Letters to the Editor

Treatment of Acute Mania With Gabapentin

TO THE EDITOR: Gabapentin, currently marketed as an antiepileptic drug, has been shown to be an effective adjunctive therapy in the treatment of partial seizures with and without secondary generalization (1). The most common side effects are sedation and ataxia (1). Two other antiepileptic drugs, valproate and carbamazepine, have proven effective in the treatment of acute mania in randomized, double-blind, placebo-controlled trials (2), but so far the effectiveness of gabapentin as a treatment for psychiatric disorders has been little studied. Ryback and Ryback (3) reported the successful addition of gabapentin, 1200 mg/day, to a regimen of imipramine in the treatment of behavioral dyscontrol in an adolescent with intermittent explosive disorder, attention deficit hyperactivity disorder, and an organic mood disorder that was secondary to a closed head injury. Conversely, Short and Cooke (4) described the occurrence of hypomanic symptoms after gabapentin, 300 mg/day, was added to a regimen of carbamazepine and lamotrigine in the treatment of a patient with epilepsy. We report here a successful treatment of mania with gabapentin.

Mr. A, a 40-year-old white man with DSM-IV bipolar I disorder and alcohol dependence, was admitted for his first psychiatric hospitalization. In the 4 months before admission, he had experienced severe irritability, violent outbursts, racing thoughts, marked distractibility, greater libido, grandiose and persecutory delusions, less need for sleep (3–4 hours/night without daytime napping), pressured speech, and auditory hallucinations. Similar, although less severe, episodes of these manic symptoms had occurred since the age of 30. His alcohol dependence began at age 35. Mr. A also had experienced a bilateral frontal lobe injury with bilateral intracranial hematomas after a motor vehicle accident 2 years earlier. The intracranial hematomas resolved 1 month after the accident without surgical drainage. Results of an EEG during sleep-deprived conditions revealed no abnormality, and earlier EEG studies performed after the accident that were not done during sleep-deprived conditions revealed no evidence of paroxysmal activity. A computerized tomography scan of his brain revealed mild bilateral frontal atrophy. Results of neuropsychological tests revealed only mild cognitive impairment that was consistent with head trauma, alcohol use, or psychotic mood disorder. Results of laboratory tests performed at admission noted elevated hepatic transaminase concentrations, mild thrombocytopenia, and elevated prothrombin time.

Mr. A refused a trial of lithium, and we were reluctant to initiate a regimen of valproate or carbamazepine given his impaired hepatic function, thrombocytopenia, and elevated prothrombin time. After written informed consent was obtained, a regimen of gabapentin, 900 mg/day, was initiated and increased daily by 900 mg until a dose level of 3600 mg/day was achieved after 4 days. The Young Mania Rating Scale was administered daily by a blind rater to assess manic symptoms. Mr. A's score on the Young Mania Rating Scale decreased from 34 at baseline (before gabapentin administration) to 17 after 10 days of gabapentin monotherapy. Specifically, Mr. A displayed reductions in irritability, racing thoughts, pressured speech, behavioral disorganization, auditory hallucinations, libido, and insomnia (with sleep normalizing to 8 hours/night). Both Mr. A and his wife reported that his improvement was dramatic, and no side effects were reported.

Although anecdotal, the response of this patient's manic symptoms to gabapentin monotherapy suggests that gabapentin may have antimanic efficacy. The promising response of this patient's manic symptoms to gabapentin suggests that further study of this agent in the treatment of acute mania is warranted.

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SEAN P. STANTON, B.A.
PAUL E. KECK, JR., M.D.
SUSAN L. MCELROY, M.D.
Cincinnati, Ohio

Systematic Desensitization as an Alternative Exposure Strategy for PTSD

TO THE EDITOR: Although intensive exposure therapy for veterans with combat-related posttraumatic stress disorder (PTSD) has shown promising results (1), this treatment strategy may not be applicable in every case (e.g., patients with heart disease). Systematic desensitization (2), through graduated rather than intensive exposure, is a widely accepted treatment for phobias and may offer a reasonable alternative strategy for engineering therapeutic exposure to traumatic stimulus cues in individuals with PTSD. This approach takes a learning theory perspective in which extinction of a conditioned fear response is achieved through graduated exposure to the anxiety-producing stimuli while inducing a physiological state that inhibits anxiety (e.g., deep muscle relaxation). The reciprocal inhibition of the anxiety response during exposure should weaken the relationship between the trauma-related cues and the conditioned response, thus reducing the anxiety responses. Because most of the symptoms of PTSD are related to maladaptive fear and anxiety associated with the trauma, reduction of this fear and anxiety reaction leads to improvement in a number of areas. Unfortunately, although

single case studies have demonstrated the potential of systematic desensitization (3, 4), to date no controlled studies have examined its efficacy for treatment of PTSD. We present a case study for illustrative purposes.

Mr. A was a 34-year-old, recently divorced black man with a 10-year history of PTSD, major depression, panic attacks, guilt, and dissociative symptoms that resulted from a military training accident in which he was severely injured and a soldier under his command was killed. His psychiatric symptoms led to marital problems and divorce (and subsequent estrangement from his two children), as well as occupational troubles that resulted in a 12-month layoff from his job with the post office. He was treated first in a private practice setting and then at a veterans' outpatient clinic for 4 years. During this time, a number of treatment approaches were attempted, including pharmacological treatments (e.g., buspirone, trazodone, bupropion, diazepam, chloral hydrate, haloperidol), two psychiatric hospitalizations, marital counseling, cognitive treatment of depression, and intensive exposure therapy. Mr. A's symptoms did not improve with treatment, and he had a particularly strong reaction to his lone intensive exposure therapy session, during which he became physically ill and terminated the session early. He reported that the combination of psychotherapy and psychiatric medications allowed for some management of symptoms but did not lead to a substantial reduction of distress or an increase in behavioral or emotional control.

