Topiramate-Induced Depression

TO THE EDITOR: Topiramate, an antiepileptic medication, is often used as an adjunctive mood stabilizer for patients with bipolar disorder (1). Potential weight loss makes this medication appealing; however, depression is another reported side effect (2). We report on three patients with bipolar disorder in which topiramate may have exacerbated depression. Topiramate was prescribed in lieu of higher doses of the patients' current mood stabilizers because of concerns about weight gain.

Ms. A, a 24-year-old woman, was seen with irritability and mild depression. She was currently taking gabapentin and zolpidem. Treatment with topiramate was initiated at 25 mg/day and titrated to 50 mg/day. After 2 days at the higher dose, Ms. A reported severe depression and suicidal ideation. Topiramate was promptly discontinued; 1 week later Ms. A no longer felt hopeless or suicidal.

Ms. B, a 40-year-old woman, reported racing thoughts but no depressive symptoms; her current medications were valproic acid, risperidone, and cetirizine. Treatment with topiramate was titrated to 50 mg/day over 1 week. One week later Ms. B reported severe depression with anergia and anhedonia. Decreasing her dose of topiramate stepwise over 2 days relieved her depressive symptoms.

Ms. C, a 34-year-old woman taking fluoxetine, thyroxine, and valproic acid, was seen with irritability, racing thoughts, psychomotor agitation, and anxiety. Topiramate therapy was initiated, and the dose was titrated over 1 week to 50 mg/day. Two weeks later Ms. C called to report severe depression, vague suicidal ideation, and anhedonia. Her dose of topiramate was decreased to 25 mg/day and discontinued 3 days later. Three days after discontinuation Ms. C reported not being depressed.

We report on these patients to highlight a possible relationship between topiramate and substantial depression in patients with bipolar disorder. Symptoms of depression began or increased within 1 week of topiramate treatment or with titration to 50 mg/day. Each of the patients experienced significant relief from depression 1 to 2 weeks after discontinuation of topiramate. The close association with onset of the most severe depression these patients had ever experienced is notable. However, although no new medications had been initiated in the previous 3 months in any of these cases, all of the patients had a diagnosis of bipolar disorder, so the onset of depression could have been coincidental. Their depression may also have been due to a synergistic interaction between topiramate and their other medications. These symptoms of depression correlate with the neurology literature (2, 3), in which psychiatric disorders are noted to occur with topiramate therapy. Although topiramate has been shown to be effective in mood stabilization, physicians prescribing it should be aware that serious depression might be an adverse effect. This observation merits further research.

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Agranulocytosis and Neutropenia With Typical and Atypical Neuroleptics

TO THE EDITOR: Antipsychotic drugs can induce neutropenia, which can be followed by agranulocytosis and even be fatal if drug therapy is not interrupted. Olanzapine and risperidone are newer antipsychotic drugs that tend to reduce the risk of hematotoxicity. Nevertheless, there have been reports of olanzapine- and risperidone-induced agranulocytosis (1, 2). We report a rare case of typical (perphenazine) and atypical (clozapine, olanzapine, and risperidone) antipsychotics associated with neutropenia and agranulocytosis, respectively.

Ms. A was a 19-year-old woman with a diagnosis of schizophrenia. She had been receiving clozapine (up to 400 mg/day) for 7 weeks when she developed a temperature of 40°C. Her WBC count was 0.5×10^9/liter, and her absolute neutrophil count was 0.2×10^9/liter. Her WBC count continued to decrease to 0.1×10^9/liter, and she had a zero absolute neutrophil count the next day. A bone marrow biopsy revealed almost complete discontinuation of the proliferation and maturation involved in granulocytopoiesis, and so granulocyte-colony-stimulating factor was administered to Ms. A in addition to supportive measures. On the 24th day after treatment, her blood counts returned to normal.

One year later, Ms. A had a relapse of schizophrenia. She began taking perphenazine (up to 20 mg/day). In the 4th week, her WBC count was 3.0×10^9/liter, and her absolute neutrophil count was 1.2×10^9/liter. She stopped taking perphenazine. On the 14th day after discontinuation Ms. A had normal blood counts. One month later, Ms. A began taking olanzapine, 2.5 mg/day; on the 8th day of treatment, her dose was 5 mg/day. On the 17th day, her WBC count was 2.0×10^9/liter, and her absolute neutrophil count was 0.88×10^9/liter. She stopped taking olanzapine. Granulocyte-colony-stimulating factor was again administered. Ten days later Ms. A's blood profiles had again returned to normal.

Three months later, Ms. A experienced again psychotic symptoms, including auditory hallucinations; she began taking risperidone, 1 mg/day. On the 14th day of treatment, her WBC count was 3.0×10^9/liter, and her absolute neutrophil count was 0.75×10^9/liter. She then stopped taking risperidone.

In this case, which involved no other potentially hematogenous disease, the patient had normal blood counts before she began taking four different antipsychotic drugs. It is not clear whether these neuroleptics possess the same iatrogenic effect, but the patient may have had genetic determinants for drug-induced agranulocytosis (3). The only strategy for preventing such an effect is with early diagnosis by frequent, periodic absolute neutrophil counts.

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Quetiapine-Related Tardive Dyskinesia

TO THE EDITOR: Although cases of tardive dyskinesia associated with atypical neuroleptic agents have been reported, most such cases involve individuals with previous long-term histories of treatment with traditional neuroleptic agents. Thus, later development of tardive dyskinesia cannot be definitively ascribed to the effects of atypical neuroleptics alone. Specifically, quetiapine has been reported to produce low rates of extrapyramidal symptoms and of dopamine D_2 receptor blockade, even at high doses (1). We are aware of only one previously reported case of tardive dyskinesia associated with quetiapine, which occurred in a 44-year-old woman with schizophrenia who had received treatment with typical neuroleptics for many years (2). We report a case of apparent quetiapine-related tardive dyskinesia in a young woman who had never been exposed to typical neuroleptics.

