue. This degree of openness is highly unusual in industry-sponsored studies.

This article focused on a comparison of the three points in time in which patients were randomly crossed over from drug treatment to placebo. This narrow comparison helped produce a significant and succinct set of study data. A very pertinent question that might have been posed by Dr. Travers was whether there were unique side effects or risks associated with each of these three crossover points. So far none has been identified.

Finally, to summarize our findings with respect to risk, the data strongly suggest that long-term therapy with fluoxetine is well tolerated and that the risks of early discontinuation of therapy (i.e., the consequences of depressive relapse) far outweigh the risks related to adverse events. All common adverse events specific to fluoxetine treatment during the initiation of therapy declined significantly over time, and

previously uncommon categories of adverse events did not become common late in treatment (1).

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Antidepressant-Benzodiazepine Combination Therapy

TO THE EDITOR: Ward T. Smith, M.D., and his colleagues' (1) recent randomized controlled trial of fluoxetine and fluoxetine plus clonazepam represents an important contribution to the problem of antidepressant-benzodiazepine combination therapy for major depression, which is widely practiced in the real world but may not have a solid evidence base. The editor of the *Journal,* Nancy C. Andreasen, M.D., Ph.D., called the rapidity of the response to this combination therapy striking.

Dr. Smith et al.'s review of the extant literature on this topic, however, is slanted. The authors cite four randomized controlled trials in which they claim to have demonstrated positive results for a combination therapy of tricyclics and benzodiazepine. There are many ways that the experimental therapy can be better than the control therapy, but when we limit ourselves to the primary end point measure of depression, at least one (2) and possibly two more (3, 4) of these four did not report any positive results. More important, a systematic search of MEDLINE revealed at least five more relevant randomized controlled trials, three of which were negative (5–7), and another randomized controlled trial that reported significant worsening of depression upon discontinuation of benzodiazepine after successful combination therapy.

The effectiveness of a treatment should be judged on the basis of the totality of the evidence available to humankind, because any one randomized controlled trial, even when not subject to publication bias, is always subject to random variation, and if you conduct enough trials, there will almost always be those with positive results. The researchers need to conduct their own study and allow readers to view it under the appropriate perspectives.

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TOSHIAKI FURUKAWA, M.D., PH.D.
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Dr. Smith and Colleagues Reply

TO THE EDITOR: Dr. Furukawa is justified in calling our attention to negative results in some studies of benzodiazepine when used as monotherapy or to augment tricyclic antidepressant therapy in the treatment of major depression. In retrospect, it may have been desirable to broaden the context of our study of clonazepam's augmentation of fluoxetine, as he suggested, although it was not our intention to present a comprehensive review of the literature. Instead, we wished to point to some successes in the use of benzodiazepine in treating depression as a part of the basis for extending this practice to the augmentation of selective serotonin reuptake inhibitors. We are not advocating a return to benzodiazepine augmentation of tricyclic antidepressants nor do we recommend benzodiazepine monotherapy in treating depression, even though the latter is not uncommon and may often be successful—for example, when agitated depression has been misdiagnosed as an anxiety disorder. Our highlighting of some positive results of benzodiazepine therapy in the treatment of depression served as a prelude to our research with clonazepam and suggested a more attractive risk-reward ratio concerning this class of drugs. It is our view that, on balance, contemporary negative consensus about the use of benzodiazepines in the treatment of depression has been excessive.

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PETER D. LONDBORG, M.D.
VINCENT GLAUDIN, PH.D.
JOHN R. PAINTER, PH.D.
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Interrater Agreement Among Psychiatrists Regarding Emergency Psychiatric Assessments

TO THE EDITOR: We read with great interest the article by Bruce B. Way, Ph.D., and colleagues (1) regarding poor assessment reliability among psychiatrists in the emergency room setting. In the discussion, the authors suggested that the development of a screening tool with structured clinical interview characteristics that might be used more reliably in

this setting would be useful. We have recently published data on just such a brief scale that is designed to be used in emergent psychiatric intake settings to determine medical necessity (2).