After four sessions of progressive muscle relaxation training and one session that was devoted to developing a fear hierarchy of trauma cues, 15 weekly 50-minute sessions of systematic desensitization were conducted. Each systematic desensitization session began with 5–10 minutes of progressive muscle relaxation, followed by graduated exposure to imaginal trauma cues on the fear hierarchy concurrent with the state of relaxation, which was maintained throughout. After 4 months, Mr. A reported substantial decreases in intrusive symptoms, physiological reactivity, panic attacks, and depressed mood, and his sleep and energy levels improved. Anxiety reduction was substantiated by his score on the Hamilton anxiety scale, which fell from 43 to 22. In addition, toward the end of treatment he returned to work full-time at the post office, developed a stable romantic relationship, and resumed the role of responsible father to his two children.

Although systematic desensitization is a widely used behavioral treatment for phobia, almost no empirical evidence currently exists to suggest how this treatment may be successfully engineered with PTSD patients and whether it would be efficacious. The reduction of PTSD and anxiety symptoms in this patient was attributed to the weakening of the conditioned fear response, achieved by reciprocal inhibition of the patient's anxiety during imaginal exposure to trauma-related cues while he was deeply relaxed. It is believed that systematic desensitization may be an effective alternative to intensive exposure therapy for some cases of chronic PTSD, and further research should be conducted to determine the degree of its efficacy and to determine for which patients it would be most suitable.

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B. CHRISTOPHER FRUEH, PH.D.
MICHAEL A. DE ARELLANO, M.A.
SAMUEL M. TURNER, PH.D.
Charleston, S.C.

Nefazodone-Induced Hypoglycemia in a Diabetic Patient With Major Depression

TO THE EDITOR: Various classes of antidepressants are known to affect the serum glucose level of depressed patients who have diabetes mellitus. The monoamine oxidase inhibitors and the selective serotonin reuptake inhibitors (SSRIs) may decrease serum glucose levels by 35% and 20%, respectively, and tricyclic antidepressants have been noted to increase serum glucose levels by up to 150% (1). Nefazodone is an antidepressant that also appears to affect glucose regulation, as the following case demonstrates.

Ms. A, a 54-year-old married woman, was referred for evaluation and treatment of major depression. Six years earlier, she had been diagnosed with diabetes mellitus that did not require insulin, so she was given an oral hypoglycemic agent. Three years later, insulin became necessary to control the diabetic symptoms. Ms. A had a history of at least two episodes of major depression. At her initial visit, she weighed 240 pounds. Her morning, noon, and evening doses of regular insulin were 40, 30, and 30 units, respectively, along with 50 units of NPH insulin at bedtime. She was prescribed nefazodone, 100 mg b.i.d., for treatment of her current depressive symptoms. At her next visit 1 week later, she reported having experienced two hypoglycemic episodes. Her serum glucose levels on the fifth and sixth days after the initiation of nefazodone treatment had been 65 mg/dl and 41 mg/dl, respectively. Because she had driven home from work with symptoms of hypoglycemia, she was instructed not to drive when her serum glucose level was less than 70 mg/dl. She had contacted her endocrinologist, who had decreased her noon, evening, and bedtime doses to 25, 25, and 35 units, respectively. She reported improved sleep, no crying spells, and a decrease in appetite. Her nefazodone regimen was increased to 150 mg b.i.d.

The following week, her blood sugar level fluctuated between 60 and 170 mg/dl. Her endocrinologist decreased her noon, evening, and bedtime doses an additional five units. Her depressive symptoms continued to improve, and her nefazodone dose was increased to 200 mg b.i.d.

At the 1-month follow-up examination, both Ms. A and her endocrinologist were pleased with her progress. The morning insulin dose was lowered to 15 units, and the noon and evening doses were decreased an additional five units; Ms. A's weight fell to 235 pounds. She began to exercise and continued to have a decrease in appetite, and the depressive symptoms continued to improve. After 8 weeks, Ms. A noted that she felt in control of her eating habits and continued her daily walking. Her weight had fallen to 233 pounds, with the only change in her insulin regimen being a five-unit reduction at noon.

One year later, Ms. A weighed 212 pounds. Her insulin regimen at this time consisted of morning, noon, and evening doses of 10, 5, and 10 units of regular insulin, respectively, and 25 units of NPH at bedtime. Her depression has remained in remission.

The prevalence of depression in patients with diabetes varies from 8.5% to 27.3% (1). It appears that treating this patient's major depression substantially improved her ability to manage her diabetes. The patient noted that she was able to control eating habits and increase dietary compliance and exercise. Nefazodone and SSRIs do not cause the carbohydrate craving or weight gain that are commonly associated with tricyclic antidepressants. Additionally, nefazodone may indirectly act to reduce plasma glucose because of its increase in serotonin. Serotonin reuptake blockers have been noted to have a dose-dependent significant decrease in plasma glucose (2). An abrupt drop in serum glucose level, as experienced by this patient, could have serious consequences, especially while driving. Potential benefits and adverse effects of antidepressant treatment should be discussed carefully with all patients. Patients with diabetes mellitus who are treated for depression with nefazodone should be advised of possible changes in serum glucose level.

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JULIA K. WARNOCK, M.D., PH.D.
FAYE BIGGS
Tulsa, Okla.

Compulsive Computer Use

TO THE EDITOR: Recently, numerous popular media stories have appeared that describe people who spend excessive time using computers. Poorly controlled computer use appears to be compulsive. It takes precedence over work and family in affected individuals. The subject described here excessively used the computer despite substantial negative consequences.

Adam was raised in an intact, middle-class family. He had normal emotional and social development and graduated from high school with a 3.5 grade point average. During his first college semester, he communicated with his hometown girlfriend on-line for 4 hours a day. His semester grade point average was 3.0. In the second semester, he skipped classes to increase on-line time. He would use his roommate's modem, and two sources reported that Adam's on-line time came to average over 10 hours a day! His major activity was frequenting electronic bulletin board forums on mountain biking and body piercing.

