Letters to the Editor

Use of Fluoxetine for Obsessive-Compulsive Behavior in Adults With Autism

TO THE EDITOR: Fluoxetine has relieved symptoms in patients with depression and obsessive-compulsive disorder (1). Occasional case reports have suggested novel uses for fluoxetine and other selective serotonin reuptake inhibitors (SSRIs), such as symptomatic relief for patients with violent behaviors (2) and treatment of aggression in a patient with mental retardation (3). I wish to report on the treatment of two adult patients with autism whose symptoms of obsessive-compulsive behavior were long-standing and untreated.

Mr. A was a 26-year-old man with autism and mild mental retardation. He was competent in his activities of daily living, and he lived with his family. He was prone to isolative and withdrawn behavior that coincided with what appeared to be anxiety concerning his mother and her health. His daily routine was punctuated with rituals around bathing, eating, and preparing for his day program. For many years, these rituals were assumed to be characteristic of his autistic behavior. Mr. A was an excellent artist and drew cartoons that depicted various members of his treatment team. He was well liked by most staff members. When he became anxious, he would make animal noises, his rituals would become more elaborate and abundant, and he would avoid all eye contact. His eye contact to begin with was poor. After a prolonged period of anxiety, Mr. A was referred for psychiatric evaluation; a regimen of fluoxetine, 20 mg/day, was started to address the obsessive-compulsive and anxiety symptoms.

The response was dramatic. Mr. A began to maintain constant eye contact, his behavior became more social, and his artwork moved from cartoon stereotypes to more free-form and creative subjects. His daily rituals ceased, and 4 months after the initiation of fluoxetine, he reported symptom relief and had enrolled in an art class at a local university.

Ms. B was a 42-year-old woman with autism and moderate mental retardation. Her lifelong history was significant for poor social interaction, isolative behavior, and minimal communication. Her preoccupation with order and cleanliness was also noted. A new counselor in her group home recommended an evaluation for depression. On evaluation, she demonstrated signs of preoccupation, poor eye contact, hypersomnia (she would sleep up to 14 hours a day), and withdrawn behavior—all of which were seen as usual and part of Ms. B's autistic condition. She was started on a regimen of fluoxetine, 20 mg/day. Over the next month, her daily sleeping time decreased to about 7 hours, and she displayed brighter affect, improved quality and quantity of communication, and more frustration tolerance. She began helping with household chores, including cooking.

These cases show a dramatic response to fluoxetine in autistic adults whose usual behaviors, although suggesting pure depression, were typical of the obsessive-compulsive behaviors of autism with overlying depression (4). Various mechanisms for the role of serotonin in autism have been proposed that suggest that serotonin inactivity is a hallmark of the autistic condition (5, 6). While some authors have posited that SSRIs ameliorate stereotypic behavior such as anger and compulsive, ritualized behaviors (7), others have observed that serotonin antagonists are useful in the control of these behaviors (8).

This newest class of antidepressant may have a significant impact on patients with depressive symptoms who would not ordinarily be treated for depression or who might be given neuroleptic medication for treatment of disturbing or repetitive behaviors.

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Nefazodone-Induced Mania

TO THE EDITOR: Jeffries and al-Jeshi (1) recently reported the development of manic symptoms with psychosis in a patient with bipolar disorder 2 days after initiation of nefazodone treatment. The symptoms persisted despite nefazodone discontinuation but responded to six courses of ECT. The authors urged caution in using nefazodone in patients with bipolar disorder. We wish to describe what we believe is the first reported case of nefazodone-induced mania in a patient with no prior manic history.

Ms. A was a 55-year-old white woman who had been followed at our clinic for 6 years. She had a history of recurrent episodes of depression that began at age 42, but she had received no treatment until she had come to our facility. She had reported alcohol abuse, and 2 years into treatment she became abstinent. There was no history of mania or hypomania. A review of her family history revealed a son with bipolar disorder and alcohol dependence in her father. During the past 6 years she had had three recurrences of depressive episodes. Nortriptyline treatment was not effective, and three brief trials of fluoxetine were discontinued because of panic symptoms. She did well on a regimen of desipramine, 225 mg/day, for 9 months and sertraline, 200 mg/day, for 23 months. There had been no manic symptoms at any time during treatment.

When depression recurred during sertraline treatment, Ms. A was started on a regimen of paroxetine, which was of no benefit. After paroxetine washout, an oral regimen of nefazodone, 100 mg b.i.d., was started. One week later, she came for a routine appointment dressed in bright clothing and garish makeup. She reported racing thoughts and was hypersexual, grandiose, and disinhibited. Nefazodone treatment was discontinued. Over the next 4 weeks she exhibited rapid shifts in mood from euphoria to irritability and depression. Treatment with valproic acid was not helpful. A regimen of sertraline, up to 200 mg/day, was initiated. The combination of carbamazepine and sertraline led to improvement in manic symptoms and mood stabilization, but moderate symptoms of depression persisted.

Just as in the previous case of nefazodone-induced mania (1), the patient developed this complication for the first time despite having been treated with multiple antidepressants in the past. In both cases, symptoms did not resolve after nefazodone discontinuation.

It has been suggested that a particular agent may possess antidepressant efficacy if mania is induced (2). Therefore, nefazodone's ability to induce mania may serve as further evidence of its utility in the treatment of depression.

According to the 1995 edition of *Physician's Desk Reference*, premarketing studies revealed a 0.3% rate of hypomania or mania with nefazodone treatment, a rate that was lower than that found for tricyclic antidepressants and was similar to that of placebo. All currently available antidepressant agents appear able to induce hypomanic and manic reactions (1). These reactions occur in perhaps 50% of patients with bipolar disorder (3) but only 9% of patients with unipolar illness (4). Development of mania in this case should alert clinicians that this potential toxicity of nefazodone treatment can occur even in patients with unipolar illness.

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Efficacy of Papaverine Addition for Treatment-Refractory Major Depression

TO THE EDITOR: Recent insights into the molecular and cellular adaptations produced by antidepressant medications have focused attention on intracellular second messenger systems as common targets of antidepressant action. From the theory that elevated levels of cAMP and its transcription factor (cAMP response element binding protein) are central to antidepressant efficacy (1), we hypothesized that adding a cyclic nucleotide phosphodiesterase inhibitor to a previously ineffective antidepressant would result in an improvement in depressive symptoms. We report a case that supports this hypothesis and suggests the efficacy of papaverine addition for the treatment of refractory major depression.

Ms. A was a 56-year-old woman with a 7-year history of recurrent major depression. She presented to our research clinic after a relapse of her depressive symptoms. Her mood disturbance was of moderate severity (Hamilton depression scale score of 22 and Beck Depression Inventory score of 26) and was characterized by marked anhedonia, anergy, hopelessness, insomnia, and suicidal ideation. Prior episodes had been resistant to ECT and several pharmacotherapy regimens, including adequate trials of tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors.