This brief, 11-item scale covers most of the items examined in Dr. Way et al.'s study (psychosis, depression, suicidality or homocidality, hostility or aggression, uncooperativeness, treatment noncompliance, substance abuse, physical dysfunction, role dysfunction, and social support), and it is interesting that it rates them on a similar 0–6 Likert scale. Reliabilities were originally reported for only the three subscales that emerged from factor analysis in the published article (0.96, 0.92, 0.79), but we reanalyzed the items individually, and they showed interrater reliabilities that, except for homicidality (0.28), ranged from 0.68 to 0.88. Reliability was facilitated by the use of behavioral descriptor anchor points for each pair of 0–6 ratings (mild=1–2, moderate=3–4, severe=5–6). This type of scaling method, originally used by Bigelow and Berthot (3) with the Psychiatric System Assessment Scale (3), has been used for a larger inpatient scale at our facility (4), developed as a modification of the Psychiatric System Assessment Scale, and has facilitated accurate and reliable ratings in our clinical setting. We also demonstrated that this medical necessity scale was valid on the basis of correlations with subsequent inpatient ratings that were carried out independently by different clinicians, including inpatient length of stay, and on the basis of its ability to discriminate between patients requiring and not requiring hospitalization.

We would like to make an important point regarding implementation of such a scale: while a scale with 11 items may seem rather brief, it has been an onerous task for our emergency staff over the past year of implementation. However, we have been successful and have shown an internal consistency reliability of 0.78 with our first 168 subjects. The authors' proposal to use "a small number of questions for each dimension" would result in a scale several times larger than ours. While such a scale would certainly be more comprehensive, it would be unlikely to work well and be hard to implement in a busy clinical setting.

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PETER P. ROY-BYRNE, M.D.
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Dr. Way and Colleagues Reply

TO THE EDITOR: We are pleased that Drs. Roy-Byrne and Russo found our report on psychiatric emergency room decisions to be of interest and applaud their efforts to develop a scale that can be used as a screening tool in such settings.

Their preliminary results concerning scale reliability and accuracy are encouraging. We hope that similarly strong results are obtained when use of the scale is extended to a wider variety of clinical settings with diverse populations of patients and raters. We have found that videotaped interviews can be an effective method for assessing interrater reliability across settings.

We are concerned, however, about the confusion regarding what the goals of a psychiatric emergency service and the associated standard of care should be. Is the emergency assessment driven by therapeutic, legal, or economic considerations? Can any limited or triage screening consistently serve all of these purposes? For example, can a defensible suicide risk assessment be accomplished without a reliable diagnostic assessment? Is it a good, thorough assessment, leading to prompt treatment, or is it a decision based on legal considerations or medical necessity? We think that there may need to be a categorization of psychiatric emergency service capabilities, as previously proposed by the American Medical Association (1), that takes these different goals into account.

Drs. Roy-Byrne and Russo's last comment points to the difficulty in the context of psychiatric emergency assessments of developing support tools for decision making that are simultaneously reliable, accurate, and practical. Longer scales are almost always more reliable than shorter ones, but they are also less likely to be used carefully—or used at all. Given the importance of the decisions that are made in psychiatric emergency settings, however, all trade-offs between time and quality of information need to be weighed carefully.

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Informed Consent and Psychiatric Patients

TO THE EDITOR: The article by Donna A. Wirshing, M.D., and colleagues (1) and the related editorial by Paul S. Appelbaum, M.D. (2), underscore the salience of the informed consent process in research involving psychiatric patients. Dr. Wirshing et al. provide new data on the ability of 49 patients with schizophrenia at a Veterans Administration Medical Center to learn and remember information about proffered medication research studies. It is indeed reassuring that these patients felt informed and performed well on a test of the relevant material presented to them.

This article and its companion editorial address only the informational component of informed consent; there remains another critical component about which empirical data are still lacking. The term "voluntary," as applied to informed consent, refers to the capacity to act without undue influence or coercion (3). The importance of choice in this context has historical roots dating to the seventeenth-century concept of free will as essential to our status as human beings. That citizens, patients, and prisoners have at various

times been commandeered as unwilling subjects in medical research is well documented (4–6).

The challenge for our profession today is to validate the informed consent process by protecting potential subjects from the possibility of unwitting exploitation by well-intended but overzealous research clinicians. To do so, principal investigators and institutional research boards should consider explicitly the following factors influencing volition: who is responsible for subject recruitment (reflecting an awareness of the transference effect of the treating psychiatrist as researcher), what special status and benefits are offered uniquely to subjects (including monetary compensation, free care, and prolonged hospitalization), and who will supervise and intervene on behalf of the patient in the event that the patient's competence erodes during the course of the study.