Ms. A, a 25-year-old woman with type I bipolar disorder, was seen in consultation. She had been diagnosed and treated for bipolar disorder for the previous 4 years with combinations of mood stabilizers, anticonvulsants, and atypical antipsychotic agents. She had never taken typical neuroleptic medications. Among her previous medications were lithium, carbamazepine, divalproex sodium, lamotrigine, fluoxetine, bupropion, gabapentin, and topiramate. She took olanzapine for 1 month but discontinued it because of weight gain. She took risperidone for less than 1 week, discontinuing it because she developed a rash. She received quetiapine as an alternative to olanzapine when the latter was discontinued.

The indication for treatment was persistent rapid-cycling mood episodes despite concomitant treatment with gabapentin, 4400 mg/day, and lithium, 900 mg/day. Ms. A's quetiapine dose was gradually increased to a maintenance dose of 125 mg/day. Repetitive involuntary jaw movements were noticeable within 6 weeks of the initiation of quetiapine treatment and persisted despite a decreased dose. Quetiapine was discontinued after 13 weeks of treatment because of the jaw movements. Ten months after the initiation of quetiapine Ms. A's mild repetitive involuntary lower jaw movements remained. Her mood symptoms had improved with 4400 mg/day of gabapentin, 900 mg/day of lithium, and 200 mg/day of topiramate. No other involuntary movements were noted.

This case suggests that quetiapine can be associated with abnormal involuntary movements, even in someone never exposed to traditional neuroleptics. This patient suffered from bipolar disorder, rather than schizophrenia, which may increase the risk of tardive dyskinesia. It is important to note that despite these occasional instances of tardive dyskinesia, large controlled studies suggest that the rates of association with atypical neuroleptic agents are low, near the spontaneous rate of association with schizophrenia (3–5). In our extensive experience using atypical neuroleptic agents to treat mood disorders, we have rarely observed tardive dyskinesia.

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Addition of Olanzapine for Treatment-Resistant Depression

TO THE EDITOR: Olanzapine is a newer atypical antipsychotic with a broad spectrum of affinity for several receptors (serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_6 and dopamine $D_{1–5}$, α_1, histamine H_1, and muscarinic $M_{1–5}$). Some reports have suggested that olanzapine can have antidepressant properties (1–3). We describe the case of a woman with a long history of treatment-resistant nonpsychotic chronic depression who exhibited a dramatic improvement after the addition of olanzapine to her venlafaxine treatment.

Ms. A was a 40-year-old woman with a 10-year history of unipolar nonpsychotic major depression. She had been treated with several antidepressants, including tricyclics such as amitriptyline and clomipramine, which were prescribed at doses higher than 200 mg/day for at least 8 weeks, and selective serotonin reuptake inhibitors (paroxetine, 40 mg/day, fluoxetine, 40 mg/day) for more than 12 weeks. We had also tried augmentation with lithium, 750 mg/day, and carbamazepine, 600 mg/day, without success.

During a particularly severe depressive episode (21-item Hamilton Depression Rating Scale score of 36), Ms. A was consecutively treated with iproclozide, a monoamine oxidase inhibitor, and ECT, but she experienced only a partial response. All of these trials appeared unsuccessful in achieving remission, and Ms. A remained chronically depressed for several years, with a score regularly higher than 15 on the 21-item Hamilton depression scale. Her last treatment with venlafaxine, 300 mg/day, was associated with a moderate improvement in her depressive symptom profile (Hamilton depression scale score of 16). Because of mild nausea and sedation, her venlafaxine dose was decreased to 225 mg/day over about 1 year.

On the basis of the potential antidepressant effect of the newer antipsychotics, we decided to add olanzapine, 5 mg/day, to her treatment with venlafaxine, 225 mg/day.

After 2–3 days Ms. A experienced an impressive improvement in her depressive symptoms, achieving a complete remission for the first time in 10 years (Hamilton depression scale score of 0). Olanzapine was well tolerated, with the exception of mild weight gain. Unfortunately, Ms. A considered the weight increase a major side effect and stopped taking olanzapine. After 4–5 days she experienced a new depressive symptom profile, consisting of a depressed mood, sadness, insomnia, a decrease in activities, and feelings of guilt and anxiety (Hamilton depression scale score of 14).

After 1 month she agreed to take olanzapine again, which was associated with a further dramatic antidepressant response after 3 days of administration. Her Clinical Global Impression (CGI) score for severity of illness was 1, and the CGI global improvement score was 1. Ms. A's family described this improvement as unexpected. Currently, her full remission has been maintained for 15 months.

This report provides additional evidence of the possible usefulness of atypical antipsychotics, and in particular olanzapine, in the management of treatment-resistant depression. Indeed, recently, in a randomized, double-blind, amitriptyline-controlled study, Svestka and Synek (3) demonstrated the antidepressant efficacy of olanzapine in the treatment of depressed patients with bipolar and unipolar disorder. Shelton et al. (4) also observed the superior efficacy of olanzapine with fluoxetine compared to olanzapine or fluoxetine alone. In fact, atypical antipsychotics such as olanzapine could be particularly effective as an adjunctive treatment (5). However, further studies are needed to determine whether the augmentation effect of olanzapine is observed with other antidepressant medications.

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Estrogen-Replacement Therapy for Depression

TO THE EDITOR: Women are more vulnerable to a depressed mood during the perimenopausal years than during the premenopausal years (1). Estrogen-replacement therapy has been suggested as a potential treatment for a depressed mood during perimenopause (1). Whether to treat a perimenopausal woman who has depression with estrogen alone, an antidepressant alone, or a combination of both of these medications is controversial.

We evaluated 10 treatment-naive perimenopausal women (mean age=48.8 years, SD=2.9; mean education=15.2 years, SD=3.2) who came to the Mood Disorders Clinic at the University of California at Los Angeles (UCLA) for the treatment of major depressive disorder. Perimenopause was defined as irregular menstrual periods or an absence of menstrual periods for less than 1 year, with plasma levels of follicle-stimulating hormone greater than 20 IU/liter. Subjects were excluded if they received hormonal medication or had a medical illness, a history of drug or alcohol abuse, or a psychiatric disorder other than depression.

