Letters to the Editor

Risperidone for the Treatment of Monosymptomatic Hypochondriacal Psychosis

Sir: Risperidone is a novel antipsychotic agent that blocks the dopamine (e.g., D_2) as well as the serotonin (e.g., $5\text{-}HT_2$) families of receptors.[1] We report a case of monosymptomatic hypochondriacal psychosis that responded to risperidone.

Case report. Mr. A, a 23-year-old man, had complaints concerning his eyes. He had suffered from continuous pain and the feeling that his eyes were sliding down his face during the 2 weeks before he sought treatment. For this reason, he described that he could not look at mirrors. He also reported that he tried to avoid people in order to prevent them from looking at his eyes. He insistently wanted to have an operation on his eyes. Upon examination, he had no schizophrenic or affective symptoms. He had no personal or family history of mood or psychotic disorders. At the time of assessment, he was receiving no psychotropic drugs. His ophthalmological examination showed no disturbances. No relevant preceding lifestyle, personality, or prodromal factors were present, and he had no history of brain damage or substance abuse. Results of neurologic and physical examinations were normal. Electroencephalogram and cranial computerized tomography revealed no abnormalities. Mr. A was diagnosed with monosymptomatic hypochondriacal psychosis. Risperidone was started at a low dose (2 mg/day) and increased to 4 mg/day 3 days later. Mr. A showed a robust response to risperidone. After 2 weeks, he was completely improved. The improvement was sustained for 4 weeks, and he was discharged. Risperidone was continued to that point. After Mr. A was discharged, he was assessed twice a month for 2 months. The improvement was sustained for this follow-up period.

Monosymptomatic hypochondriacal psychosis is a syndrome that is classified in the DSM-IV as a subtype of paranoia (somatic subtype; delusional disorder). Although it presents with a variety of delusional complaints in individual cases, the condition appears to represent a relatively discrete diagnostic entity. The illness is characterized by a single delusional system—in this instance, with hypochondriacal content—that can be present at any age from late adolescence onward, appears to affect the sexes equally, and has a very poor prognosis without treatment. Its presentation appears to be relatively independent of cultural factors. A previous history, or a family history, of psychotic illness seems very uncommon in patients with this disorder. However, substance abuse and/or head injury appear to be background factors in a high proportion of younger patients, and the aging of the brain may play a role in this illness in the elderly (for a review, see reference 2).

Previously, it was reported that pimozide, a neuroleptic that appears to have a selective ability to block central dopaminergic receptors, is an effective treatment for delusional disorder and monosymptomatic hypochondriacal psychosis (for an overview, see reference 3). Pimozide, a diphenylbutylpiperidine neuroleptic approved by the U.S. Food and Drug Administration as a backup treatment for Gilles de la Tourette's syndrome, has been used outside the United States for many years as a treatment for schizophrenia and has been reported to be particularly effective in treating monosymptomatic hypochondriacal psychosis and delusional jealousy.[4] However, it may cause extrapyramidal side effects. Our patient showed a good response to risperidone. To our knowledge, this is the first case report of risperidone treatment for monosymptomatic hypochondriacal psychosis. Thus, it may be suggested that risperidone may be a new, novel alternative to pimozide in the treatment of cases of monosymptomatic hypochondriacal psychosis.

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Rap and Mania

Sir: Psychopathology frequently borrows its context and content from current events and cultural developments. In the heyday of *Star Wars*, psychotic patients presented with delusions about Darth Vader; Easter annually evokes paranoid religious delusions in individuals who see themselves as Christ. The emergence of rap music has produced a small psychiatric literature on its sexual, violent style and lyrics (e.g., reference 1). The literature has not remarked, however, on the neat convergence of rap music with mania. (A computerized literature search revealed links between mania and *rape,* but not rap.) An illustrative case:

Case report. Mr. A, a 24-year-old college freshman, was transferred to the psychiatric emergency room after 2 weeks at another hospital. His third episode of mania within the year had been partially treated there with lithium and quetiapine. Mr. A had slowed movements and a blunted affect. In monotonic, minimally pressured speech, he reported that he had bipolar disorder, had been brought in by the police and involuntarily admitted, and had nearly fully recovered on his current regimen. He recalled having had racing thoughts, heightened energy, and impulsivity, but denied having had psychotic symptoms and generally minimized the severity of his symptoms.