Gradually, Adam became more socially isolated. When his roommate requested a 2-hour on-line time limit, Adam purchased his own modem and continued to monopolize the telephone. The two separated because of increasing tension. Adam's semester grade point average was 1.9. That summer he had no access to the Internet so he played video games instead. Excessive usage resumed the next semester. His new roommate, who was also an Internet user, would wake up at 1:30 a.m. to log on himself after Adam had finished. When denied access because of system shutdowns, Adam felt anxious and irritated. His semester grade point average fell to 0.6, which resulted in academic probation.

Adam would have been expelled the following semester had he not experienced a severe traumatic injury sustained while riding his bicycle down stairs. He had fractured his skull, which necessitated a medical withdrawal that semester. He returned to school, but his Internet access was limited because his modem was broken. He reported attending more classes and having initiated an intimate relationship. In evaluation, he demonstrated a history of impulsive behavior but no established DSM-IV axis I or II diagnosis.

Impulse control disorders, per DSM-IV, are the "failure to resist an impulse . . . to perform an act that is harmful." They are characterized by an increasing tension before committing the act, then pleasure and, possibly, guilt afterward. This case demonstrates impaired academic and social functioning due to excessive recreational computer use that involved tension and pleasure. The subject's usage patterns were situational, occurring only with ready computer access. This is also the case with other compulsive disorders, such as gambling. One experiences a reduced urge to act impulsively when the preferred expressive method is unavailable.

We encourage other clinicians who encounter this phenomenon to report their experiences.

TARA J. BELSARE, M.D.
GARY R. GAFFNEY, M.D.
DONALD W. BLACK, M.D.
Philadelphia, Pa.

Risperidone Overdose

TO THE EDITOR: Risperidone is a benzisoxazole compound that was approved for use in the United States in 1994. It has potent serotonergic and dopamine receptor blockade. It also produces antagonism of α-adrenergic and histamine receptors. The half-life of risperidone is 3.6 hours, and its active metabolite, 9-hydroxyrisperidone, has a half-life of 22 hours. Risperidone and haloperidol have equal antipsychotic efficacy, but risperidone causes fewer extrapyramidal side effects. Full antipsychotic efficacy with few side effects (such as extrapyramidal symptoms, seizures, sedation, hypotension, or difficulty in concentration) is manifest, on the average, at a dose of 6 mg/day. We report a case of risperidone overdose.

Ms. A was a 35-year-old white woman with a long-standing history of schizophrenia who presented to our emergency room about 20 minutes after she had taken 228 mg of risperidone (57 4-mg tablets). She was awake, alert, and oriented to time, place, and person but tearful and depressed. It was of interest that for the first time in many years her auditory hallucinations had disappeared and did not return for 30 hours. Results of a physical examination revealed no abnormality except for akathisia. Her blood pressure on admission was 102/60 mm Hg and ranged from 104/66 mm Hg to 130/80 mm Hg throughout her 8-day stay in the hospital. Her pulse ranged from 72 bpm to 96 bpm and remained in sinus rhythm. The only abnormal laboratory result was a mildly elevated lactic dehydrogenase level of 264 μ/liter. No lavage was performed, but she was given an oral 50-g dose of activated charcoal with sorbitol, and four 25-g doses of activated charcoal (one

dose every 4 hours). Treatment with risperidone, 3 mg b.i.d., was resumed 48 hours after her overdose, and her akathisia, depression, and hallucinations improved.

We could find only one previous report (1) of a risperidone overdose, in which a 29-year-old man came to the emergency room 45 hours after taking 240 mg of risperidone (120 2-mg tablets). He was alert, oriented, and physically normal. Systolic blood pressure, the only one reported, was 132 mm Hg, and his pulse was 68 bpm. His ECG reading was abnormal (QRS=112 msec, QT=565 msec) but returned to normal in 12 hours. The only laboratory abnormalities were serum levels of sodium (125 mmol/liter) and potassium (2.9 mmol/liter).

These two suicide attempts by risperidone overdose (with 228 and 240 mg, respectively) indicate that this antipsychotic medication is relatively safe. The previously published case (1) suggests that cardiac monitoring is indicated, especially in the early hours after ingestion.

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NORMAN C. MOORE, M.D.
PARAM SHUKLA, M.D.
Macon, Ga.

Gaucher's Disease Initially Diagnosed as Depression

TO THE EDITOR: Gaucher's disease is a panethnic, rare congenital glycolipid storage disease identified by reduced levels of the catabolic enzyme glucocerebrosidase (1). Adults may remain largely asymptomatic or develop characteristic bone pain, pathological fractures, or sequelae of organ dysfunction. Although adult type I Gaucher's disease is characterized by its lack of central nervous system involvement, we present a case in which severe psychiatric symptoms were the presenting manifestation.

Ms. A, a 20-year-old white woman, sought medical attention after 4 months of fatigue, easy bruising, and pain in the back and hip that had been refractory to nonsteroidal medications. In addition, she had developed anorexia, weight loss, insomnia, depressed mood, and suicidal ideation. There was no personal or family history of mental illness or alcohol or drug abuse. She was diagnosed with major depressive disorder, and a regimen of paroxetine, 20 mg/day, was started. Results of a physical examination revealed a depressed affect, sallow complexion, and splenomegaly. The neurologic examination was nonfocal. Laboratory examination revealed a leukocyte count of 3500/mm^3, with a platelet count of 67,000/mm^3 and a hemoglobin of 11 g/dl. Results of function tests of the liver, thyroid, and RPR revealed no abnormality, and a urine pregnancy screen was negative. Radiographs of the axial skeleton and technetium bone scan were normal. Bone marrow biopsy demonstrated sheets of lipid-laden macrophages with "crumpled tissue paper" cytoplasmic features that displaced normal hematopoietic elements. Leukocyte acid β-glucosidase level was 0.90/nmol/hour/mg (normal level=1.9–6.5) These features were characteristic of Gaucher's disease.