The diagnosis of major depressive disorder was made on the basis of the Structured Clinical Interview for DSM-IV, Patient Edition. The Hamilton Depression Rating Scale was administered to subjects at baseline and weekly thereafter as the outcome variable for the assessment of the degree of remission from depressive symptoms. A response was defined as a final Hamilton depression scale score of 50% or less of the subject's baseline level. Remission was defined as a final Hamilton depression scale score of 7 or lower. The subjects' mean Hamilton depression score at baseline was 18.1 (SD=3.1). All subjects gave written informed consent to participate in an open trial of estrogen-replacement monotherapy for 8 weeks. The UCLA institutional review board approved this study protocol. All patients received 0.3 mg/day of 17β-estradiol without progesterone or an antidepressant for 8 weeks.

Depression had remitted in six of the 10 women by the end of the trial. Three additional subjects met the criteria for response, and one subject had no response to treatment. Degree of remission was not associated with the demographic or clinical characteristics of the patients. No patients reported any adverse effects. Overall, the subjects' mood had improved after the first week of treatment ($t=2.61$, $df=9$, $p<0.05$). This improvement continued throughout the study ($F=10.71$, $df=8, 112$, $p<0.001$).

This study suggests the efficacy of estrogen-replacement therapy in depressed perimenopausal women (1). Consideration of the use of estrogen-replacement therapy as an alternative to standard antidepressant treatment may be in order if future research demonstrates the clinical efficacy of estrogen in the treatment of depression.

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Complaints of Impaired Memory in Veterans With PTSD

TO THE EDITOR: Given the research identifying the existence of memory deficits in people with chronic combat-related posttraumatic stress disorder (PTSD) (1), it is not surprising that so many veterans complain of memory difficulties (2). Unfortunately, there are few data on the relationship between subjective and objective memory deficits. We examined archival data to evaluate this relationship.

Data came from 129 consecutive male veterans seen at the Central Arkansas Veterans Healthcare System's PTSD Evaluation Program. After a psychiatric interview in which the diagnosis of PTSD was confirmed, all patients completed a program assessment, which consisted of a number of clinician-administered and self-report evaluations and measures of intelligence and memory, as well as a measure of subjective memory. The patient group had a mean age of 52 years (SD=7) and a mean education level of 12 years (SD=2). An abbreviated form of the WAIS-R yielded scores within the average range (full-scale IQ: mean=97, SD=11; verbal IQ: mean=96, SD=11; performance IQ: mean=99, SD=13). Likewise, a score falling within the average range was generated on a measure of immediate verbal memory, the memory index of the Wechsler Memory Scale III (3) (mean=90, SD=17).

Psychopathology was measured with the Beck Depression Inventory (mean score=28, SD=9), the Brief Symptom Inventory (4) (mean global severity index=2.4, SD=0.5), the Dissociative Experiences Scale (5) (mean score=26, SD=15), and the Mississippi Scale for Combat-Related PTSD (6) (mean score=128, SD=17). Subjective memory was assessed with the Everyday Memory Scale (7) (mean score=103, SD=51).

The veterans' Everyday Memory Scale scores were not significantly correlated with the verbal memory index ($r=-0.05$, $N=105$, $p=0.60$), nor were they significantly correlated with any of the IQs (full-scale IQ: $r=-0.18$, $N=105$, $p=0.06$; verbal IQ: $r=1.19$, $N=105$, $p=0.054$; performance IQ: $r=-0.16$, $N=105$, $p=0.11$). The Everyday Memory Scale, however, was significantly correlated with each of the measures of psychopathology: the Beck Depression Inventory ($r=0.48$, $N=105$, $p<0.001$), the global severity index from the Brief Symptom Inventory ($r=0.53$, $N=105$, $p<0.001$), the Dissociative Experiences Scale ($r=0.34$, $N=105$, $p<0.001$), and the Mississippi Scale for Combat-Related PTSD ($r=0.42$, $N=105$, $p<0.001$). This pilot study, derived from archival data, suggests that self-reports of poor memory may not reliably reflect the degree of memory impairment these veterans experience. Rather, such self-reports may be effective indicators of emotional distress. Control for substance abuse and other comorbid diagnoses, as well as the addition of a more thorough evaluation of memory functioning, would help to determine the accuracy of these findings.

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Fluvoxamine for Postpartum Depression

TO THE EDITOR: To our knowledge, only two studies have systematically examined the treatment of postpartum depression with standard antidepressants. One found that fluoxetine or cognitive behavior therapy was effective for treatment of major or minor depression appearing in the first 8 postpartum weeks (1). In another open study, sertraline was found to be effective for treatment of major depression occurring within 6 months of delivery (2).

We report on an 8-week, open-label trial of six subjects, approved by the University of California at Los Angeles institutional review board. Primary inclusion criteria consisted of outpatient status, female sex, age between 18 and 45 years, onset of major depression in the first 8 postnatal weeks, and scores of 17 or higher on the 21-item Hamilton Depression Rating Scale and 12 on the Edinburgh Postnatal Depression Scale (3). Subjects with an onset of depression during pregnancy, the presence of psychosis, active suicidal ideation, hypothyroidism, or a history of alcohol or substance abuse within the 12 months before screening were excluded from the study. We obtained written informed consent from all subjects after the study had been explained to them. Subjects began fluvoxamine treatment, 50 mg/day, and were followed with weekly clinical interviews and administration of the Hamilton depression rating scale by a blind rater. Over the first 2 weeks of the study, fluvoxamine doses were titrated to 150 mg/day to achieve clinical response with minimal or no side effects. The primary outcome variable was remission, operationalized as a Hamilton depression scale score of 7 or less.