On the basis of this history, we initiated a series of unsuccessful trials that combined venlafaxine, 375 mg/day, with lithium, 900 mg/day, for 6 weeks; lithium, 15 mg/day, and pindolol, 30 mg/day, for 4 weeks; and lithium and buspirone, up to 60 mg/day, for 7 weeks. After a 1-week washout period, papaverine was added to Ms. A's ongoing venlafaxine treatment. Over a 2-week interval, the dose was titrated from 150 mg/day to 600 mg/day. Papaverine treatment was well-tolerated, and there were no side effects. Two weeks later, Ms. A experienced a dramatic remission in her depressive symptoms, as evidenced by Hamilton and Beck depression scale scores of 9 and 8, respectively. At the 12-week follow-up examination, this mood response was maintained.

To our knowledge, this is the first report to describe the clinical utility of papaverine addition in the treatment of major depression. Papaverine, a nonnarcotic alkaloid and nonselective phosphodiesterase inhibitor, is a well-characterized smooth muscle relaxant (2). Because of its vasodilatory properties, papaverine has been used with limited success in the pharmacotherapy of organic brain syndromes secondary to cerebrovascular deficiencies (3). It is of interest that in this population, earlier studies documented positive, albeit mild, improvements in depressive symptoms (4, 5). The notion that inhibition of neuronal cAMP metabolism might constitute a viable treatment for major depression was later supported by clinical studies that suggested the efficacy of rolipram, a selective phosphodiesterase inhibitor (6–8). These trials certainly raise the possibility that papaverine alone may have accounted for our patient's positive mood response. Conversely, basic neurobiological research has shown that antidepressants and phosphodiesterase inhibitors can work cooperatively to accelerate the activation of neuronal cAMP systems and, in turn, target gene expression (e.g., cAMP response element binding proteins and brain-derived neurotrophic factors) (1). Thus, the importance of combination therapy cannot be excluded. In either case, our report suggests that phosphodiesterase inhibition should be considered as a potentially efficacious pharmacotherapeutic strategy for antidepressant-resistant patients.

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Recurrent Hyponatremia Associated With Sertraline and Lofepramine

TO THE EDITOR: Hyponatremia secondary to a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is an underrecognized and serious complication of treatment with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, particularly in the elderly. Hyponatremia that develops from treatment with one SSRI may recur if a second SSRI is introduced (1, 2). However, it has been unclear whether hyponatremia that develops from treatment with one SSRI will recur if a tricyclic antidepressant is introduced (3). We report a case of recurrent hyponatremia in a patient after separate trials of sertraline and lofepramine.

Ms. A, a 78-year-old woman with a 6-month history of first-episode major depression, was treated at home with a regimen of sertraline, 50 mg every morning. One week after beginning therapy she was admitted to our ward because she complained of feeling increasingly depressed, weak, and lethargic. Her serum sodium level was 117 mmol/liter, potassium level was 4.0 mmol/liter, serum osmolality was 245 mmol/kg, urine sodium level was 21 mmol/liter, and urine osmolality was 314 mmol/kg. The sertraline treatment was discontinued, and fluids were restricted to 1 liter/day. After 1 week, the hyponatremia had resolved (serum sodium level was 135 mmol/liter), and Ms. A started a regimen of lofepramine, 70 mg/day; the dose was increased to 140 mg/day after 3 days. However, 2 weeks after she started this medication, her serum sodium level fell to 128 mmol/liter, serum osmolality was 259 mmol/kg, and urine osmolality was 581 mmol/kg. Her lofepramine treatment was discontinued, and the 1-liter fluid restriction was resumed. Normalization of her laboratory values occurred within 1 week. Ms. A was treated with a course of ECT, made a full recovery, and was discharged on a regimen of citalopram, 20 mg/day.

The diagnosis of SIADH in this patient was made because of profound hyponatremia, low serum and high urine osmolality, the return of laboratory values to normal after discontinuation of sertraline and lofepramine, and the lack of any other known cause of SIADH. Previous case reports described similar results in elderly patients who developed SIADH after initiation of fluoxetine treatment and were later rechallenged with the same class of medication (1, 2).

Our case demonstrates that hyponatremia and SIADH are not necessarily class effects of the SSRIs; there also might be a crossover effect with tricyclic antidepressants. Therefore, a patient who develops hyponatremia and SIADH with one SSRI may do so again when treated with a tricyclic antidepressant and should thus be carefully monitored. From the current reports in the literature, it seems that elderly patients are particularly at risk.

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Response of Kleptomania and Mixed Mania to Valproate

TO THE EDITOR: Preliminary phenomenologic, comorbidity, and treatment response data suggest that kleptomania may be related to bipolar disorder (1). Kleptomania is associated with mood and energy elevation similar to that of hypomania and is often followed by depressed mood, guilt, and fatigue similar to that found in bipolar depression. High rates of bipolar disorder have been reported in patients with kleptomania, and kleptomanic impulses have been reported to respond to treatment with antidepressants, mood stabilizers, and ECT. We describe a woman who presented with severe kleptomania and mixed mania, both of which worsened with fluoxetine treatment but responded to a regimen of valproate.

Ms. A was a 36-year-old married mother who was employed full time. She initially came to us for consultation after she had been hospitalized for recurrent shoplifting and severe depression. She described a near constant and impossible-to-resist urge to steal (she would shoplift an average of four times every day) and very rapid (ultradian) and severe mood and energy swings. Ms. A's stealing met DSM-III-R criteria for kleptomania, and her affective symptoms met DSM-III-R criteria for bipolar disorder, mixed. Ms. A described the course of both her kleptomania and mixed mania as chronic, with near daily symptoms since she was 15 and 14 years old, respectively.

It was recommended that Ms. A begin a regimen of valproate for treatment of her mixed mania. Upon discharge, however, she was treated intermittently with fluoxetine. When she came once again to our center after 1 month of continuous fluoxetine treatment (20 mg/day), Ms. A continued to meet DSM-III-R criteria for kleptomania and bipolar disorder, mixed. Moreover, she reported that the rapidity and severity of her mood swings, as well as the frequency and severity of her stealing impulses and behavior, had increased since she began taking fluoxetine (she was stealing seven to eight times every day). A regimen of valproate was added to the fluoxetine therapy. Within 1 month, on a regimen of valproate, 1500 mg/day, and fluoxetine, 20 mg/day, Ms. A reported a marked improvement in her mood swings as well as a reduction in the frequency and intensity of her stealing impulses and episodes. Her valproate regimen was increased to 2000 mg/day, and fluoxetine treatment was discontinued. One month later, Ms. A described a further decrease in mood swings, complete resolution of stealing impulses, and continued remission of stealing behavior. After 8 months of valproate treatment, Ms. A reported mild but manageable mood swings, continued resolution of stealing impulses, and no further stealing.