Mr. A had indicated an aspiration to produce a rap record. Asked about the song he had composed, he volunteered to sing it. He reeled off a pressured, funny, creative, clanging and rhyming lyric full of sexual aggression (and fear), grandiosity, and psychotic symptoms ("I foretold history . . . men mocked me"). Some sample lyrics:

"Watch how I boast . . . / When I'm masturbatin'/ Girls think I'm Satan / I've got more energy than Kuwait 'n' / Iraq . . . / My neighbors will knock me / So it won't shock me . . . / When I rhyme / Sharing knowledge of the divine . . . / Metamorphically, freestyle / I flow like the river Nile. . . . "

When interrupted several minutes into this performance, he agreed with the interviewer's suggestion that the song was about him and his manic episode. He had previously denied delusions of grandeur, but now responded to the question of whether he had thought of himself as God: "Well, I wouldn't have said that; but since you said it. . . . "

Mr. A's rap provided a detailed history of the current episode that he could or would not describe directly. Rap music shares many characteristics of mania: its content is aggressive, sexually explicit, and often grandiosely self-referential, with a matching macho, rapid, rhyming, posturing delivery. Given the manic flair of rap music, some young manic patients may be drawn to or show a flair for it. This intersection of life and psychopathology bears further observation.

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Defining Psychosis in PTSD

Sir: David et al.[1] (January 1999 issue) provide important data on the prevalence of hallucinations and delusions in patients with combat-related posttraumatic stress disorder (PTSD). Of the 53 patients studied, 21 (40%) are said to have shown "psychotic" symptoms, of which auditory hallucinations were the most common (95% of cases). Hallucinatory experiences were considered psychotic "if they were not accompanied by the perception of being back in the traumatic situation (i.e., flashbacks) and if there was at least momentary disturbance in reality testing (i.e., behavioral response to hearing voices, experiencing voices as 'real')."[1(p30)] The authors go on to ask whether "neuroleptic treatment would be beneficial in PTSD patient subpopulations with psychotic features" and cite a recent case by Hamner[2] in which clozapine was useful for comorbid psychosis and PTSD.

The authors' criteria for considering a hallucination "psychotic" are reasonable, but problematic in the context of PTSD. While the term *psychotic* is itself a subject of controversy—and is used in a variety of ways in DSM-IV—the *absence of insight* has been one of the historic "markers" for psychosis, and by extension, for genuine hallucinations. As Nemiah puts it, " . . . both the delusion and the hallucination differ from the obsession in carrying with them *a conviction* of their intrinsic verity that is absent from the obsession"[3] (italics mine). The key word, in my view, is *conviction; that is, a strong opinion or belief.* I regard a "momentary disturbance in reality testing" as insufficient to es-

tablish that an internal stimulus is psychotic in nature, and I fear that such attenuation of the definition of psychosis may lead to overzealous (and ineffectual) use of antipsychotics in patients with PTSD. Notwithstanding a few intriguing case reports in which atypical antipsychotics have been helpful in comorbid psychosis and PTSD,[2,4] there is little evidence that antipsychotics play a useful role in the pharmacotherapy of PTSD in general.[5]

Given the risks of tardive dyskinesia and neuroleptic malignant syndrome, our threshold for antipsychotic use in PTSD ought to be high. For PTSD patients who are *not* comorbid for schizophrenia, schizoaffective disorder, or psychotic mood disorder, I suggest a more stringent set of criteria than those proposed by David et al. In such cases, an internal perception would be deemed psychotic (i.e., a true hallucination) only if the patient meets *one or more* of the following criteria: (1) The patient persistently (over hours to days) fails to recognize that the internal stimulus (e.g., "voice") is abnormal or unreal; (2) The patient persistently attributes the internal stimulus to an external source *of a delusional nature* (e.g., "The voice is coming from my dead platoon commander"); or (3) Regardless of the patient's beliefs about the internal stimulus, his or her behavior over extended periods of time (hours or longer) is consonant with the nature or content of the stimulus (e.g., the patient seeks out the "enemy behind the voice" by stalking other patients). Absent such criteria, I believe that PTSD-related internal stimuli are best described and treated as dissociative phenomena of a nonpsychotic nature.