Statistical analysis of response was performed for all six subjects. Data analysis included the last observation carried forward for a nonresponder who discontinued treatment at week 5. Four subjects (67%) became euthymic, with a mean time to response of 6 weeks (SD=1). Final Hamilton depression scale scores ranged from 2 to 5 for the four responders and 16 to 18 for the two nonresponders. Baseline demographic characteristics and severity of depression did not differ between responders and nonresponders. Past history of depression or prior response to treatment were not predictive of treatment response. The mean final daily dose of fluvoxamine for all subjects was 142 mg/day (SD=20) (150 mg/day for the three responders and both nonresponders and 100 mg/day for one responder). Repeated measures analysis of variance indicated a significant linear decline in Hamilton depression scale scores over time ($F=12.00$, $df=1, 5$, $p=0.02$). Paired t tests demonstrated that the greatest degree of improvement occurred between weeks 2 and 3 ($t=5.48$, $df=5$, $p=0.003$).

Our findings, although limited by our small group size, the single-blind study design, and the lack of a placebo control group, suggest that fluvoxamine is effective in the treatment of postpartum depression. Given the prevalence and complications of postpartum depression, future large-scale studies are warranted.

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Long-Term Lithium for Bipolar Disorder

TO THE EDITOR: We recently discovered an artifact bearing on the effects of time from illness onset to the start of lithium maintenance treatment and measures of treatment responsiveness in patients with bipolar disorder (1). Such findings are pertinent to early intervention in bipolar disorder, a matter of considerable clinical and public health importance. In 1998 we noted an association between shorter latency to treatment and apparently superior treatment response, as measured by the percentage of time ill during lithium maintenance therapy subtracted from the percentage of time ill before treatment. In a later study (2) we analyzed the relationship of treatment latency or pretreatment episode number to morbidity during maintenance treatment in the same clinical population. Response was defined by a survival analysis using length of the first interepisode wellness interval and the percentage of time ill during the treatment. Neither outcome was associated with treatment latency or number of pretreatment episodes.

These inconsistencies led us to reanalyze treatment outcomes in an expanded study group from the same clinical group. We found a striking inverse association between treatment latency and percentage of time ill *before* treatment (r_s= –0.67, N=376, p<0.0001) but no relationship to illness during treatment (r_s=–0.03, N=376, p=0.51). That is, a shorter time to treatment was strongly associated with greater pretreatment morbidity. In turn, outcomes evaluated as change in percentage of time ill were inflated at shorter treatment latencies (r_s= –0.55, N=376, p<0.0001). This effect no doubt contributed to an impression that earlier intervention yielded superior outcomes (1). Instead, this finding appears to derive from an association of a greater treatment-associated change with a greater level of pretreatment morbidity.

Interpretation of the association of greater morbidity with shorter treatment latency is not entirely clear. It may reflect a clinical urgency to start treatment early with very ill patients, or it may represent a mathematically higher proportion of time ill with shorter exposure times. We apologize for any confusion occasioned by our seemingly inconsistent findings and urge caution in use of change in morbidity to evaluate treatment response. In general, there is a need for wider consensus on measures of treatment effectiveness in studies of bipolar disorder (3). Finally, we strongly support efforts at early recognition and clinical intervention in this potentially disabling or lethal illness, without prejudice about potential treatment response based on delay of treatment.

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Gene Expression in Schizophrenia

TO THE EDITOR: Hisham M. Ibrahim, M.D., et al. (1) carried out a postmortem study of schizophrenia brains in which they found low subregional *N*-methyl-D-aspartic acid (NMDA) receptor (NR) NR_1 and NR_2 gene expression in the thalami of their patients. Dr. Ibrahim et al. discounted the possibility that long-term antipsychotic treatment before death could have caused the observed lowering of NMDA, AMPA, and kainate mRNA and receptor expression by citing a single study that indicated that haloperidol did not cause decreased NR_1 binding (2). We note that Dr. Ibrahim et al. did not refer to our own two articles (3, 4), which examined the effects of the antipsychotic flupenthixol on NMDA, AMPA, and kainate receptors in the rat brain.

We used a multiprobe oligonucleotide solution hybridization technique to examine the regulation of gene expression of NR_1, NR_{2A}, NR_{2B}, NR_{2C}, and NR_{2D} in the left rat brain after treatment with the optical isomers of flupenthixol. At a dose of 0.2 mg/kg per day over 1, 2, 4, 8, 12, and 24 weeks, we found that both isomers downregulated the expression of NR_1 mRNA in most regions of the brain. NR_{2A}, NR_{2B}, and NR_{2C} showed significantly decreased expression from 12 to 24 weeks of treatment, but after 2 weeks NR_{2B}, NR_{2C}, and NR_{2D} expression had increased in several brain regions. NR_1 immunoreactivity in the right brain after 4 and 24 weeks of drug treatment was also examined with Western blotting. Both cis- and transflupenthixol significantly decreased NR_1 immunoreactivity in the right cerebellum after 24 weeks of treatment. Expression of the GluR1–7, KA1, and KA2 glutamate receptor mRNAs in the left rat brain were also studied. Neither cis- nor transflupenthixol was found to alter the gene expression of any of the nine non–NMDA glutamate receptor subunits. On the other hand, we found a nearly twofold increase in gene expression of the dopamine D_2 receptor in specific brain regions.

Our results suggest that the observed mRNA changes in NR_1 and NR_2 found by Dr. Ibrahim et al. in the postmortem brain are likely to have been caused by antipsychotic treatment and are not related to the disease process. However, the lowered expression of AMPA and kainate receptor RNAs found by Dr. Ibrahim et al. could indeed be related to schizophrenia itself rather than be an effect of treatment. Findings of previous postmortem studies of glutamate receptors by ligand binding in the schizophrenic brain have been contradictory. Now that all the human genes expressed in the brain have been identified and because genetic linkages on specific chromosomes in schizophrenia are beginning to be well replicated, it seems most likely that progress in this field will pri-

marily result from the identification of genes with mutations that increase susceptibility to schizophrenia. Following this, the various secondary and/or treatment pathways that interact with these primary genetic causes will then become identifiable.