This case suggests that kleptomania accompanied by mixed mania may worsen with antidepressant treatment but respond to a mood stabilizer. Although it is unknown whether kleptomania without comorbid bipolar disorder would respond to a mood stabilizer, this case is consistent with the hypothesis that kleptomania and bipolar disorder may be related. Further study of kleptomania's relationship to mood disorders and its treatment with thymoleptics appears warranted.

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Delirium Associated With Paroxetine and Benztropine Combination

TO THE EDITOR: We wish to report a case of delirium in a patient who was taking benztropine and paroxetine concomitantly. Previous reports have indicated that benztropine used with selective serotonin reuptake inhibitors (SSRIs) can cause delirium, presumably an anticholinergic delirium because of raised levels of benztropine (1, 2). The mechanism is believed to be from SSRI inhibition of the microsomal isoenzyme cytochrome P450 2D6 (3, 4). This case report differs from the previous reports in two aspects: 1) paroxetine was singly implicated in the raising of benztropine levels, and 2) a benztropine level was obtained to confirm toxicity.

Alex was a 17-year-old boy with bipolar disorder, mild mental retardation, and grand mal seizures who developed depression. Paroxetine, 20 mg/day, was added to his regimen of haloperidol, 5 mg/day; benztropine, 2 mg b.i.d.; valproic acid, 1750 mg/day; gabapentin, 300 mg/day; and buspirone, 5 mg b.i.d. On day 8 of paroxetine treatment, Alex reported dry mouth and nausea and presented with symptoms consistent with delirium: he was disoriented to time, disorganized, forgetful, and lethargic with slurred speech. Vital signs were unremarkable, and he demonstrated no extrapyramidal symptoms. His pupils were dilated and sluggish to respond. The paroxetine, haloperidol, benztropine, and valproic acid regimens were discontinued. Valproic acid level, which had been consistently 103–105 μg/ml for several months, was 119 μg/ml. The haloperidol level was 2.9 ng/ml (normal level=5–12 ng/ml), and serum gabapentin level was 4.1 μg/ml (normal level=4–16 μg/ml). Serum benztropine level was 35.9 ng/ml; toxicity at our laboratory is defined as a level greater than 25 ng/ml. Results of liver function tests were within normal limits, as were electrolyte and serum ammonia, creatinine, iron, and creatine phosphokinase levels. The day after discontinuation of the medications, Alex was able to eat breakfast but otherwise did not feel much better. Results of another examination of laboratory values revealed no abnormality. Two days after discontinuation of the medications, Alex reported feeling much better. Treatment with haloperidol and valproic acid was restarted without incident. Another antidepressant was started without subsequent problems.

This case strongly suggests that the addition of paroxetine led to greater serum levels of benztropine, which led to an anticholinergic delirium. Although we did not obtain a benztropine level before the patient became symptomatic, it was the only abnormal laboratory value obtained when the patient was symptomatic. Several possibilities were entertained as the cause for the patient's symptoms. Neuroleptic malignant syndrome was the most worrisome in our differential diagnosis. However, except for the confusion, the results of the physical and laboratory examinations were not consistent with this diagnosis. Elevated valproic acid levels can cause confusion, but the patient's valproic acid level had been within normal limits and essentially was unchanged from previous routine measurements. Additionally, valproic acid is metabolized primarily through glucuronidation and microsomal β oxidation, with only 15%–20% being metabolized by cytochrome P450 2C9 (Abbott Laboratories, personal communication, 1996). Haloperidol is metabolized by cytochrome P450 2D6 (3), and elevated haloperidol levels could cause sedation and confusion, but the relatively low level of haloperidol points away from this drug as being a cause for the patient's abrupt mental status changes. Gabapentin, a new antiseizure medication, is not metabolized by the liver (1995 *Physician's Desk Reference*) and is excreted unchanged in the urine; hence, it was not felt to be the cause for the patient's symptoms.

Roth et al. (1) reported two cases of delirium associated with concomitant paroxetine and benztropine use. In one case, however, fluoxetine, which is an inhibitor of cytochrome P450 2D6 (3, 4), was discontinued just before starting paroxetine, benztropine, and a neuroleptic. In the other case, the delirium could well have been from inhibition of fluphenazine metabolism, since there was a sixfold increase in fluphenazine levels; benztropine levels were not obtained. In the previous cases of SSRI- and benztropine-induced delirium, no benztropine levels were obtained (cases involved fluoxetine and sertraline as well as paroxetine). Therefore, we believe this is the first unequivocal case of benztropine causing an anticholinergic delirium in a patient who was taking paroxetine concomitantly.

Previous cases of SSRI- and benztropine-induced delirium have assumed the mechanism is from SSRI inhibition of benztropine's metabolism by cytochrome P450 2D6, thus raising the levels of benztropine. This mechanism seems very reason-

able to us. Benztropine is an older medication and was not evaluated regarding its microsomal isoenzyme metabolism and inhibition profile before it was marketed (Merck and Co., Inc., personal communication, 1996). On the basis of this report, which confirmed elevated levels of benztropine when used with paroxetine, we believe it is safe to assume that a major metabolic step for benztropine is through the cytochrome P450 2D6 isoenzyme and that all medications that potentially inhibit this isoenzyme should be used cautiously with benztropine.

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Treatment of Risperidone-Induced Obsessive-Compulsive Symptoms With Sertraline

TO THE EDITOR: We report a case of risperidone-induced obsessive-compulsive symptoms that responded to sertraline administration. A MEDLINE search revealed several cases in which these symptoms developed after clozapine treatment. However, we found only two previously reported cases of obsessive-compulsive symptoms that occurred after the use of risperidone (1, 2).

Mr. A was a 46-year-old man with chronic, treatment-resistant schizophrenia who had been hospitalized after an exacerbation of his illness. A prehospitalization regimen of fluphenazine decanoate, 62.5 mg every 2 weeks, was discontinued, and risperidone therapy was initiated and titrated over 3 days to 6 mg/day. Approximately 1 week after risperidone treatment had begun, Mr. A reported experiencing new-onset ruminative thoughts with obsessive characteristics. After 5 months of treatment with risperidone, 6 mg/day, he still complained of almost constant auditory hallucinations and fixed delusions. To reduce the psychotic symptoms, risperidone was titrated over a 4-month period to 12 mg/day, which resulted in a marked decrease in these symptoms. However, as the risperidone dose was titrated from 6 mg/day to 12 mg/day, Mr. A's obsessions increased from mild to severe. The obsessions included thoughts of passengers falling out of his car and intrusive images of severe car wrecks on the highway. Eleven months after the start of risperidone treatment, Mr. A reported the onset of compulsions that consisted of repeated checking of locks and hand washing. Although he acknowledged that these thoughts and actions were unrealistic and excessive, Mr. A experienced severe distress and began to avoid highway driving.