Treatment with enzyme replacement therapy with alglucerase (mannose-terminated-glucocerebrosidase derived from human placenta) was started. Despite therapy with paroxetine, Ms. A experienced minimal improvement of her depressed mood. For treatment of her pain and depression she was given nortriptyline and an oral regimen of sustained-release oral morphine. She achieved relief from depression and all neurovegetative symptoms at a nortriptyline serum level of 55–65 μg/liter, which is lower than the therapeutic range for depression. After 12 months of therapy (during which time her morphine treatment was discontinued), her bone pain resolved, her CBC count normalized, her splenic volume index decreased 50%, and her depression resolved. She returned to gainful employment.

Clinical suspicion of psychiatric disease in the setting of bone pain, cytopenias, or visceromegaly should prompt a diagnostic evaluation for Gaucher's disease. While brain parenchymal infiltration is not significant in type I disease, Gaucher's disease may induce significant reactive depression. Although compelling societal issues regarding the procurement of alglucerase (the world's most expensive drug [2]) remain problematic, dramatic clinical responses should be expected (3).

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JEANNETTE CLEMONS, M.D.
M. ZUHDI JASSER, M.D.
GARY NOBLE, M.D.
BRIAN P. MONAHAN, M.D.
Bethesda, Md.

Propofol for Sedation During Rapid Opiate Detoxification

TO THE EDITOR: The technique of using the narcotic antagonists naloxone or naltrexone for rapid or ultrashort opiate detoxification of opiate-dependent patients has been described (1–3). To lessen or prevent the discomfort of the withdrawal syndrome, sedatives, including methohexitone (3) and midazolam (1, 2), have been employed. We report here the successful use of intravenous propofol for sedation during rapid opiate detoxification.

Mr. A was a 29-year-old man with no prior addiction treatment history who reported an 8-year history of opiate dependence. He injected $30–$40 worth of heroin per day, a habit that he had tapered down from $60–$80 per day. He denied the use of alcohol, cocaine, sedatives, or marijuana. He smoked 1½ packs of cigarettes per day. There was no other significant medical or psychiatric history. He was admitted to the hospital the day before the detoxification procedure and given clonidine and oxazepam, as needed, to suppress opiate withdrawal symptoms.

At 5:00 a.m. the next morning, Mr. A was given 0.3 mg of clonidine (7 μg/kg), 150 mg of nizatidine, and 10 mg of oral metoclopramide. At 8:00 a.m., he was taken to the postanesthesia care unit, at which intravenous access and

hemodynamic monitoring were established. After initial preprocedure intravenous doses of midazolam, 2 mg, and ondansetron, 8 mg, 1 mg/kg of intravenous propofol was administered, which resulted in slight sedation. Five minutes later the bolus dose of propofol was repeated to deepen the sedation, and a maintenance infusion of 200 μg/kg/min was established. An intravenous bolus injection of naloxone, 10 mg, was then administered, which resulted in the immediate onset of mydriasis, piloerection, a slight increase in pulse and blood pressure, and mild restlessness. After 20 minutes, the propofol infusion was decreased to 100 μg/kg/min for 10 minutes more, then discontinued. A 1-mg challenge dose of naloxone failed to produce any subsequent evidence of increased mydriasis, piloerection, hemodynamic changes, or change in motor activity. Thirty minutes after discontinuation of propofol, Mr. A was awake, fully oriented, and following commands. On a scale of 0–10, he gave his withdrawal symptoms a severity rating of 1. He denied muscle or joint aches, sneezing, or nausea but did complain of some abdominal cramping and a cold feeling. At this point an intravenous challenge dose of naloxone, 2 mg, did not produce a further change in his hemodynamics or opiate withdrawal symptoms. Because of persistent complaints of abdominal cramps, a 40-mg oral dose of dicyclomine was given, which provided some relief. An oral dose of naltrexone, 200 mg, was then given. At this point, 70 minutes had lapsed since the initial propofol dose. Fully recovered from sedation, Mr. A was returned to his hospital room.

The following day, Mr. A reported feeling weak with lingering opiate withdrawal symptoms that on a scale of 0–10, he rated as ranging from 1 to 4. He was discharged that day and lost to follow-up.

Propofol is an intravenous sedative-hypnotic that causes rapid and reliable sedation, is noted for its quick offset and smooth recovery, and has a shorter recovery time than midazolam. Because of propofol's rapid onset and short duration, the dose is easily titrated so as to blunt the dysphoric symptoms that are associated with opiate withdrawal and hemodynamic lability while maintaining amnesia, spontaneous respirations, and intact airway reflexes. While the exact mechanism and utility of rapid opiate detoxification is still unknown, it appears that the use of propofol can substantially decrease the procedure time to about 1 hour.

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PETER A. DEMARIA, JR., M.D.
CARLA RODGERS, M.D.
GREGORY BRACCIA, M.D.
Philadelphia, Pa.

Gabapentin in the Treatment of Bipolar Disorder

TO THE EDITOR: Treatment of patients with bipolar disorder who experience hypomanic or manic episodes usually includes lithium, valproate, or carbamazepine. Certain subtypes of bipolar patients (e.g., those with rapid cycling mood swings and mixed symptoms) may be more difficult to treat (1). Clinicians who treat this patient population would benefit from the availability of additional mood-stabilizing agents.

Gabapentin is an anticonvulsant agent that has recently been approved for the adjunct treatment of patients with partial seizures (2). Since valproate and carbamazepine also have been used to treat patients with partial seizures, one could speculate that gabapentin might have mood-stabilizing properties as well. Since there have been no reports to date of the use of gabapentin therapy for bipolar disorder, we attempted to treat a group of patients with refractory bipolar disorder with gabapentin.