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Drs. David and Mellman Reply

Sir: We appreciate Dr. Pies' interest in our paper and the opportunity to address the complex nosological issues raised in his letter.

Dr. Pies refers to the controversy regarding the term *psychosis,* for which there are several definitions in the DSM-IV. The more restrictive definition requires the absence of insight; however, the less restrictive definition includes "prominent hallucinations that the individual realizes are hallucinatory experiences."[1(p273)] All of our subjects met this less restrictive definition of psychosis, while sustained lack of insight regarding psychotic symptoms was present only in the 2 subjects who met criteria for schizoaffective disorder.

Dissociation is defined in the DSM-IV as "a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment."[1(p477)] It is not clear that the symptoms we described meet the above definition of dissociation, nor do they take the form of specific dissociative disorders

(e.g., amnesia, fugue, dissociative identity disorder, or depersonalization). Rather, they seem to best fit the definitions of hallucinations and delusions. In addition, our data, albeit preliminary, do not show a significant difference in scores on the Dissociative Experiences Scale between patients with and without psychotic symptoms.[2]

With regard to DSM-IV categories, the patients in our study did not meet diagnostic criteria for schizophrenia, and only a minority met criteria for comorbid schizoaffective disorder or major depression with psychotic features. We believe that the diagnosis that best fits these symptoms in the majority of the subjects is psychosis not otherwise specified. Perhaps a subtype of PTSD with psychotic features, similar to what exists for major depression, should be considered for future DSM editions.

We share the concerns regarding inappropriate use of neuroleptic medications for PTSD patients. However, the benefits of conventional pharmacologic treatments for the severely affected subpopulation represented in our paper appear to be limited. Given the improved safety profile of atypical neuroleptics over traditional neuroleptics and a recent positive report of open-label treatment with an atypical antipsychotic,[3] we feel that further evaluation of the use of atypical antipsychotics in severe and chronic PTSD is warranted.

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Patient's Coping Skills and Environmental Stress Important to Understanding Recurrence During Antidepressant Maintenance

Sir: Recently, Byrne and Rothschild[1] reported on possible mechanisms for loss of antidepressant efficacy during maintenance therapy. Although I would agree with the theoretical mechanisms cited by the authors, there is a glaring oversight in their thinking about this important issue, specifically, the role of new psychosocial stresses encountered by the patient during the maintenance period, the cumulative effect of ongoing chronic psychosocial stress in the patient's life, and ongoing coping deficits. Psychosocial stress that the patient cannot manage could overwhelm all or part of a previously positive biological antidepressant response. Byrne and Rothschild's thinking makes several problematic assumptions: (1) all patients have the same level of psychosocial stress in their lives; (2) all patients have the same level of skill at handling stresses when they encounter them; (3) the level of psychosocial stress remains a constant for patients throughout the acute, continuation, and maintenance phases of antidepressant treatment; and/or (4) life events and ability to cope with them are trivial in relation to the course of affective disorders. These assumptions lead to the position that the effect of the medication is the only important independent variable to be considered during the maintenance period.

The "biological disease" of depression cannot be separated from the environmental context of the patient or the coping skills of the patient. For example, people with personality disorders or with detrimental personality traits are both less likely to cope well with certain environmental stresses when they occur and more likely to create frequent or painful psychosocial stresses in their lives. The ongoing grinding stress of poverty or abusive relationships is depressogenic, presumably especially in people with a biological diathesis for affective disorder. A divorce, job loss, poor job evaluation, etc., during the maintenance period may precipitate the relapse or recurrence of a full affective syndrome in susceptible individuals. Possibilities of important factors other than biological medication effect are numerous.