Because the obsessive-compulsive symptoms remained severe 6 months after the risperidone dose had been increased to 12 mg/day, a regimen of sertraline was started and gradually titrated to 100 mg/day. After 4 weeks of sertraline treatment, Mr. A subjectively reported a 30%–40% decrease in obsessive-compulsive symptoms as well as continued stability of his schizophrenia. During weeks 5–8 of sertraline therapy, the dose was titrated to 150 mg/day. By week 13 of sertraline treatment, Mr. A reported a 60% reduction in the intensity of his obsessive-compulsive symptoms, as well as a decrease in daily hours spent on obsessions and compulsions (from 6 hours, the amount of time spent on obsessions and compulsions before the initiation of sertraline, to 2–3 hours a day). After 10 months, these improvements had been maintained.

This case, the third report of risperidone-induced obsessive-compulsive symptoms, appears to demonstrate a relationship between the severity of obsessive-compulsive symptoms and increasing doses of risperidone. Our report also suggests that clinicians should be aware that risperidone-related obsessive-compulsive symptoms may be responsive to sertraline. This is significant in light of previous trials that have questioned the efficacy of sertraline in the treatment of obsessive-compulsive disorder (3, 4). Obviously, further study is warranted to explore the precise role that this agent might play in the treatment of obsessive-compulsive disorder, particularly when the symptoms are precipitated by serotonin$_2$-dopamine$_2$ antagonists such as risperidone.

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Clozapine and Fertility

TO THE EDITOR: Outcome measures beyond standard psychopathology scales are now recognized as essential to capture the multiple and diverse impacts that clozapine may have on patients, families, and society (1). An important dimension of outcome that has been relatively neglected is fertility, or lack thereof, which can have a profound effect on an individual's quality of life.

Clozapine, unlike traditional neuroleptics, does not cause sustained increases in serum prolactin levels (2). Hyperprolactinemia secondary to neuroleptic treatment can cause impotence in men and anovulatory cycles or amenorrhea in women, which have an obvious impact on fertility. It has been known for many years that normalization of prolactin secretion may restore reproductive function in patients with hyperprolactinemia not induced by neuroleptics (3). Both wanted (4) and unwanted (5) pregnancies have been reported in female patients treated with clozapine. While clozapine-associated retrograde ejaculation has been reported (6), fertility of male patients treated with clozapine has not been commented on in the literature.

At the Calgary General Day Hospital, a program that treats 235 patients with psychotic disorders, primarily schizophrenia, 12% of the clinic population are currently taking clozapine. In this small group, one male patient fathered a child, one female patient (who received clozapine throughout her pregnancy) delivered a healthy baby, and one male patient's partner delivered twins. The clinic patients who were not treated with clozapine (88%) produced five children in the same time period; two were fathered by the same male patient. These numbers, while small and not controlled for age, sex, and marital status, suggest that the birth rate in patients treated with clozapine may be higher than that in patients taking conventional neuroleptics. Theoretically, both resolution of impaired sexual functioning secondary to hyperprolactinemia and improved social interactions secondary to clozapine treatment have the potential to improve the reproductive ability of both sexes.

The study of fertility is complex; a multitude of biological and psychosocial factors influence reproductive rates (7). The limited literature on clozapine and fertility has focused exclusively on women and pregnancy. However, more male than female patients are treated with clozapine, and the number of reproductive years for men greatly exceeds that of women. Given that fertility includes both the ability to induce conception and the capacity to conceive, clozapine's effect on fertility for both men and women requires further study.

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Alternative Treatment for Poststroke Depression

TO THE EDITOR: Both depressive and anxiety disorders are common after stroke (1). Treatment with antidepressants has been shown to positively influence the psychiatric as well as the neurologic and cognitive restitution. Recently, a small open study of poststroke depression and fluoxetine was reported (2). In the search for antidepressants without unfavorable side effects, our choice fell on buspirone, a partial serotonin (5-HT)$_{1A}$-agonist with anxiolytic and antidepressive effects (3). Data from rodent models of ischemic stroke that have shown that 5-HT$_{1A}$-agonists may provide neuroprotective effects further increased our interest (3).

Eight consecutive men and women (mean age=69 years [SD=12], range=53–86) who developed DSM-III-R major depression within the first month after stroke took part in an open 8-week pilot study. The treatment was recommended to continue for up to 24 weeks. We used the Montgomery-Åsberg Depression Rating Scale (4) and Clinical Global Impression (CGI) (5) to assess depression severity. Stroke outcome was assessed by ratings of activities of daily living, speech, and cognitive performance. A mental status examination was administered both to study patients and to a comparison group of nondepressed stroke patients (N=31). Safety assessment was based on vital signs, ECG recordings, and clinical laboratory tests. Side effects were recorded on the UKU side effect rating scale (6). Drug effects and side effect ratings were assessed at baseline, at weeks 1–5, and at week 8. Written informed consent was obtained from all patients after the procedure had been fully explained.

Two patients received 30 mg/day of buspirone, two received 60 mg/day, and the remaining patients received 40 mg/day. The patients could be described as having been mildly to moderately depressed. After 8 weeks of treatment, the mean score on the Montgomery-Åsberg Depression Rating Scale decreased from 20.4 (SD=5.5) to 8.8 (SD=9.4), and mean score on the CGI decreased from 4.4 (SD=0.9) to 2.5 (SD=1.1). Six out of eight patients were considered as having responded (a greater than 50% decrease in Montgomery-Åsberg depression scale score). In general, the neurological impairment improved. Cognitive level tended to be lower for the depressed patients at baseline but was equivalent to that of the comparison group at retest (8 weeks). The treatment was well tolerated, and no unexpected side effects were observed.

In one patient, an apparently treatment-refractory poststroke pain was partly alleviated by buspirone. Another patient accidentally stopped his medication, which caused the cessation of initial improvement and a deterioration of both aphasia and depressive symptoms. After buspirone treatment was restarted, aphasia and depression symptoms improved once again, which suggests an interesting connection among buspirone, depression, and aphasia.

In conclusion, buspirone seems to be both a safe and an effective alternative in the treatment of poststroke depression. There is a need for alternatives to treatment with tricyclic antidepressants, and buspirone could be a well-suited candidate, particularly in cases that involve comorbid generalized anxiety. However, these preliminary results concerning a 5-HT$_{1A}$-agonist in poststroke depression must be confirmed in double-blind, placebo-controlled studies.