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Dr. Meador-Woodruff Replies

TO THE EDITOR: In their letter addressing our publication on glutamate receptor expression in the thalamus in schizophrenia, Drs. Gurling and Chen raise the issue that plagues the vast majority of postmortem studies in schizophrenia, that of antipsychotic treatment as a potential confounding variable. We suggested in our report that the abnormalities of NR subunit expression that we found in patients with schizophrenia might not be due to long-term antipsychotic treatment, on the basis of an earlier report that antipsychotic treatment did not affect the expression of these molecules in the thalamus (Ulas, 1993).

We recently reviewed the literature on the effects of antipsychotic treatment on the expression of receptors associated with multiple neurotransmitter systems (1). Three interesting observations emerged from this review: neurotransmitter receptors are not regulated by antipsychotics in the same manner throughout the brain but, rather, are altered in a fashion specific to each brain region and circuit; typical and atypical antipsychotics have differential effects on the expression of a number of neurotransmitter receptors in a given region of the brain, and there is considerable variability in published reports, in part attributable to different study methods, drug doses, administration schedules, and discrepancies in the definitions of the brain regions studied. In the specific case of NR subunits that Drs. Gurling and Chen raise, the literature is contradictory, but most studies suggest that in many regions of the brain these molecules are in fact increased in number by antipsychotic treatment (Ulas, 1993) and not decreased, as suggested by Drs. Gurling and Chen.

There are literally hundreds of published reports on the effects of antipsychotics on neurotransmitter receptor expression. Given the emerging evidence for brain region–specific regulation of glutamate (and other) receptors by antipsychotics, we cited the only article of which we are aware that specifically studied the thalamus (Ulas, 1993). In the investigation by the letter authors' group (Chen et al., 1998), the thalamus was not specifically studied; rather, the subject was a gross subcortical dissection, which included a number of structures, likely including the striatum and pallidum in addition to the thalamus. Given that this large body of literature points to differential effects of typical antipsychotics on the expression of NR subunits in various brain areas, this earlier report from Drs. Gurling and Chen's group is relatively uninterpretable vis-à-vis any thalamus-specific effects.

The effect of antipsychotic treatment is a critical issue in the interpretation of postmortem studies in schizophrenia. We feel that given the regional variability of antipsychotic effects in the brain, it is difficult to generalize results from one brain region to another. Of course, our original findings could nonetheless be related to antipsychotic exposure, but the only report of which we are aware that directly addresses this question in the thalamus suggests otherwise (Ulas, 1993). We agree with Drs. Gurling and Chen that the recent completion of the sequencing of the human genome is an exciting development, and as the expression of even more genes is studied in brains from mentally ill subjects, issues such as this will remain an important problem in the interpretation of the voluminous data that are sure to be forthcoming.

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JAMES H. MEADOR-WOODRUFF, M.D.
Ann Arbor, Mich.

Lithium Discontinuation During Pregnancy

TO THE EDITOR: The article on lithium discontinuation during pregnancy by Adele C. Viguera, M.D., et al. (1) raised perplexing questions. They reported that 52% of pregnant patients and 58% of nonpregnant patients relapse in the first 40 weeks after discontinuation. Among pregnant subjects, 64% of episodes were of depressive or mixed type. This raises the question whether some women should receive prophylactic antidepressant therapy during pregnancy after discontinuing lithium. That might reduce the number of depressive episodes but increase the number of manic episodes that occur. Perhaps consideration of the nature of the most recent episode would help prediction sufficiently to justify such prophylaxis.

Morbidity from severe congenital abnormalities associated with lithium treatment during the first trimester of pregnancy is so great that it outweighs the morbidity of bipolar relapses, especially if close psychiatric supervision provides prompt diagnosis and treatment. I would be very reluctant to prescribe lithium to women in the first trimester of pregnancy.

Reference

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ARTHUR RIFKIN, M.D.
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Dr. Viguera and Colleagues Reply

TO THE EDITOR: We thank Dr. Rifkin for raising important issues regarding the optimal care of pregnant women with bipolar disorder. We found that two-thirds of illness recurrences during pregnancy after discontinuation of maintenance lithium treatment were depressive and that depression is the major source of morbidity and mortality in bipolar disorder (1). Optimal management of bipolar depression, even in nonpregnant patients, has only recently been studied in a systematic fashion. However, the suggestion by Dr. Rifkin that prophylactic antidepressant treatment theoretically might be beneficial in the absence of coadministration of a mood stabilizer raises obvious concern with respect to risk for induction of dangerous maternal affective instability with attendant morbidity and uncertain effects on the fetus. In the study group on which we reported, we noted that reintroduction of lithium monotherapy was most often sufficient to restore euthymia. For patients who relapse into mania during pregnancy after discontinuation of a mood stabilizer, reintroduction of the mood stabilizer with adjunctive antipsychotics can also be used with relative safety. ECT may also be used to treat mania as well as depression during pregnancy when expeditious treatment is imperative (2).

Dr. Rifkin's reluctance to prescribe lithium at all in the first trimester of pregnancy is shared by many clinicians given concerns about the real but relatively small (0.05%) teratogenic risk associated with prenatal exposure to lithium during fetal heart development. We do not advocate arbitrary use of lithium for pregnant women with bipolar disorder. Whether and when to prescribe lithium during pregnancy requires a careful weighing of the risks of fetal drug exposure versus the risks of an untreated disorder. The morbidity associated with Ebstein's anomaly is, as Dr. Rifkin points out, high, but the absolute risk of the anomaly after first-trimester exposure is small (3). The revised teratogenic risk estimates with lithium (3), as well as the high risk of recurrence after discontinuation of lithium (particularly when done abruptly) (4), encourage balanced consideration of rational options and challenge the traditional view that pregnancy requires immediate cessation of early fetal exposure to all drugs.