I am not arguing the reverse extreme point of view, that only psychological and environmental factors cause depression or affective disorders. However, psychiatric literature frequently ignores obvious and salient psychosocial factors impacting the disorders it studies. The quality of our science suffers because of our biological tunnel vision.

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New-Onset Diabetes Mellitus Associated With the Initiation of Quetiapine Treatment

Sir: Quetiapine is a novel antipsychotic that antagonizes both serotonergic ($5\text{-}HT_{1A}$ and $5\text{-}HT_2$) and dopaminergic (D_1 and D_2) receptors. The manufacturer describes hypoglycemia, hyperglycemia, and diabetes mellitus as infrequent side effects (0.1%–1.0%).[1] The following is a case report of possible quetiapine-induced onset of diabetes mellitus.

Case report. Mr. A, a 42-year-old white man with a history of bipolar disorder, type I, was seen by the psychiatry consultation service after admission for new-onset diabetes mellitus. Mr. A had no prior history of glucose intolerance or hyperglycemia, and, 4 months before his admission to the hospital, the results of random blood glucose tests were 126 and 107 mg/dL. He did have hypertriglyceridemia, which had been noted for more than a year prior to this admission. His family history was negative for diabetes. His bipolar disorder had been managed with a combination of lithium carbonate, 900 mg daily; gabapentin, 2000 mg daily; clonazepam, 1 mg at night; and venlafaxine, 37.5 mg daily. Quetiapine had been added to his regimen 1 month before his admission to the hospital and titrated to 200 mg at night.

Mr. A was admitted to the medicine ward after several days of nausea, vomiting, polyuria, and confusion. At the time of admission, he was noted to have a blood glucose level of 607 mg/dL and was started on intravenous fluids and a sliding-scale insulin regimen. He was eventually discharged from the hospital on a regimen of 17 units regular and 33 units NPH insulin in the morning and 6 units regular and 10 units NPH insulin in the

evening. He was also started on gemfibrozil treatment for hypertriglyceridemia at the time of discharge.

After discharge, he was seen in follow-up in the psychiatry and medicine clinics. His quetiapine dosage was reduced and then discontinued over the course of 9 days. Since the discontinuation of quetiapine, Mr. A's insulin requirements have decreased markedly. His insulin was eventually discontinued 5 months after the admission.

Clearly, there is no absolute proof in this case report that this patient's apparently transient episode of diabetes was caused by the quetiapine. However, we are reasonably sure that other explanations were ruled out. Although there have been case reports of clozapine-associated hyperglycemia and diabetes mellitus,[2–4] a MEDLINE search does not reveal any case reports of this association with quetiapine. There have been no reports of any adverse interactions between quetiapine and the patient's other medications. Clinicians should be aware of this possible adverse effect and should use caution when prescribing quetiapine in patients with known glucose intolerance or frank diabetes mellitus.

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Valproate-Induced Hyperammonemia in the Psychiatric Setting: 2 Cases

Sir: Although several case reports have described valproate-induced reversible elevation of serum ammonia levels, this problem may not be recognized quickly owing to lack of sufficient awareness. A high level of suspicion will enable the busy clinician to identify and intervene promptly in this clinical setting. This is particularly relevant in today's clinical psychiatric practice owing to the current widespread use of valproate in the acute and maintenance treatment of psychiatric disorders. Also, hyperammonemia manifests as mental status change, which is likely to be attributed to a worsening of psychosis or mania. Furthermore, the typical absence of abnormalities in routine liver function testing makes the clinician who relies on these tests likely to overlook this interesting and relatively infrequent adverse effect.

Case 1. Ms. A, a 53-year-old single white woman with a long-standing diagnosis of bipolar disorder type I and alcohol dependence, was admitted to the inpatient psychiatric and substance abuse treatment unit for treatment of mania with psychotic features, detoxification, and early-phase rehabilitation of alcoholism. She was brought to the psychiatric emergency ser-

vice by the police after she was found by staff of a local hotel to be aggressive, argumentative, and demonstrating a delusional belief that she was the personal assistant to a famous songwriter who was staying at the same hotel. Other symptoms included decreased sleep, increased goal-directed behavior, and intermittent auditory hallucinations of grandiose nature. She also had been drinking 6 to 10 beers (of unspecified size) daily for 2 weeks prior to presentation. For over 1 year before hospitalization, Ms. A had taken no psychotropic medications and had had no psychiatric follow-up.