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Opiate Withdrawal With Dextromethorphan

TO THE EDITOR: Animal studies suggest that N-methyl-D-aspartate (NMDA) antagonists can attenuate the physical and motivational signs of the opiate abstinence syndrome (1). The widely used nonopioid antitussive drug dextromethorphan has a low affinity as a noncompetitive NMDA antagonist. Dextromethorphan also has an extremely favorable safety profile (2). The tolerability of high doses has been established in clinical trials in patients with neurologic diseases (3). We thus hypothesized that treatment with dextromethorphan would diminish the signs, symptoms, and craving characteristic of withdrawal from opioids in opioid-dependent human subjects. Earlier studies carried out in Turkey showed dextromethorphan to be effective in the treatment of heroin withdrawal in a double-blind trial that compared chlorpromazine with dextromethorphan (4).

In this study, we included six male patients who came to our chemical dependency unit for treatment of heroin addiction. Three patients were African-American, two were Caucasian, and one was Latino. The group ranged in age from 25 to 65 years old. All patients met DSM-III-R criteria for current opioid dependence. Four were intravenous and two intranasal daily heroin users. Duration of heroin use ranged from 5 to 26 years. All subjects had several previous inpatient detoxifications. Individuals with evidence of major psychiatric disorders or alcohol abuse were excluded from the study. A urine toxicology screen was used to confirm recent use of opiates. All subjects accepted for the study gave written informed consent, and no financial incentives were offered for participation in this study.

Subjects were hospitalized for the length of the study. The Subjective Opiate Withdrawal Scale, the Objective Opiate Withdrawal Scale, and the Craving Analog Scale were the measurements used to evaluate opiate withdrawal (5). All measurements were recorded at baseline and three times per day subsequently. After a baseline evaluation, each subject received 75 mg of dextromethorphan five times per day (total 375 mg/day). No other medications were offered except as-needed doses of hydroxyzine, acetaminophen, and ibuprofen.

Two patients requested a change to methadone during the first day of treatment. Both complained of discomfort and had symptoms of withdrawal. Neither of them completed detoxification.

All patients who completed the study had a rapid and complete attenuation of signs, symptoms, and craving by the fourth day of treatment. Improvement, particularly in the alleviation of craving, was most prominent during the first 2 days. Patients were discharged after 1 day free from medication, which occurred on average after 6 days of active treatment. Patients who successfully completed the trial reported a subjective difference from previous detoxifications with methadone in the positive effect of treatment on relief from craving. Patients tolerated dextromethorphan well, and side effects were minimal.

Results of our study provide a preliminary suggestion of the safety and feasibility of dextromethorphan in detoxification for opioid-dependent individuals. This is a confirmation of earlier published findings in which a similar dose of dextromethorphan was used. Furthermore, there is some evidence that dextromethorphan may be an advantageous alternative to current methods of detoxification. It may result in a shorter length of treatment and greater reduction in craving than methadone detoxification.

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Festschrift for John Nemiah

TO THE EDITOR: Congratulations on the "Festschrift in Honor of John C. Nemiah, M.D." (July 1996 supplement). Nancy Andreasen's introduction gives the measure of the man, one of the great psychiatrists of our time. One small addition. He mentored not only the current editor of "the green journal" but the current editor of "the orange journal" as well. When asked to be a candidate, I spotted Dr. Nemiah and asked whether I could pick his brain about what an editor does. "Dinner," he exclaimed. "You and Sally come up and spend a couple of days with us." We did and received a firsthand look at an editor at work. Beyond the technical part of the job, John combined scholarship with common sense. But the sauce that made the editorial dish a gourmet delight was the warm hospitality (and impish wit) of John and Margarete Nemiah.

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Dr. McDermott is Editor of the Journal of the American Academy of Child and Adolescent Psychiatry.

Image on Progressive Dysarthria

TO THE EDITOR: I read with interest the Images in Neuroscience article by Oleh A. Selnes, Ph.D., and colleagues (1) regarding the 57-year-old man with progressive dysarthria. The anatomic and functional neuroimages over a 5-year period were indeed quite compelling.

I am most dismayed, however, that no reference was made to formalized speech language pathology or neurolinguistic assessment and treatment for this individual. Although neuropsychological assessments are quite helpful in obtaining a broad-spectrum picture of an individual's functioning in many domains, more precise elucidation of neurolinguistic deficits is the providence of speech language pathology. The authors apparently were unaware of this critical feature in their discussion.

In general, I am deeply concerned that a medical specialty in which communicative intent and language function are such a critical component of assessment and treatment modalities can have such an extremely low comfort level in referring to and using speech language pathology. Perhaps we could benefit, as our British colleagues do (2), from increasing our familiarity with neurolinguistic and speech language pathology assessment and treatment. I would be interested in any information regarding treatment course for this unfortunate 57-year-old gentleman if the authors would be so inclined.

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Dr. Selnes and Colleagues Reply

TO THE EDITOR: We appreciate Dr. O'Shanick's comments regarding our patient with primary progressive dysarthria. We agree that careful evaluation of speech and language functions can be of invaluable importance in the workup of patients with atypical neurological conditions. The focus of our brief report was, however, on the radiological features of the case. Neuropsychological and speech/language testing was performed during the patient's first visit to our clinic. At that time his speech and language symptoms were too subtle to make a diagnosis, and results of the remainder of his neuropsychological examination were within normal limits. On subsequent follow-up testing, and with progression of his symptoms, quantitative and qualitative analysis of his speech and language symptoms allowed us to make the diagnosis of primary progressive dysarthria, which is a very rare condition. Additional follow-up documented the lack of significant involvement of the disease in cognitive domains other than language, a crucial feature of the diagnosis. Our patient was seen for formal speech and language therapy, but because of the relentlessly progressive nature of his disease, he became frustrated with the lack of progress. He has, nonetheless, enjoyed some success with a computer-assisted speech device.

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Visual Perception in Medicated Schizophrenic Patients

TO THE EDITOR: We read with great interest the article by Brian F. O'Donnell, Ph.D., and colleagues (1) about selective deficits in visual perception and recognition in schizophrenia. Results showed that schizophrenic patients exhibited slower and less accurate responses in tests of visual perception and visual recognition. However, since patients in this study were medicated, it appears difficult to link schizophrenia and visual impairment. Dopamine exerts a strong influence on visual perception and reaction time. Visual contrast sensitivity is particularly impaired in Parkinson's disease (2). Moreover, in visual contrast sensitivity tests, levodopa treatment is able to restore an almost normal visual pattern in patients suffering from Parkinson's disease (3, 4). Neuroleptics also impair visual contrast sensitivity and may exert a negative influence on reaction time response (5, 6). Therefore, medicated patients are very likely to present visual disturbances. New studies with nonmedicated schizophrenic patients are now necessary both to assess any visual abnormality that is directly linked to schizophrenia and to research the respective characteristics of treatment and disease.