We believe that the role of the psychiatrist who chooses to manage the treatment of women with bipolar disorder during pregnancy is to inform patients of the relative risks associated with and without treatment with medications; only then can women make informed decisions. Dictating care precludes adequate patient participation in extremely important and personal treatment decisions. Decisions about what constitutes "reasonable risk during pregnancy" requires shared responsibility but ultimately rests with the informed pregnant patient. Well-informed choices coupled with close clinical follow-up, which Dr. Rifkin advocates, is an ideal formula for collaborative care, particularly when managing psychiatric disorders during pregnancy.

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ADELE C. VIGUERA, M.D.
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LEONARDO TONDO, M.D.
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Boston, Mass.

End-of-Life Questions

TO THE EDITOR: The essay by Barry R. Berkey, M.D. (1), was both thought-provoking and heartrending. The author feels that we show more compassion and more respect for the dignity of a dumb animal (yes, famous, cuddly, and beloved but still only an animal) than for that of human beings—in this case for Floyd, the author's brother—in allowing him to live for 6 years in what seems to be essentially a decerebrate condition. And all this—the author does not spell it out, but it seems obvious—quite paradoxically precisely out of alleged respect for Floyd's humanity.

But wait a minute! How can, in the circumstances described, anybody—even the most compassionate and loving brother—know with true certainty what Floyd would have wanted? A panda, no matter how seemingly intelligent, cannot tell us and cannot think, even in the best of circumstances, at least not as humans do. So we feel authorized, even obliged, to make life-and-death decisions for it (especially after we have already decided, presumably without its informed consent, to remove it from its native habitat and hold it in lifelong confinement for the amusement and maudlin sentimentality of us humans). But Floyd was not a panda, and that, precisely, is the difference. Only with the greatest hubris could any of us presume to know with moral certainty what he would have wished—except, perhaps, that he wanted physical comfort and tangible signs of loving care, both of which, in fact, he received in abundant—nay, superabundant—measure. By what (mis)interpretation of love or dignity would we want to deprive him of that?

The moment comes (and 6 years is a long time) when we must admit, no matter how reluctantly, that we have reached the end of our financial and emotional endurance, that any further efforts to keep Floyd alive assertively would interfere with other duties, more or at least equally important, vis-à-vis others or ourselves. Even the Judeo-Christian Bible (and, I reckon, the Buddha and the authors of the Qur'an and Vedanta Veda would agree) bids us to love our neighbor as, but not necessarily more, than ourselves. But even then there

is a world of difference between ceasing all action to sustain life, providing mere freedom from pain and discomfort and letting nature take its course to a natural death, and actively intervening specifically to end life itself. Furthermore, it is one thing to do this because we admit honestly in our consciences that we cannot afford to do more and totally another thing to arrogate to ourselves—whether a doctor, family member, or the highest court in the land—the ability or right to divine what the patient would have wanted to have done or to decide what is in the patient's best interest.

I cannot read the mind of Floyd nor anyone else in a similar condition. I know for certain that I, for one, would vehemently object to any legislation or directive authorizing anyone to directly end my life, even if the person had to conclude that he or she could not ethically afford to do more than keep me free of pain while nature took its course.

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EDMUND F. KAL, M.D.
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Dr. Berkey Replies

TO THE EDITOR: I thank Dr. Kal for responding to my essay. My metaphorical use of the life and death of Hsing-Hsing was intended to reflect my deeply held views that we, as physicians and psychiatrists, must go beyond *talking* about compassion for the hopelessly ill. Thoughtfully confronting end-of-life issues is merely the first step; I feel we need to set into motion concrete protocols offering help for stricken individuals and their families. Everyone acknowledges the potentially serious abuses of euthanasia and physician-assisted suicide, but at the very least I would like APA to establish itself as a leader among medical groups by publicly expressing a willingness to reach out to the terminally ill and their families about alternatives to pain, helplessness, suffering, and indignity.

BARRY R. BERKEY, M.D.
Fairfax, Va.

Bipolar Disorder Questionnaire

TO THE EDITOR: The development of a screening questionnaire for bipolar spectrum disorder, described by Robert M.A. Hirschfeld, M.D., et al. (1), was long overdue and will certainly help focus attention on the recognition and treatment of these disorders. Although clinicians and researchers alike will find this study of great interest, I would like to point out some factors that may affect the assessment of this instrument.

First, bipolar spectrum disorders are likely quite heterogeneous with regard to their ease of diagnosis. It is generally much more difficult to elicit a history of bipolar II disorder or cyclothymia than of bipolar I disorder. The patient may think that the periods of elevated mood are simply a normal period of joy expressed when he or she recovers from the more obvious depressive episodes. On the other hand, persons prone to have a relatively changeable affect (e.g., those with borderline personality disorder) may erroneously report their very transitory (e.g., 1-hour) periods of excitement as hypomanic episodes. Furthermore, precisely because of the difficulty in detecting these illness subcategories, a good screening instrument is sorely needed. Thus, although the numbers of patients diagnosed with bipolar II disorder (N=26) or bipolar disorder not otherwise specified (N=13) in this study were much lower than those diagnosed with bipolar I disorder (N=70), it would be interesting to know how the instrument performed in detecting the subcategories of bipolar disorder in patients. I would speculate that while the overall sensitivity of the instrument in this study (0.73) is adequate, it might not be so for these subcategories.

Second, the authors did not mention how the questionnaire was presented to the patients (appropriately, its title does not give away its intent), what proportion of the patients who were asked to complete the questionnaire did so, and whether all of those who filled in the questionnaire completed the Structured Clinical Interview for DSM-IV (SCID). All these factors may have had a bearing on potential biases in the study. For example, those who recognized some of the symptoms in the questionnaire may have been more likely to complete it and the SCID.

Third, that current patient clinical status may have affected the performance of the instrument is not mentioned. In clinical practice, patients who are currently depressed or hypomanic both tend to minimize or deny their hypomanic episodes. An interesting exercise in a study such as this would be a qualitative questioning of those for whom the results of the screening instrument and the SCID diagnosis were discrepant to determine the reasons for such discrepancies.