Twenty-eight patients with bipolar disorder were chosen for this study. Written informed consent was obtained from all patients for the use of gabapentin, which had not been approved by the Food and Drug Administration as a treatment for bipolar disorder. The patients ranged in age from 21 to 56 years. There were four men and 24 women; all were treated in a private outpatient setting. Each was diagnosed with a type of bipolar disorder: bipolar I (N=10), bipolar II (N=10), cyclothymic disorder (N=7), or bipolar disorder not otherwise specified (N=1). None of the patients had achieved a satisfactory response to previous treatment with standard mood-stabilizing agents (lithium, valproate, or carbamazepine). Several of the patients required concomitant psychiatric medications while taking gabapentin. These other medicines included antianxiety agents (mostly benzodiazepines), antidepressants, antipsychotics, or other anticonvulsants. None of the patients was eliminated from gabapentin treatment because of a medical condition.

Of the 28 patients treated with gabapentin, 18 had a positive response as judged by both the treating psychiatrist and the patient. As of this writing, the 18 patients had been receiving gabapentin for at least 9 months (N=10), 6 months (N=6), or 1–3 months (N=2). Gabapentin treatment was discontinued in 10 patients because of inadequate clinical response (N=2) or intolerable side effects (N=8). The most common side effects were oversedation or overactivation, and two patients had to discontinue gabapentin because of greater rapid cycling.

This naturalistic study resulted in enough positive clinical responses to warrant more formal research investigations with blind ratings, random patient assignment, and control group comparisons. If these encouraging results are duplicated by others, gabapentin should be considered for patients with refractory bipolar disorder who do not respond to standard mood-stabilizing agents.

Gabapentin is a relatively safe medication according to the neurological literature (3). It is not metabolized by the liver and does not bind to plasma proteins. It seems to be tolerated well in most seizure patients who are also taking valproate and carbamazepine. It is excreted almost entirely by the kidney; patients with impaired renal functioning should be monitored closely. The risk of serious drug-drug interactions with nonseizure medicines remains to be determined. The recommended daily dose range for seizure patients is 900 mg–1800 mg. The average dose used to treat our psychiatric patients was 539 mg (range=33–2700). Determination of the standard therapeutic dose for psychiatric patients will require additional trials in more formalized research settings.

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CHARLES B. SCHAFFER, M.D.
LINDA C. SCHAFFER, M.D.
Sacramento, Calif.

Nemonapride for the Treatment of Schizophrenia

TO THE EDITOR: Recently, a novel neuroleptic, nemonapride, was manufactured by Yamanouchi Pharmaceuticals and released in Japan. This benzamide derivative (YM-09151-2) is a potent and highly selective dopamine D_2 antagonist (1). In an early clinical trial, this drug was shown to be effective against positive symptoms of schizophrenia (2). We report here an open trial study on the use of nemonapride in the treatment of schizophrenia with particular interest in negative symptoms.

The subjects were 19 adult in- or outpatients with a DSM-IV diagnosis of schizophrenia. The mean age of the patients was 37.7 years (SD=15.2; range 16–71), and the average duration of illness was 148 months (SD=171). After written informed consent to participate was obtained from all subjects, oral nemonapride was administered at daily doses of 3–50 mg (mean maximal dose=18.5 mg) during the 8-week trial. Scores on the Global Assessment Scale substantially improved for approximately 73% of the patients at week 8, and nine patients were rated by their primary clinicians as extremely or moderately improved. Scores on individual items of the Brief Psychiatric Rating Scale (BPRS) were reduced by week 8, and statistically significant reductions (paired t test, $p<0.05$) were observed in the ratings of five BPRS items (somatic concern, anxiety [psychic], emotional withdrawal, depressive mood, and hallucinations). The Scale for the Assessment of Negative Symptoms was given to half of the patients, and improvements were observed in scores on the following scales: affective flattening, poverty of thought, and anhedonia. The major side effects of nemonapride were akathisia and drowsiness, but there were no severe extrapyramidal symptoms.

The mechanism of action of nemonapride is not proven, but we believe that its unique antipsychotic effect arises from its selective binding to the dopamine D_2 receptor family (3). Clozapine is well known for its low extrapyramidal side effect profile and its effect on negative symptoms of schizophrenia, and this atypical neuroleptic has been shown to exhibit high affinity for dopamine D_4 receptors (3). Since nemonapride has high affinity for D_3 and D_4 dopamine receptors, it is conceivable that its effect on negative symptoms might result from blockade of these receptors. Animal studies have suggested that nemonapride has pharmacological features that are different from those of typical neuroleptics. The low extrapyramidal side effect profile of nemonapride treatment appears to coincide with the characteristic features of another benzamide derivative, remoxipride. In summary, the present open trial indicated that nemonapride is a highly effective drug for treating positive and negative symptoms of schizophrenia without serious extrapyramidal side effects.

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KEIJI SATOH, M.D.
TOSHIYUKI SOMEYA, M.D.
MORIKAZU SHIBASAKI, M.D.
Otsu, Japan

Maternal Infectious Illness and Schizophrenia

TO THE EDITOR: We congratulate Padraig Wright, M.R.C. Psych., and colleagues (1) on their important finding that among mothers of schizophrenic patients there was a significantly higher rate of gestational infection in the second trimester and that these influenza-exposed patients were more likely to experience further obstetric complications.

This study replicated and confirmed for the first time our 1992 finding of a link among the recollection of maternal infectious disease, obstetric complications, and schizophrenia (2, 3). This finding has been substantiated in an extended sample with 80 patients and 80 matched control subjects (4, 5). The high rate of correspondence between the results of both studies is exciting not only because of the fact that each used a different ethnic group (British versus German parentage) and different diagnostic procedures but also because Wright and colleagues used a slightly different interview structure. Unfortunately, Wright and colleagues referred to our study, which had presented most of the relevant findings of their own study years earlier, only briefly and inaccurately.