Results of laboratory studies upon admission were all within normal limits, including complete blood cell count, aspartate aminotransferase, and alanine aminotransferase, alkaline phosphatase, and bilirubin levels. She successfully completed alcohol detoxification in 5 days and was given a loading dose of divalproex sodium, 500 mg p.o. t.i.d., to treat the mania. Haloperidol, 5 mg p.o. b.i.d., and benztropine, 1 mg p.o. b.i.d., were also started to treat the acute psychotic symptoms. Five days after she started valproate treatment, irritability and aggressiveness began to decrease, and her serum valproic acid level was 74 μg/mL. Several days later, the dose of divalproex was increased by 250 mg/day to a total daily dose of 1750 mg, and over the next 5 days mania further improved and psychosis began to resolve.

However, over the next few days, Ms. A began to complain of feeling very lethargic, wandered into other patients' rooms, had intermittently illogical speech, and would often be found to be napping in the day room. Valproic acid level was 107 μg/mL, and all liver function indices were well within normal limits. A serum ammonia level was obtained and found to be 79 μmol/L (normal range, 11–35 μmol/L). The dose of valproate was decreased by over one half to 250 mg p.o. t.i.d., and lithium was started at 300 mg p.o. b.i.d. in an effort to prevent reemergence of mania. Serum ammonia level dropped to 54 μmol/L 2 days later, and within 3 days of the reduction in dose of valproate, sensorium returned to normal with no evidence of mania. One week after the dose of valproate was decreased, serum ammonia level was 30 μmol/L, and valproic acid level was 43 μg/mL with no further mental status change. Ms. A was discharged a few days later.

Case 2. Mr. B, a 23-year-old single white man with a diagnosis of schizoaffective disorder and mania, was admitted to the inpatient psychiatric and substance abuse treatment unit for treatment of a progressively worsening bizarre thought disorder and mania. He also had a long history of alcohol dependence and crack cocaine abuse. He had drunk up to a 6-pack of beer per day for the last several years and smoked crack cocaine intermittently. His last use of alcohol and cocaine was over 2 weeks before admission, and detoxification was not necessary. He was started on treatment with olanzapine, 10 mg p.o. q.d., and divalproex, 500 mg p.o. t.i.d. Initial laboratory values, including liver function test results, were all within normal limits. Valproic acid levels during the first 10 days of hospitalization were therapeutic in the 70- to 80-μg/mL range.

By the end of the second week of hospitalization, Mr. B appeared to be lethargic during the day and more bizarre in his speech, which was initially attributed to exacerbation of psychosis. Serum ammonia level was 54 μmol/L, and liver function values were normal. Over the next week, he became more confused, and a repeat serum ammonia level was 193 μmol/L. Liver function and metabolic profiles were normal. Valproate was discontinued promptly, and Mr. B was given lactulose for several days. Lithium, 300 mg p.o. b.i.d., was started for prophylaxis of mania. Within the next 2 days, Mr. B's sensorium fully cleared, and his ammonia level decreased to 44 μmol/L. There was no emergence of mania. Mr. B remained on treatment

with olanzapine and lithium at therapeutic serum levels and was transferred to a state psychiatric facility several weeks later.

Hyperammonemia manifests as mental status change, lethargy,[1] somnolence, reversible cognitive deficits, or full-blown delirium if prompt intervention is not made. It is the goal of this report to alert clinicians to monitor ammonia levels promptly, in addition to liver function testing, if any of these presentations occur in patients currently receiving valproate therapy. As pointed out in previous reports,[2] symptomatic hyperammonemia induced by valproic acid does not indicate impending liver failure, and the liver function tests in both cases remained normal despite elevated ammonia levels. A reduction in dosage or discontinuation of valproate and monitoring of ammonia level are warranted, and the condition is fully reversible. Supplementation with carnitine, 2 g/day, has been suggested as an alternative to avoid the risks associated with discontinuation of valproate therapy.[2] Also, clinical evidence suggests that a reduction in dose is often effective in lowering ammonia levels (case 1). However, discontinuation of valproate may be necessary in some cases for prompt reversal of hyperammonemia (case 2).