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RAJNISH MAGO, M.D.
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Dr. Hirschfeld Replies

TO THE EDITOR: In response to the letter from Dr. Mago regarding the Mood Disorder Questionnaire, I agree fully that bipolar spectrum disorders are heterogeneous and differ substantially in ease of diagnosis. Patients with bipolar II disorder may well be more difficult to diagnose than patients with bipolar I disorder because they may not regard themselves as having a mood disorder.

We have no exact numbers on how many patients refused to fill out the questionnaire, but our impression was that the overwhelming majority agreed to complete it. A random sample of those who filled out the Mood Disorder Questionnaire was chosen to complete the SCID telephone interview. Those selected for interviewing ranged from those who checked a large number of symptom items to those who checked none or only a few.

We agree that the clinical state of the individual at the time of completion of the Mood Disorder Questionnaire might well affect the responses. This idea was not addressed in the original study, but we have begun an ongoing study that will examine this important issue. We remind Dr. Mago that the Mood Disorder Questionnaire is a screening form and not a diag-

nostic instrument. It cannot substitute for the comprehensive psychiatric evaluation of a patient.

ROBERT M.A. HIRSCHFELD, M.D.
Galveston, Tex.

Use of Alternative Medicine

TO THE EDITOR: Jürgen Unützer, M.D., M.P.H., et al. (1), in their survey of the use of alternative medicine, found, as have others, that people with major depressive disorder and panic disorder are particularly likely to seek alternative therapies. "Persons with high levels of psychological distress," they suggest, "may be more likely to use a range of available treatments" (p. 1856). They also suggest that depressed and anxious patients may turn to alternative therapies because they are dissatisfied with conventional medical treatments.

All this may be true. But there is another explanation as well: alternative therapies are especially likely to benefit these people. With the possible exception of some of the botanicals, alternative therapies—certainly the wackier, biologically implausible ones—provide whatever benefit they do through the placebo effect. Major depressive disorder and panic disorder are highly placebo responsive and are, in fact, the mental disorders with the highest placebo response rates (30%–40% and 40%–50%, respectively). People with depression and panic disorder who turn to alternative therapies may do so because, for them, these therapies *work*.

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WALTER A. BROWN, M.D.
Tiverton, R.I.

Use of Psychiatric Records

TO THE EDITOR: As chairperson of APA's Committee on Confidentiality, I am responding to the three articles regarding researchers' use of psychiatric records (1–3). There is no question about the value of epidemiological research. However, as more and more uses are sought for the expanding database of patient information, it is important that organized psychiatry carefully consider the clinical, ethical, and research implications of these developments. Notions that we must balance research needs and privacy (1) and combat stigmatization by not allowing too much privacy protection (2) pit privacy against other laudable aims. Workable policies for database research must incorporate, rather than compete with, patient privacy. This principle was bolstered by the Supreme Court's rejection of the balancing test for psychotherapy privilege in *Jaffe v. Redmond* (1996) " because it would eviscerate the effectiveness of the privilege" (4).

Furthermore, the reliability and accuracy of research using health plan or insurance claim data is questionable owing to the current practice of physicians manipulating reimbursement rules (i.e., exaggerating patients' conditions, changing billing diagnoses, and/or falsely reporting patients' symptoms) in order to secure needed coverage for patients. This, too, must be addressed. It is easy to imagine that physicians' and patients' privacy concerns could increase this unfortunate trend.

I agree with the recommendation of Paul S. Appelbaum, M.D. (3), that patients' consent should be obtained prospectively when information is collected for future research purposes. Gregory E. Simon, M.D., and colleagues (2) appeared to support this approach when they suggested that informed consent should be obtained for the use of clinical data whenever possible.

I also agree that the solution is less clear-cut when we are dealing with existing records or databases that were not originally collected or intended for research purposes. But I disagree with a policy that allows researchers to use existing identifiable patient records after receipt of only institutional review board approval. Dr. Appelbaum considers a possible policy of obtaining patients' prospective blanket consent for research, and he is aptly troubled by the absence of true informed consent. But leaving patients completely out of the loop by using institutional research board approval as a fallback mechanism fails to solve this dilemma, because it deprives patients of the opportunity to choose at all.

Such a policy would allow our patients' clinical records, created for their care, to be viewed by researchers without regard to patients' right to privacy in treatment. This is a dangerous precedent, because it would destroy people's trust in psychiatry and psychiatrists. We now have strong evidence that patients' privacy concerns result in thwarted communication and tainted data (5). This adversely affects both care and research.

Ethically, that kind of policy ignores some key principles in the Nuremberg Code (1947) and the Declaration of Helsinki (1964), in which respect for individual autonomy was to supercede "scientific and societal goals" (6). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was also concerned about the implications of using medical records for research and defined that practice as research with human subjects (7). In its 1978 Belmont Report (8) the commission recommended that the rights of subjects were to be respected, specifically by obtaining their informed consent to participate.

But the commission members, too, recognized the difficulties of obtaining informed consent from each patient for each research use of his or her records, often years after the patient had left a health care institution or provider. Thus the commission recommended patients be given the opportunity at admission to opt in or out of the research use of their medical records (9).

I suggest an alternative policy for the protection of privacy in research, based on the commission's 1978 reports (8, 10) and developed by the National Coalition for Patient Rights (9) For planned prospective uses of patient records, informed consent should be sought. However, for retrospective research using patient records, the model suggests that prospective consent should be obtained when patients enter a health plan or health care setting. To ensure an added layer of protection, this consent is delegated to a board specifically designed to review these matters: a medical records review board. Such a board would relieve already overworked institutional review boards of an additional burden, would not suffer the institutional conflicts of interest inherent in institutional review boards, and would contain more community

representation than institutional review boards. In their article Dr. Simon et al. alluded to this kind of policy when they noted that "health insurers have numerous opportunities to communicate with members regarding research uses of health care data" (2, p. 1735). They suggested that abbreviated or simple consent procedures be incorporated into routine practice and that they might be "preferable to complete waiver of consent" (p. 1735).