Both studies relied on the validity of maternal recollection of gestational infection and obstetric complications, which we have reported showed good agreement with records of the maternity hospital (6). To avoid any methodological bias, the interviewer in our study was unaware of the differentiation of the diagnoses *and* the patient's family history, and we used a matched control sample. We found that it was not the frequency but rather the monthly distribution of gestational infections in the mothers of schizophrenic patients that was significantly different from the comparison group. A similar rate of infection was reported in both the mothers of control subjects (13%) and the mothers of schizophrenic patients (20%). The mothers of schizophrenic patients, however, reported more infections during the second trimester (2, 3), especially during the fifth month of gestation ($p<0.05$). The incidence of maternal infection in the fifth month of pregnancy was higher than that in any other month. In both our and Wright et al.'s studies, mothers of schizophrenic patients experienced significantly more infections in the second trimester than in the first and third trimesters. Influenza and respiratory infections were the most frequent, having accounted for 70% of the second-trimester infections in Wright et al.'s study and 64% in our study.

Wright and colleagues confirmed our finding that those with maternal infection were significantly more likely to have additional obstetric complications than those without. Of the schizophrenic patients with maternal infection, 13 of 16 (81%) suffered from additional obstetric complications (4). Beyond that, Wright and colleagues confirmed two of our other main findings: maternal infection is obviously not associated with cases of high genetic loading (i.e., with a schizophrenic first-degree relative), but familial/sporadic distribution in DSM-III-R schizophrenia is not distinct (2). We found

maternal infection mainly confined to systematic schizophrenias according to Leonhard, i.e., a schizophrenic subgroup with low genetic loading and a chronic nonremitting course with severe psychopathology. Infections during the fifth month of gestation were reported exclusively in systematic schizophrenias and thus appear to be an important causative factor in these distinct subforms of schizophrenia.

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GERALD STÖBER, M.D.
ERNST FRANZEK, M.D.
HELMUT BECKMANN, M.D.
Würzburg, Germany

Dr. Wright and Colleagues Reply

TO THE EDITOR: We are grateful to Dr. Stöber and his colleagues for their comments on our article and for bringing their own work in the German literature to our attention. We accept that our reference to their English papers lacked clarity in that we should have stated explicitly that the excess of second trimester influenza we referred to was expressed as a proportion of mothers of patients who reported gestational infections, rather than as a proportion of mothers of all patients.

There are several methodological differences between our work and that of Dr. Stöber and his colleagues. We determined history of schizophrenia in patients' first-degree relatives by use of an operational diagnostic instrument, while our German counterparts used hospital records to identify schizophrenia in both first- and second-degree relatives. We used an operational diagnosis for influenza infection, did not divide our cohort into diagnostic subgroups, used a more extensive and trimester-specific instrument to elicit information about gestational infections and obstetric complications, used cues to accurately date such adverse events, and additionally questioned interviewees about medicines and vaccines that were administered during the index pregnancy. Finally, it is likely that British and German obstetric practices may differ considerably.

Nevertheless, and despite these methodological differences, in the two case control studies reported by Stöber's group and ourselves, the findings largely concur. What is puzzling is why two cohort studies that have prospectively followed up large birth cohorts (1, 2) have failed to find a relationship between prenatal exposure to influenza and later risk of schizophrenia. One possibility is that gene-environmental interactions may be involved, and we are presently attempting to unravel potential molecular mechanisms that may be responsible for this effect (3).

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PADRAIG WRIGHT, M.R.C.PSYCH.
NORIYOSHI TAKEI, M.D., M.SC.
LARRY RIFKIN, M.R.C.PSYCH.
ROBIN M. MURRAY, D.SC., F.R.C.PSYCH.
London, England

Hallucinatory Changes

TO THE EDITOR: Laura J. Miller, M.D. (1), described changes in auditory hallucinations of psychiatric inpatients who continued to hallucinate, in spite of treatment, from the time of admission to the time of discharge. Her finding, namely that treatment reduced frequency and intensity of hallucinations and overt behavioral responses, is in agreement with other studies in the literature. A previous report found that phenothiazines reduced frequency, loudness, and emotional reactions to hallucinations in newly admitted schizophrenic patient (2). The opposite, namely an increase in frequency, loudness, and emotional reactions, occurred in treated but still hallucinating patients with chronic schizophrenia after their phenothiazine regimen had been discontinued. Other characteristics of hallucinations changed infrequently. In most patients, two or more characteristics changed simultaneously but in some patients only a single one. This confirmed Bleuler's observations that characteristics of hallucinations can change independently (3). I agree with Dr. Miller's conclusion that multiple factors act together to reach a threshold level of hallucinatory experience. However, it appears that frequency and loudness of hallucinations are the most direct expression of cerebral dysfunction. The relationship between the affective states and hallucinations appears to be more complex.

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RUDOLF HOEHN-SARIC, M.D.
Baltimore, Md.

Dr. Miller Replies

TO THE EDITOR: I agree with Dr. Hoehn-Saric that the relationship between affective states and hallucinations is complex. As one approach to understand this relationship, my

group examined patients' attitudes toward their hallucinations and the relationship of those attitudes to treatment response (1). We found that patients who valued hallucinations more before treatment were significantly more likely to be hallucinating after treatment. We interpreted these findings as supporting the idea that psychological factors contribute to the expression of hallucinations.

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LAURA J. MILLER, M.D.
Chicago, Ill.

Assisted Suicide for HIV Patients

TO THE EDITOR: The recent article by William J. Breitbart, M.D., and colleagues (1) represents another important demonstration of the significance of social and psychiatric considerations in the debate about voluntary euthanasia and assisted suicide. This and other related studies (2–4) are making it increasingly clear that depression and inadequate social support would be major factors that contribute to patient requests for euthanasia and assisted suicide, whereas the role of physical symptoms may be "more complex than often presumed" (1, p. 241).