The articles in the November 1998 issue are a timely reminder that the 50 years of progress in the scientific conduct of controlled drug trials for schizophrenia (7) should be matched by comparable advances in research ethics.

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TO THE EDITOR: Both the editorial by Dr. Appelbaum and the article on informed consent procedure by Dr. Wirshing and colleagues raise serious concerns. The approach presented in these two articles is technical and nominalistic. It appears to be based on an assumption that understanding the information in a consent form is equivalent to the ability to give consent.

Dr. Wirshing and colleagues applied a rigorous procedure to maximize patients' potential for understanding and to assess their ability to understand. In their Method section, the authors wrote about understanding, comprehension, knowledge, and the ability to grasp. They kept administering the Informed Consent Survey "until the patient answered all items of the survey correctly, *at which point the informed consent form was signed*" (italics added) (p. 1509). Evidently, the procedure was not about assessment of comprehension only. It was about securing the consent. Despite their acknowledgment of "a phase for decision making" (p. 1508), the authors reduced the consent process to a phase in which information is transmitted.

However, is being able to learn the "correct" answers to a series of questions by heart the same as being capable of giving informed consent to having one's treatment possibly postponed or significantly altered?

Dr. Appelbaum writes that "even substantially impaired understanding does not mean that a person with schizophrenia cannot comprehend information about a research project" (p. 1487). Well, is the ability to comprehend information about a research project the same as the ability to appreciate the consequences of a decision to partake in this research or to refuse participation in it? Is it mainly the impairment of understanding that affects informed decision making in patients with schizophrenia?

Many of these patients, frequently those with unaffected intelligence, understand the information provided or, at least, are able to comprehend and memorize it after repetitive teaching. But what about their ability to appreciate the meaning of their choice, the value of the consequences of a decision that may be based on peculiarities of their delusional thinking and hallucinatory perceptions?

Such an impairment does not necessarily interfere with the ability to understand the information, as Dr. Wirshing and colleagues found, not surprisingly, and presented in table 2 of their article. But the very decision (to consent or not) can still be based on reasoning stemming from psychopathology, reasoning so alien to and distant from those mental processes that allow for appreciation of the real consequences of such a decision.

The ability to understand the information is only one of the capacities necessary to give informed consent—a necessary one, but not sufficient.

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St. Thomas, Ont., Canada

Dr. Wirshing and Colleagues Reply

TO THE EDITOR: We found the letters from Drs. Eth and Wystanski challenging and worthy of thought and a reply. In general, the more discussion that is generated around issues related to informed consent in treatment and research, the better our field will become. Although our article did not address the component of consent on which Dr. Eth comments, our future research is pursuing this very avenue. Dr. Eth comments on the impact of transference in influencing the decision to participate in research. While they were undoubtedly true for our population, transference issues influence patients treated by other medical specialists as well. There is little difficulty, for example, in recruiting heart transplant patients for studies of medications to prevent rejection of their newly transplanted hearts. Patients who have undergone life-saving transplant surgeries will naturally be very willing participants in studies suggested to them by their surgeons. We scrutinize the ability of subjects with schizophrenia to give informed consent because they are generally perceived to be members of a vulnerable population. But are they in fact more vulnerable and therefore more exploited than other medical patients with incurable illnesses (e.g., AIDS, various malignancies, Alzheimer's disease, Parkinson's disease)?

Dr. Wystanski correctly points out that understanding the information conveyed in consent forms is not the only capacity required to give informed consent. Our goal is to teach our patients to become effective and knowledgeable advocates of their own participation (or nonparticipation) in our research protocols. Understanding the details of the protocol is simply the first small step toward this end. One method that we are developing is a CD-ROM (sponsored by the National Institute of Mental Health; Jim Mintz, principal investigator) that will engage medical and psychiatric patients interactively in a learning process so that they will be able to acquire more information about the associated benefits and

risks before deciding to become involved in treatment research. Additionally, we will provide these patients with a workbook so that they can be active learners, and we will assist them with decisions about their own treatment. We realize that it is vitally important to provide the best care for our patients and to engage them in clinical trials that will improve not only their treatment but the treatment of other patients with the afflictions from which they suffer. Our program of research, now under way in earnest, is aimed at improving the consent process for patients with a wide variety of psychiatric and medical disorders.