A previous report implicated valproate-induced carnitine deficiency and inhibition of carbamyl phosphate synthetase enzyme (urea cycle) as one mechanism of hyperammonemia,[2] resulting in reductions in the conversion of ammonia to urea. That report stated that carnitine deficiency is likely to increase the risk of hyperammonemia and suggested carnitine replacement as a treatment option for valproate-induced hyperammonemia. For example, carnitine deficiency may occur in children under 2 years of age, vegetarians (inadequate dietary intake of carnitine), and individuals with inborn errors of metabolism. Additionally, carnitine has been reported to stimulate transcription of enzymes of the urea cycle,[3] and carnitine deficiency has been demonstrated to cause hyperammonemia in animal models.[4]

Although valproate-induced reduction in carnitine is a well-established finding,[5] and although carnitine supplementation has been shown to be beneficial in this scenario, studies in normal healthy subjects treated with valproate have concluded that the kidneys adapt to conserve carnitine by way of increased reabsorption in the setting of continued valproate therapy. In one recent study, plasma and free carnitine concentrations decreased during the initial phase of valproate therapy (16 days), but normalized subsequently (28 days) in spite of continued valproate administration.[6] Reductions in the renal excretion of carnitine by as much as 50% (14–30 days) contributed to normalization of carnitine levels. Possible mechanisms by which valproate may cause reductions in carnitine are under investigation. Valproate excretion in the form of carnitine esters[7,8] has been reported previously. In addition, some reports have suggested that valproate may also inhibit the biosynthesis of carnitine.[9] Therefore, valproate therapy can potentially cause carnitine deficiency. In any case, one could argue that valproate-induced carnitine deficiency may indeed be transient and correctable in otherwise healthy individuals, and a short-term lowering of dose and carnitine supplementation may be all that is needed rather than discontinuation of valproate.

Congenital enzyme abnormalities of the urea cycle (ornithine transcarbamylase deficiency) have been cited as possible predisposing mechanisms. Oechsner et al.[10] described a subject with inborn ornithine transcarbamylase enzyme defect who developed hyperammonemia after initiation of valproate therapy. Therefore, valproate can, due to metabolic abnormalities, cause worsening of preexisting hyperammonemia or induce hyperammonemia in healthy subjects even in the absence of such enzyme defects.

Valproate may increase the transport, uptake, and conversion of glutamine to ammonia in renal mitochondria, resulting in increased renal production of ammonia. However, the precise mechanism remains unclear, and some studies have attributed this increase to the membrane effects of valproate,[11] whereas other studies have suggested possible effects of valproate on glutaminase enzyme.[12] Thus, current research supports the view stated in previous clinical reports[2] that valproic acid causes hyperammonemia by increasing the renal production of ammonia and decreasing the hepatic conversion of ammonia to urea.

Another study investigated the various biochemical and metabolic parameters associated with valproate therapy in 98 patients.[13] This study found no causal association between hyperammonemia and the hepatotoxic metabolites of valproate (2-propyl-4-pentenoic acid) and concluded that factors such as young age and high valproate levels within the therapeutic range did not contribute to increased ammonia levels. It was also noted that the subset of 45 patients on concurrent treatment with other antiepileptic drugs (polypharmacy group) had higher levels of ammonia, serum glutamic pyruvic transaminase and γ-glutamyl transpeptidase. The implications of these findings remain to be fully elucidated.

In conclusion, clinicians should always consider hyperammonemia in all patients who present with mental status change while on valproate therapy. Ammonia levels should be obtained in addition to liver function tests, which are often normal. Dietary supplementation with carnitine (1–2 g/day) and reduction in dosage or discontinuation of valproate followed by monitoring of ammonia levels are possible interventions in this clinical setting. We also speculate that factors such as recent alcoholism and nutritional deficits may contribute to predisposition and increased vulnerability to this side effect.