In one respect, however, the results of this study must be placed in their proper context. Specifically, the finding that 55% of ambulatory HIV-infected patients would consider physician-assisted suicide should be viewed very cautiously as an estimate of the rate in which this patient group would actually make assisted-suicide requests. For more realistic estimates, we must turn to studies of patients who are in advanced stages of illness, when choices around life and death are focused even more sharply. In this regard, we know that about 8.5% of patients who receive palliative care for advanced cancer report a pervasive desire for death (2), and about 3.6% of patients who die had discussed a wish for euthanasia with family members (3). In the Netherlands, about 9.9% of patients who are approaching death from nonacute causes make requests for euthanasia or assisted suicide, and about 3% die by these methods (4). Only studies that include patients in the earlier stages of illness find that as many as one-third would consider euthanasia or assisted suicide. Among the general population, 48% of physically healthy individuals report that they would consider assisted suicide "if" they had a terminal illness (5). Perhaps more than anything, this speaks to the limitations of our ability to accurately anticipate end-of-life decision preferences from the vantage point of "health."

Overall, the discrepancies across studies suggest that there is a sharp line between people who are dying and people who are not, even if the latter group includes patients in the early stages of an incurable disease. If legalized, assisted suicide would likely only be requested by a minority of terminally ill individuals. It is to this minority that we should now turn our attention. Breitbart et al. may have a unique opportunity to follow their cohort prospectively as they move toward more advanced and terminal stages of illness. This would provide a much-needed perspective on the trajectory of end-of-life decision making in the face of advancing disease. Ultimately, the clearest and most accurate picture of euthanasia and assisted suicide will emerge only from studies of patients who face imminent death.

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HARVEY MAX CHOCHINOV, M.D., F.R.C.P.C.
Winnipeg, Man., Canada
KEITH G. WILSON, PH.D.
Ottawa, Ont., Canada

Dr. Breitbart and Colleagues Reply

TO THE EDITOR: Drs. Chochinov and Wilson have contributed substantially to the growing body of literature on issues related to assisted suicide and euthanasia, and so their thoughtful comments on our recent article are appreciated. They accurately point out that our finding that 55% of ambulatory HIV-infected patients would consider physician-assisted suicide should be viewed cautiously as an estimate of the rate in which this patient group would actually request assisted suicide.

Drs. Chochinov and Wilson present data, including their own exemplary work, that show that the rate at which terminally ill patients approaching death express a desire for death or make actual requests for assisted suicide or euthanasia is likely below 10%. It is of interest that in a recent survey of physicians in Washington State (1), 12% of responding physicians reported one or more explicit requests for physician-assisted suicide, and 4% received one or more requests for euthanasia.

As clinicians who regularly treat patients with advanced cancer and AIDS, we agree that the process of coping with a life-threatening illness is just that—a process. Many patients change or modify their attitudes about end-of-life issues over the course of the illness and only infrequently seek to hasten their deaths. By the time a disease reaches the terminal stage, multiple adjustments and accommodations to living with illness have been made. Thus, if patients have not yet made these accommodations, it would be difficult for them to project what their preferences will be.

Drs. Chochinov and Wilson caution that our findings regarding patient interest in physician-assisted suicide may be inflated because of the ambulatory nature of our study group. They imply that the patients studied in our survey were relatively healthy and, therefore, not forced to confront end-of-life issues. Although we agree that our data do not reflect actual requests for physician-assisted suicide, and our cohort was not necessarily in the very latest stages of AIDS, that does not justify the assumption that the subjects were relatively healthy. In fact, 90% of our cohort were diagnosed with AIDS and were highly burdened with physical symptoms. Moreover, many patients died in the 4 months between the time these data were collected and the planned follow-up evaluation (data not yet published).

We are also concerned that the experience of patients with AIDS may be qualitatively different from that of patients with other life-threatening illnesses. For example, we have recently

demonstrated that pain is dramatically undertreated in patients with AIDS, substantially more so than among patients with cancer (2). There are also many social factors specific to HIV and AIDS that may increase the likelihood of interest in physician-assisted suicide/euthanasia for some patients (e.g., social stigma, multiple bereavements, inadequate palliative care). Our clinical experience has also suggested that inadequate palliative care, which is common among patients with AIDS, may actually result in a greater interest in physician-assisted suicide. Many patients with AIDS have already witnessed the death of a friend or family member who did not have the benefit of adequate palliative care and may, therefore, be more likely to seek for themselves a means to avoid such suffering. Recent legal decisions that have overturned legislation that banned physician-assisted suicide, including one such decision in New York State, heighten the importance of understanding the basis of patients' interest in hastening death and will likely provide opportunities to directly examine these issues in patients who actually request assisted suicide.

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WILLIAM BREITBART, M.D.
BARRY D. ROSENFELD, PH.D.
STEVEN D. PASSIK, PH.D.
New York, N.Y.

Reviewing a Review

TO THE EDITOR: I am delighted that Paul S. Appelbaum, M.D., found my book interesting and readable (1). However, he faults my overlooking empirical research in the area. Actually, the references that he says that I overlooked are cited in my book, and I have used one of them in a seminar.

Dr. Appelbaum stated, for example, that I am in error in writing that defendants with prior criminal records avoid pleading insanity because of fear that their criminal history will be brought to the attention of the jury. I stand by my statement. What's more, the American Law Institute test of criminal responsibility states that repeated criminal or antisocial conduct does not of itself demonstrate mental illness.

Dr. Appelbaum also stated that I give more attention to less important clinical syndromes, like multiple personality disorder, than to more important ones, like schizophrenia, which "might be expected from a nonclinican." Actually, I have both clinical and prosecutorial experience.