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TO THE EDITOR: We read with interest the article by O'Donnell and colleagues. Of particular interest was the performance of the schizophrenic patients on discrimination, recognition, and judgment tasks. The results indicated that schizophrenic patients were unimpaired in processing form attributes (high spatial frequencies and patterns) but impaired in processing motion. These findings were interpreted as suggesting that schizophrenic patients have a deficit in a discrete perceptual channel that has been characterized as highly sensitive to "transient" stimulation, luminance contrast, and low spatial frequency. This transient deficit is further associated with specific anatomic systems.

Noticeably absent was the authors' inclusion of a body of converging evidence for an "aberrant transient theory" explanation for visual information processing and for attention deficits in schizophrenic patients. Specifically, Schwartz and Winstead (1) proposed that a dysfunction in neurophysiologic visual transient channels contributed significantly to the information processing impairment in schizophrenic patients.

This study was followed by a series of approximately 15 studies, including our most recent (Schwartz et al. [2, 3]), that extended our evaluation of both spatial and temporal components of information associated with the neurophysiologic substrate of preattentive and attentive processes in schizophrenic patients. The results of these studies converged to add significant support for neurophysiologic deficit in transient channel activation that parallels the preattentive (sensory) stage of processing for schizophrenic patients. This finding has been consistently observed as being instrumental in the expression of information processing and attention disorders associated with schizophrenia (4–8). Also, a temporal epoch (70–150 msec) as reported by Schwartz et al. (1, 9) coincides with the time of temporal integration by transient cells and parallels other psychophysiologic findings for schizophrenic information processing and attention deficits.

We are encouraged that the findings of O'Donnell et al. corroborated our findings for an aberrant transient function associated with a dysfunction of the dorsal pathway of the visual system. However, the omission of the scientific papers to which their work is related impedes the progress of understanding information processing and attention in schizophrenic patients and diminishes the likelihood that the converging evidence will influence future research.

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Dr. O'Donnell and Colleagues Reply

TO THE EDITOR: We appreciate the helpful discussion by Drs. Bonnet and Chabrol regarding the influence of dopamine on visual contrast sensitivity in schizophrenia and agree that this issue warrants further investigation. Visual abnormalities due to dopaminergic dysregulation may vary with spatial frequency. Depot injections of neuroleptics in schizophrenic patients increase contrast sensitivity to low spatial frequency stimuli and reduce sensitivity to high spatial frequency stimuli (1). Neuroleptic medications may improve sensitivity to lower spatial frequencies in schizophrenia but do not return this sensitivity to normal levels. In a study of spatial frequency discrimination in 11 male medicated schizophrenic patients and 10 male comparison subjects, we found that patients showed a 12% accuracy decrement for low (0.5 cycles per degree) spatial frequency discrimination (t=2.9, df=19, p=0.009) but a nonsignificant 4% accuracy decrement on high (8 cycles per degree) spatial frequency discrimination (t=0.97, df=19).

Drs. Bonnet and Chabrol cited Bulens et al.'s 1989 study that reported preferential loss of low-to-middle spatial frequency contrast sensitivity in schizophrenic patients with drug-induced parkinsonism. It is unclear whether these visual deficits can be attributed to CNS or retinal dopaminergic abnormalities. Harris et al. (1) suggested that variations in contrast sensitivity at different spatial frequencies may reflect activity in the dopaminergic amacrine cells of the retina: greater dopaminergic activity is associated with loss of visual contrast sensitivity at low spatial frequencies, and reduced dopaminergic activity is associated with loss of sensitivity at high spatial frequencies. As Drs. Bonnet and Chabrol suggest, a comparison of visual processing in medicated and nonmedicated schizophrenic patients or in patients receiving antipsychotic medications with different pharmacological profiles could provide insight into these basic issues.

Whether disturbances in contrast and spatial frequency perception contribute to disturbances in higher-order visual cognition and memory in schizophrenia remains an intriguing question. Visual short-term memory deficits, for example, are unaffected by medication (haloperidol) status (2), which suggests that late-stage cognitive processes may be less sensitive to dopamine levels. The relationship of spatial frequency deficits to motion perception, which may preferentially use low spatial frequency information (3), is of particular theoretical interest.

We thank Drs. Schwartz and Winstead for their concise summary of the literature on visual persistence and visual masking in schizophrenia. Backward masking techniques typically involve the delivery of two short-duration stimuli in rapid succession. The first stimulus is the target, and the second is the masking stimulus. Depending on the characteristics of the stimuli and interstimulus interval, the masking stimulus may interfere or fuse with the perception of first stimulus. Patients with schizophrenia, particularly those with poor premorbid adjustment or chronic course, show greater susceptibility to backward masking than comparison subjects (4, 5). While there are a variety of theoretical interpretations of the backward masking deficit, Schwartz and Winstead argue persuasively that an underlying deficit in transient channel processing could encompass many of these findings, as well as disturbed motion perception and eye tracking. The biological substrates of early stage processing failures have now come under scrutiny at several laboratories. We have found that amplitude of early receptor potential over occipital recording sites is reduced in chronic schizophrenic patients as early as 160 msec after stimulus onset in a location discrimination task (6); this deficit was most severe on the left side of the scalp to right visual field targets. Studies that used functional magnetic resonance imaging and positron emission tomography have shown greater activation to visual stimulation in the occipital lobe of schizophrenic patients than of comparison subjects (7–9). In aggregate, we agree that these findings implicate early-stage visual processing in schizophrenia and suggest that specific channels or neural populations may be vulnerable to disruption.

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Hypnotizability Used for Diagnostic Confirmation?

TO THE EDITOR: The measuring of hypnotizability as an aid to confirming a diagnosis is favored by some but not by others. I, and other readers, I am sure, would welcome answers to the following questions to help understand what motivated the use of the Hypnotic Induction Profile in the clinical case conference of Sara L. Stein, M.D., and colleagues (1).

What was the atypical quality of this patient's hallucinations that was reminiscent of a dissociative disorder and prompted the use of this test? In view of her high score, did the authors conclude that psychosis was not part of the clinical picture? Had she scored low, would that have confirmed the presence of psychosis, ruled out a dissociative disorder, or neither?

How was the hypnosis introduced to the patient, and was she led to believe the procedure was intended to uncover past traumatic memories? Knowing what they now know, do the authors believe they would still administer the hypnotizability test and encourage the uncovering of traumatic memories in this patient?

In view of the fact that the procedure, even in experienced hands, causes patient distress without much apparent benefit, what precautions do the authors recommend to clinicians planning on measuring the hypnotic capacity in patients with long-standing histories of psychosis, delusions, and erotomania?