Clearly, this is an imperfect policy, since it does not address the problem of records that currently exist and are being sought for research. Had the U.S. Department of Health, Education, and Welfare followed the original recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, we would not be faced with this dilemma today. But if the new policy were established as I suggest, we could deal with existing records by attempting to contact patients to obtain either study-specific or delegated general consent for research. If that is not possible, the matter could be delegated to a medical records review board capable of making binding decisions. This would be preferable to giving responsibility to an institutional review board, because the medical records review board would contain more community representation and be less susceptible to institutional pressure to approve research proposals.

Patient records created after the date of the policy implementation would require "prospective delegated consent," with the added provision that patients be given the chance to revise their decisions when they return for care or to change health plans or be practicably informed about a proposed study using their records. With this policy in place, fewer and fewer patient records would be used without individuals' knowledge or consent.

This approach, with its additional steps, would allow valuable research to proceed while respecting and protecting patient privacy and dignity. This would foster trust and, because it would encourage openness and honesty with clinicians, would likely advance the kind of crucial research to which we are all committed.

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MARGO P. GOLDMAN, M.D.
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Dr. Appelbaum Replies

TO THE EDITOR: With an issue as complex as identifying an optimal policy for protection of the confidentiality of patients whose records are used for research, it is reassuring to see the outlines of a consensus beginning to emerge. The authors of the articles and Dr. Goldman all appear to agree on two essentials: whenever possible, consent should be obtained in advance from patients for the use of their records for research, and when that has not or cannot be done, some sort of external review process must examine the necessity for access and ensure protection of confidentiality.

How best to achieve these desiderata has been the subject of considerable discussion. I suggest that we are unlikely to move this process forward without data regarding the relative utility of the various options and a stipulation that these data can come only from creative experimentation.

Take the issue of advance consent, for example. In my editorial, I expressed doubt as to whether meaningful consent can be offered by a patient at the inception of treatment for the use of records that have not yet been created, the content of which the patient will be unaware, for research on a disorder that the patient does not currently have but may acquire in the future. Dr. Goldman responds that it may be possible to offer patients the option of periodically updating the scope of their consent for records use. Whether that is a viable approach seems entirely an empirical question. It would be illuminating to review data from a small number of institutions that have implemented such a policy to see how well it works.

Similarly, with regard to review of requests to access records for which consent has not been provided, the most critical question is, which of the two mechanisms being offered works best? Along with Dr. Simon et al., I suggested reliance on institutional review boards for that purpose. Dr. Goldman correctly notes that institutional review boards are already overwhelmed and expresses the belief that an independent body dedicated to this role alone might do a better job. There are a number of unanswered questions about this proposal, including whether the issue arises frequently enough at any site to warrant creation of a separate body, where the resources (human and financial) will come from to support this group, and whether it will do a better job than institutional review boards in protecting privacy while permitting important research to proceed. But we will not know the answer to these questions until we have had an opportunity to inspect such a system in operation.

We have an unfortunate and frequently remarked-on tendency in this country to implement sweeping policy initiatives on the basis of much argument and few data. The debate over protecting medical records in the research setting seems to have advanced to the point at which thoughtful experi-

mentation will provide the critical feedback to shape subsequent policy. I hope that some of our leading clinical and research institutions will seize this research opportunity.

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

Dr. Simon and Colleagues Reply

TO THE EDITOR: We worry that Dr. Goldman's letter will perpetuate unfounded fears regarding research uses of medical records. To illustrate, consider a study examining the long-term effects of psychotherapy on mortality due to alcohol abuse. Such a study would require linkage of large databases containing information on receipt of psychotherapy (insurance claims records) and causes of death (state vital statistics records). While collection of identifying information would be necessary for this electronic linkage, there would be no conceivable scientific need for examination of individual patient records. Any attempt by research staff to view individual records would be clearly inappropriate—and grounds for disciplinary action. We use this example to illustrate an essential point: quantitative research considers the average experience of large (and anonymous) groups rather than the particular experience of identifiable individuals. Research using computerized records should not allow "patients' clinical records, created for their care, to be viewed by researchers without regard to patients' right to privacy"—at least not in the usual sense of the word "viewed."

In her reference to legal decisions regarding psychotherapist-patient privilege, Dr. Goldman blurs a distinction that we had hoped to emphasize. Psychotherapy records are protected from subpoena for good reason. Adversarial legal processes are always concerned with the particular experiences of identifiable individuals. In the context of litigation or criminal proceedings, invasion of privacy is intentional (and often malicious) rather than accidental. Those requesting records often do so with the clear intent of harming our patients' or clients' interests. The methods and aims of research could not be more different. We draw paradoxical reassurance from the knowledge that, to the epidemiologist or health services researcher, each patient really is just a number. We should reemphasize the same distinction between anonymous research and other uses of health care information that focus on individuals (e.g., utilization review).

We share Dr. Goldman's concern that providers' attempts to influence coverage or reimbursement may undermine the validity of claims data. Incentives for miscoding may have large or small effects depending on the research questions and methods. Potential biases due to miscoding should be carefully considered by researchers and by institutional review boards evaluating the scientific merit of research proposals. We should add, however, that inconvenience to researchers is one of the less important ill effects of our deficient system for financing mental health care.

We agree with Dr. Goldman that patients should be allowed to opt out of records-based research. When research use is anticipated, consent should be obtained before data are collected. We do not, however, concur with her proposal that decisions regarding research use of existing data be delegated to a medical records review board. The supposed merits of such a board (community representation, independence, and authority to make binding decisions) are all legally required characteristics of institutional review boards. If existing institutional review boards fail to meet this standard, the appropriate solution seems to be reform of institutional review boards rather than creation of a separate review process for records-based research. Records-based research deserves the same level of ethical review as traditional clinical research—not more or less.

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