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Suicidal Threats and Therapists' Helplessness

TO THE EDITOR: Thomas G. Gutheil, M.D., and Diane Schetky, M.D. (1), provide useful suggestions for the clinical management of time-based and contingent suicidal intentions. The authors recommend that therapists share their feelings of helplessness with patients: "shared helplessness may provide a pathway to empathic connection" (p. 1506). It may reinforce, however, the patients' sense of control over therapists. For some patients, a time-based and contingent suicidal threat may represent an attempt to dominate therapists. Making therapists feel helpless may allow patients to not only disown this feeling in themselves but to also feel power over the therapists. This defense may be considered equivalent to a mechanism of projective identification. The interpretation of this defense may lead patients to acknowledge their own helplessness, to stop fearing retaliation from therapists, and to better benefit from support.

The authors report that, for some patients, death takes on "the qualities of an object relationship that, paradoxically, permits continued living" (p. 1503). In a similar vein, we have found that the exploration of the meanings of death and suicide in these cases suggests the role of splitting, through which suicide is fantasized about as both a means of getting rid of the bad parts of the self and the object and being reunited with the good object (2). The interpretation of the splitting defense may, without challenging directly this protective relationship, gradually lead to an alleviation of suicidal drive.

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HENRI SZTULMAN, M.D., PH.D.
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Drs. Gutheil and Schetky Reply

TO THE EDITOR: We greatly appreciate—and find ourselves largely in agreement with—the dynamic insights of our French colleagues, Dr. Chabrol et al. We, too, have observed the splitting phenomenon, wherein suicide is an attempt to destroy the bad parts of the self rather than simply to die.

We were attempting to counsel therapists to avoid power struggles (e.g., by acknowledging realistic limits on the ability to prevent suicide) more than to convey an attitude of helplessness that, as the letter notes, may promote another of the patient's attempts to control the therapist (or other persons or fate itself) through a projective identification mechanism. We did imply that the patient's feeling of helplessness may lead him or her to resort to this defense.

Finally, we are grateful for the letter writers' obviously close and thoughtful reading of our article.

THOMAS G. GUTHEIL, M.D.
DIANE SCHETKY, M.D.
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Typical Neuroleptics and Increased Subcortical Volumes

TO THE EDITOR: With regard to Raquel E. Gur, M.D., Ph.D., et al.'s (1) demonstration that higher doses of typical neuroleptics are associated with increased subcortical volumes, Nancy C. Andreasen, M.D., Ph.D., (2) wrote that 10 years ago, "no one thought that treatment could produce structural changes in the brain!" (p. 1658).

This is not the case. In 1977, Jellinger (3) reviewed the extensive literature on neuropathological changes induced by chronic neuroleptic therapy and noted that under some circumstances, neuroleptics could lead to changes that later might result in irreversible damage, especially in the caudate. As concerns over tardive dyskinesia mounted, more investigators began to pursue the association between structural brain changes, neuroleptics, and dyskinetic movements. By 1987, Waddington et al. (4) noted that eight of 11 systematic studies had found evidence of structural brain changes associated with neuroleptic-induced involuntary movements. In 1992, Dean and Borchardt (5), in a lengthy examination of the risks and the benefits of neuroleptic therapy, reviewed multiple studies performed over the previous two decades that documented ventricular enlargement, striatal atrophy, cellular degeneration, and cognitive impairment in some patients treated with neuroleptics, often in association with tardive dyskinesia.

It seems clear, then, that concerns over structural brain changes induced by neuroleptics have been present for almost three decades. There seems little doubt that such changes are in part responsible for the development of neuroleptic-induced movement disorders and cognitive impairment, although research in this area has been complicated by studies—too numerous to list here—that clearly show the presence of parkinsonism and dyskinetic movements in neuroleptic-naive patients.

Given these issues, perhaps Dr. Andreasen's editorial comments should have included a question: Why did Dr. Gur et al. fail to include data on the prevalence and severity of abnormal movements in their cohort? Correlative data on the location, severity, and laterality of abnormal movements and anatomical changes surely would have been of great interest.

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