To be sure, I focused on the interesting and intriguing, but the individual diagnosed as schizophrenic does not present any issue not discussed in the book. Daniel McNaughton, about whom much has been written, would today be diagnosed as paranoid schizophrenic. He is, of course, discussed in my book.

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RALPH SLOVENKO
Detroit, Mich.

TO THE EDITOR: The book review of *Psychiatry and Criminal Culpability* took issue with the assertion made by Professor Slovenko that defendants with prior criminal records avoid pleading insanity because of fear that criminal history will be brought out. I take issue with your reviewer. In 40 years of testifying in insanity cases, I do not recall ever testifying on behalf of an accused who had a significant criminal record. Insanity defense is asserted primarily in homicide cases in which the victim is a loved one or, if a stranger, the perpetrator was grossly psychotic.

EMANUEL TANAY, M.D.
Grosse Pointe Park, Mich.

Dr. Appelbaum Replies

TO THE EDITOR: Professor Slovenko takes issue with my reference to his "apparent unfamiliarity with the empirical literature on the insanity defense." In particular, he stands by the statement in his book that "a defendant with a criminal record rarely raises the [insanity] defense for fear that his history will be brought to the attention of the jury and will tend to guarantee conviction rather than acquittal" (1, p. 44).

The recent empirical literature leaves me less certain than Professor Slovenko about this conclusion. A massive eight-state study found that 75.6% of 8,979 persons who pled insanity had prior criminal records (2). Indeed, of the 2,565 defendants who were actually acquitted by reason of insanity, 70.2% had arrest records, which suggests that this variable plays a minor role at best in determining outcomes. Comparable results were obtained from a Connecticut study that reported that fully 65% of male acquittees (who represent 90% of acquittees) fell into this category (3); in Oregon the figure is 77% of all acquittees (4). Other studies with similar conclusions could be cited, but I think the point is clear.

Dr. Tanay, Professor Slovenko's friend and colleague at Wayne State University, echoes this misconception about the criminal records of insanity defendants. Further illustrating the dangers of generalizing from one's own limited experience, he claims that the "insanity defense is asserted primarily in homicide cases." In fact, data from the eight-state study indicate that only 13.6% of insanity pleas arose from murder cases (2). Connecticut's figures show only 12.1% of acquittees in that state were accused of murder (3); in Oregon, the rate is 3% (4).

I am uncertain as to the relevance of Professor Slovenko's comments on the American Law Institute test. As to his clinical background, I think it is inarguable both that he is not a clinician and that the casual reader of his book would be misled as to the relative frequency of diagnoses associated with insanity pleas. Perhaps citation of some of the relevant studies (2–4) would have been helpful.

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PAUL S. APPELBAUM, M.D.
Worcester, Mass.

Traumatophilic Diathesis, Complemental Series, and the Original Conceptual Basis of PTSD

TO THE EDITOR: The article by Rachel Yehuda, Ph.D., and Alexander C. McFarlane, M.D. (1), underscored empirical, theoretical, and nosological problems in the current understanding of PTSD. Regarding its conceptual origins, they alluded to the interplay of genetic predisposition, developmental fixation, and environmental stress. It is in the theorization and classification of this interplay—or, more precisely, in the frequent absence of such consideration—that conceptual problems can arise.

Several points may put some of the current conceptual conflict into historical perspective. First, although they noted that Freud's initial theory of hysteria was a traumatic one, this is only partly correct. In their *Studies on Hysteria* (2), Freud and Breuer also considered psychodynamic and innate causes, and they distinguished their understanding of the role of hereditary factors from Janet's view that the disposition was based on innate psychical weakness. Even earlier, Charcot, as well as Janet, had posited constitutional, traumatic, and ideational causes.

Second, even after Freud began to focus more on psychodynamic factors, Karl Abraham further developed the trauma theory in two of the earliest articles devoted to the interplay of constitution and trauma (3). Abraham not only focused on the actuality of traumatic experience but also furthered the idea that some patients were constitutionally vulnerable to it. A constitutional predisposition both to later psychiatric disorder and to traumatic experience would help explain a correlation between traumatic experience and later mental disorder. He believed that it was the traumatic experience itself, as opposed to the occurrence, that determined the form of the disorder. Despite certain problems in Abraham's formulation, he sought to integrate constitutional and environmental elements in a way that had contemporary relevance. He introduced the unheralded notion of a "traumatophilic diathesis," which anticipated Freud's pivotal concept of the repetition compulsion. Although initially Abraham did not elaborate on the nature of constitutional factors and the possible role of very early experiences and fixations, he laid groundwork in these areas.

Third, in 1916-1917, Freud clarified some of these nature-nurture issues with his concept of "the complemental series" (4), a term that reflects the complementary and inversely varying roles of endogenous and exogenous factors in cases of neurosis. In 1919, as well as later, Freud (5) reiterated the role of trauma in all neurotic disorders. The complemental series is a useful shorthand for integrating much of the seeming conflict about the respective roles of nature and environment (including trauma) in causing psychiatric disorders.

DSM-IV makes categorical distinctions without regard to etiologic considerations. It does not view diagnosis from the perspective of complementarity. While its theory of nosology has a rationale, its method can introduce what are only apparent conflicts in understanding, as with PTSD. Many of the issues about what is now called PTSD had been identified over a century ago. The emphasis has alternated among endowment, upbringing, and stress or trauma, as well as their biological and intrapsychic significance—but the spectrum of causative factors remains. An overall research focus on only part of the spectrum will eventually lead to explanatory insufficiency or inconsistency. Thus, recent research should be used to formulate "the next generation of conceptual issues" (1) but also should be viewed from the perspective of historical oscillations among conceptualizations.

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MICHAEL I. GOOD, M.D.
Brookline, Mass.

Reprints of letters to the Editor are not available.