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Rapid Fade of Antidepressant Effect of Nefazodone in Bipolar Depression

Sir: The treatment of bipolar depression is problematic. The generally atypical, frequently anergic presentation tends to limit antidepressant choice. Monoamine oxidase inhibitors may be particularly useful in this regard.[1] However, antidepressants have been found to induce a manic switch at a rate that is 5 to 7 times that of spontaneous switch among unmedicated depressed bipolar patients.[2,3] More ominously, antidepressant therapy has recently been implicated in induction of mixed manic states and rapid cycling.[4,5] All classes of antidepressants have been implicated, although there is a general consensus that bupropion and serotonin reuptake inhibitors may be less prone to induce mania.[6] While it is generally desirable to avoid antidepressant administration in bipolar patients, the morbidity associated with depression frequently mandates treatment.[7]

Given the great need for a safe and effective antidepressant in this population, systematic investigation of the new atypical agents seems warranted. Nefazodone is a new antidepressant that, in addition to serotonin and norepinephrine reuptake inhibition, also has postsynaptic serotonin ($5-HT_2$) blockade,[8] an action that is believed to underlie its ability to reduce agitation.[9] This property raises the possibility that nefazodone may possess beneficial effects in the treatment of bipolar depression.

Five consecutive mildly to moderately depressed DSM-IV-defined bipolar I patients with Hamilton Rating Scale for Depression (HAM-D)[10] scores (first 17 items) ≥ 15 were recruited. All patients underwent at least 1 week of antidepressant washout prior to beginning the trial. Nefazodone was added to ongoing and unchanged mood-stabilizer therapy (with confirmed adequate serum levels) in an open-label, fixed-dose design. All individuals took nefazodone, 100 mg twice daily, for 1 week, then 150 mg twice daily for 7 weeks. Patients were seen at weeks –1, 0 (baseline), 2, 4, and 8. A HAM-D, Young Mania Rating Scale,[11] and a review of adverse effects were completed each visit. Paired t tests of ratings at weeks 2, 4, and 8 were compared with baseline to evaluate efficacy.

Three men and 2 women entered the study. The mean age was 47.0 years (range, 43–50 years) among the men and 39.3 years (range, 23–48 years) among the women. The mean duration of illness was 12.2 years (range, 2–24 years). The mean duration of current depressive episode was 7.8 months (range, 1–12 months). All patients were maintained on either lithium (N = 3) or valproic acid (N = 2); 2 patients also received either clonazepam or risperidone.

Within 2 weeks, the mean ± SD HAM-D scores dropped significantly from 21.5 ± 5.07 to 11.7 ± 4.73 (p = .05). At 4 weeks, depression scores were again improved to 8.75 ± 6.29 (p = .015). However, by 8 weeks, 4 patients had relapsed, and mean HAM-D scores had climbed to 19.0 ± 11.28 (p = .6). At the end of the 8 weeks, nefazodone was increased to 400 mg/day in 1 patient who subsequently experienced a transient improvement in symptoms with relapse within 4 weeks of the dose increase.

Side effects included impotence and sedation. The sedation was particularly problematic in the patient receiving concomitant clonazepam. One patient discontinued the trial early secondary to side effects. Although the duration of treatment was brief, none of the patients experienced manic induction despite history of antidepressant-induced manic switch in 2 of the patients.

In this preliminary trial, a brief period of marked improvement was seen the first 4 weeks of open treatment with nefazodone, but nearly all subjects relapsed within the 8-week study period. The short duration of apparent efficacy in these depressed bipolar subjects is most likely the result of a placebo response. Alternative explanations that should also be considered include inadequate dosing, different pathophysiologic mechanisms in bipolar versus unipolar depression, a particularly treatment-resistant study population, or a consequence of the small sample size of this open trial.

The issue of safety in bipolar illness cannot be adequately addressed in this brief study. While manic induction was not observed, both dosage and duration of administration were relatively small.

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