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Dr. Stein and Colleagues Reply

TO THE EDITOR: We appreciate the opportunity afforded to us by Dr. Frankel, himself a contributor to the literature on hypnotizability in clinical populations, to expand upon the importance and nature of hypnotizability assessment in our clinical case conference.

As we noted, this young woman's hallucinations were atypical in that they were not merely auditory but involved visual and tactile components. Such visual hallucinations, especially in an individual with high hypnotizability, have been noted to be typical of what used to be called "hysterical psychosis" (1, 2) and would be called brief psychotic disorder in DSM-IV. She also spent considerable amounts of time in dreamlike states and would awaken at night screaming; these are both potentially dissociative symptoms.

The patient had a 6-year history of psychosis that had been refractory to typical neuroleptic pharmacotherapy. Her high hypnotizability score was not used to determine *whether* she was psychotic—she clearly was—but rather to assist in determining *what kind* of psychosis she had. The literature has shown that schizophrenic patients have generally lower, and never very high, hypnotizability (3, 4). Thus, her high score made the schizophrenic form of psychosis less likely.

Had this patient's hypnotizability score been low, it would have made an atypical psychosis such as the one she had secondary to probable neuroborreliosis less likely, and a dissociative disorder would also have been less likely. Indeed, Steingard and Frankel (5) reported on the relationship between high hypnotizability and dissociative psychosis: "Certain highly hypnotizable people may be prone to experience transient but severe psychotic states while in spontaneously occurring trance states." In that case, the patient's high hypnotizability was used effectively in differential diagnosis and in psychotherapeutic treatment.

Our patient was told that we would first assess her ability to experience hypnosis by using a standard measure and that the information we obtained might help us clarify the nature of her condition and possible means of treating it. It was clear to her that she was free at any time to refuse or interrupt the procedure. She did not. She was then told that she was quite hypnotizable and that further hypnosis might be of help to her in dealing with her symptoms. Instead of discussing her persistent erotomanic delusion, she became preoccupied with a different sexual episode.

The hypnotizability test was not traumatic to the patient. She was distressed by the subsequent exploration, which was discontinued. We found no confirmation from the patient or her family that the episode had occurred and did not imply to her that we thought it had. One of the most useful features of hypnotizability testing is that it allows for rapid and clear identification of the utility of therapeutic techniques that employ hypnosis. In this case the testing suggested that it might be useful, but the patient's response led us to search for and use other avenues of diagnosis and treatment.

After 7 months of daily intravenous antibiotics, the patient's symptoms and results of another imaging scan and additional neuropsychological testing were improved, and her cerebrospinal fluid was antibody-negative for the first time. She began a daily oral regimen of minocycline. Her daytime somnolence responded successfully to a 5-mg dose of methylphenidate at noon. While she still suffers from delusions and nightmares, they are sufficiently contained, and she was able to celebrate her 1-year anniversary of continuous part-time employment.

Taking a history, performing a physical and mental status examination, and conducting psychotherapy may cause tran-

sient distress in the service of effective treatment, which will reduce long-term distress. Measuring hypnotic capacity is an informative and benign procedure. We would do it again.

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Breast Cancer Risk in Psychiatric Patients

TO THE EDITOR: The brief report by Uriel Halbreich, M.D., and colleagues (1) suggests that chronic psychiatric patients may be at greater risk of developing breast cancer. However, several aspects of the study design predispose to biases that could be responsible for the observed association. Because of the serious nature of breast cancer, it is important that reported predilections to the disease, even if qualified by recommendations for further research, be carefully scrutinized.

One of the most concerning potential biases was the inclusion of prevalence cases of breast cancer with incidence cases. Because estimates of risk of disease development involve a specified time interval (often 1 year), only the latter should have been considered. Prevalence cases of breast cancer were included in the psychiatric population: two of seven cancer patients had been diagnosed previously, and an additional patient had a note in the record "breast malignancy found by surgeon." More subtle prevalence cases may have been included if psychiatric patients did not undergo regular breast examinations and mammograms, which led to inclusion of patients with cancer that had been present for 2 or 3 years. The extent to which prevalence cases were included in the comparison group is not clear and may have been different.

Full access to the medical records of psychiatric patients, in contrast to less complete access to the records of the comparison subjects, may have led to more frequent confirmation of breast cancer in the former and an underestimation of breast cancer in the latter—a diagnostic confirmation bias.

The chance occurrence of a cluster of cases of a disease in a given population may prompt investigation. In order to avoid overestimation of risk due to this chance clustering, the cases that led to the initial hypothesis should have been excluded and risk of disease examined in subsequent patients.

Finally, the difference in age between the two study groups is of concern. Given that risk of breast cancer increases with age, estimates of risk should have been age adjusted.

Taken together, these potential biases may have accounted for an apparent 3.5-fold greater risk of breast cancer in chronic psychiatric patients. Exclusion of patients with prior breast cancer from the psychiatric group may lower the apparent relative risk to 2. The influence of the other aforementioned biases may account for the remaining apparent elevation in risk.

Further research is necessary. However, this research will take considerable time, particularly if cohort studies, which are least susceptible to bias, are performed. In the meantime, the evidence that chronic psychiatric patients have a greater risk of developing breast cancer is weak. Instead of raising fears about greater breast cancer risk in chronic psychiatric patients, a commitment to the provision of comprehensive medical care, with a focus on breast health, is probably the most sensible approach to take until additional information is available. The literature is replete with examples of potential risk factors for breast cancer that have not been substantiated after subsequent investigation. Prudence is advised in interpreting and acting upon the results of this report.

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TO THE EDITOR: The report of Halbreich et al. is remarkable insofar as it cited none of the past studies of cancer incidence in psychiatric patients. Such studies date to 1925, and a review by Perrin and Pierce in 1959 (1) cited 21 studies done before that time. The most recent and methodologically best studies were carried out by Mortensen and Juel, who used the national psychiatric and cancer case registries in Denmark (2–4).

Specifically regarding breast cancer in psychiatric patients, Ettigi et al. (5) reported that patients with prior admissions to psychiatric hospitals had a greater risk of developing breast cancer, but studies by Overall (6), Kanhouwa et al. (7), and Mortensen (4) reported no increase. Mortensen used a case control method to examine the possible role of antipsychotic medication in causing four types of cancer and concluded that "treatment with haloperidol decreased the risk of developing breast cancer" (8), a conclusion opposite to the speculation of Halbreich et al.

Any indication of higher risk of breast cancer or other types of cancer in psychiatric patients should be carefully assessed and followed up. The evidence to date, however, suggests no such greater risk. In fact, the most striking observation to emerge from studies of cancer in psychiatric patients is the apparent lower risk of lung cancer among individuals diagnosed with schizophrenia despite very high rates of smoking in these patients (9).

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TO THE EDITOR: Halbreich et al. report to have found a higher incidence of breast cancer in chronic psychiatric patients. They conclude that this may be an effect of medication and state that screening mammograms are needed in this patient group.

However, some methodological problems make their study difficult to interpret. First, they do not describe their study population in any detail with respect to diagnoses, treatment, or duration of illness, and they do not discuss whether patients with physical health problems may have been referred more frequently to the psychiatric hospital. Also, they do not discuss the possible impact of known risk factors for breast cancer, e.g., parity, on their findings. Their calculations are not adjusted for age, and they compare the cancer rates among psychiatric patients, which were based on systematic mammogram screening, with data from the general population, which were based on other case finding strategies. Obviously, it is important to monitor possible long-term effects of treatment with psychotropic drugs. However, thus far only a few studies have addressed the issue, and none has demonstrated a greater risk associated with psychotropic drugs. Thus, Schyve et al.'s conclusion that "it is premature to mandate warning patients of an unknown and undemonstrated increase in the risk of developing breast cancer associated with neuroleptic treatment" (1) still seems reasonable, and it is equally premature to make specific recommendations regarding screening mammograms in psychiatric patients.

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Dr. Halbreich Replies

TO THE EDITOR: My colleagues and I reported that when mammograms were routinely performed with chronic psychiatric female patients, the incidence of diagnosed breast cancer was significantly higher than that found in women who were referred for mammograms in a general hospital, and much higher than the rate of the Surveillance Epidemiology and End-Result Program.

From these three letters and other communications it is obvious that awareness of that possibility has been raised. Length limitations for brief reports prohibited a critical review of the relevant literature, which I will briefly note here. Katz et al. (1) reported that between 1955 and 1961 the mortality rate from breast cancer of patients hospitalized with mental disorders was similar to that of the general population; drug history was not known. Dr. Torrey cited the study of Ettigi et al. that reported higher incidence of breast cancer than carcinoma of the colon-rectum. A recalculation of his numbers shows an incidence of 1734.1/100,000 for total psychiatric population; ages were not provided. The report of Kanhouwa et al., which used diagnoses that were derived from "annual physical examinations and chest x-rays," did not confirm these results. Dr. Torrey also cited the study of Overall that reported the incidence of schizophrenia and other psychiatric diagnoses among general hospital patients who were diagnosed as having breast cancer or cancer of other sites and did not find a substantial difference between the two cancer groups. He did not report any data on the incidence of breast cancer among psychiatric patients. The WHO project by Gulbinat et al. on cancer incidence of schizophrenic patients reported that while there was less relative risk of several cancers, at two of the three study sites (Japan and Hawaii) there was a greater risk of breast cancer among all female schizophrenic patients (with no age selection). This was not found in the Danish site. A later study that used an extended Danish database, the 1994 study of Mortensen, demonstrated an overall decrease of relative risk of several cancers in schizophrenic patients. However, even though the author concluded that "no increase of breast cancer risk was found," the incidence of breast cancer was reported as being 628.9/100,000 among all female schizophrenic patients, and the author stated that "statistical power in the present study was further compromised by the low mean age and thus low base risk for cancer of the study population." In 1987, Mortensen reported a case-controlled study of a subgroup from the Danish registry, in which a higher incidence of breast cancer was found in patients who received high doses of reserpine but not in patients who were ever treated with haloperidol or chlorpromazine, for whom doses and cutoff points were not clear. The diagnostic procedures of breast cancer in these studies of psychiatric patients are not clear, and presumably there was no special attention to breast examinations. No mammograms were performed, and the focus was not on women 40–50 years and older who are the age group at higher risk.

As for predisposed biases, our study was not initiated because of a chance cluster of cases, so there was no need for such presumed patients to be excluded. There was no inclusion of three prevalence cases; the three patients did not have a detailed copy of the post-mammogram/post-surgery pathological report in their psychiatric charts. We compared an unselected psychiatric group, all of whom had routine mammograms, to a group referred for mammography because of high risk or to rule out a suspected breast mass. If anything, higher incidence of malignancy would be anticipated in the specialized clinic—this was not the case. Some other reservations would not have been raised if the writers read the report and previous literature carefully and objectively.

The issue of any severe side effect of psychotropic medications is very sensitive, especially when emotionally loaded malignancy is at focus. A similar controversy happened very recently in Canada in conjunction with in vitro and clinical reports of possible tumor growth stimulation by some psychotropic medications (2). This issue is complex. One should distinguish among carcinogenesis, tumor growth stimulation, and tumor inhibition. Furthermore, a multitude of drugs, including some psychotropic medications, appear to have bell-shape or biphasic dose-response curves. They cause growth enhancement in low or average doses and growth inhibition in higher doses (2). The comprehensive picture needs to be objectively evaluated. Epidemiology and statistics

are the first step; they might be correct even if the underlying mechanisms are not clear yet. Wishful concerns should not cloud suspected unpleasant reality. This is a case in which I myself wish to be wrong, but the current literature casts at least a reasonable possibility that chronic psychiatric patients might be at higher risk for breast cancer. Like any other suspected adverse effect, this should be adequately studied and, if confirmed, be part of the benefit-risk evaluation. Considering the favorable outcome of early detection and treatment, the suspected greater risk of breast cancer should not deter psychiatrists from the pharmacological treatment of patients with schizophrenia. However, psychiatrists should be aware of possible side effects and actively examine for them. Obviously, psychiatric female patients—like other women—should follow the recommendations of the American Cancer Society and the National Cancer Institute that call for every woman above the age of 50 to have an annual physical examination and mammogram.

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Reprints of letters to the Editor are not available.

Corrections

In "A National Study of Psychiatrists' Professional Activities" by Robert A. Dorwart, M.D., M.P.H., et al. (November 1992, pp. 1499–1505), there are two changes to the wording of the second paragraph on page 1502. The second sentence should begin "The average work week for psychiatrists was 48 hours, ..." The last sentence in the same paragraph should read "Included in the total were 8 hours per week of professional activity that were unpaid."

In the article "Anticipation in Schizophrenia: New Light on a Controversial Problem" by Philip Gorwood, M.D., et al. (September 1996, pp. 1173–1177), the correct version of the equation in the second column on page 1174 is given below:

$$Eaao = \int_{t < aai} tg(t)dt \,/\, \int_{t < aai} g(t)dt$$

In the letter "Traumatophilic Diathesis, Complemental Series, and the Original Conceptual Basis of PTSD" by Michael S. Good, M.D. (February 1997, p. 296), on the 10th line of the third paragraph, the text should read as follows: "He [Karl Abraham] believed the traumatic experience determined the form, as opposed to the occurrence, of the disorder. Despite certain problems in Abraham's formulation, he sought to integrate constitutional and environmental elements in a way that has contemporary relevance."