Letters to the Editor

Possible Risks Associated With Valproate Treatment of AIDS-Related Mania

Sir: Recently, RachBeisel and Weintraub contributed further to the literature on the usefulness of valproate for treating AIDS-related mania.[1] Contrary to current trends, they apparently prescribed valproic acid rather than divalproex sodium—the former being less expensive, but generally less well tolerated. Given the likelihood of preexisting gastrointestinal symptoms in this population, better tolerability rather than lower cost might make divalproex sodium the preferred preparation.

The authors suggest the need for further study of the use of valproate in patients with AIDS because of uncommon reports of thrombocytopenia, hepatic dysfunction, and pancreatitis associated with the drug. They did not mention a further cause for concern, namely, that in vitro studies have found that valproate stimulates HIV-1 virus replication[2,3] and cytomegalovirus replication.[4] Were this to happen in AIDS patients, the course of the illness could be altered unfavorably.

Even though the authors of the viral replication studies used valproate concentrations similar to those attained in humans, the results of their work may not be directly applicable to the therapeutic use of valproate in humans because plasma protein binding was not taken into consideration. If one equates the in vitro drug concentrations (no protein binding) with free rather than total concentrations in vivo, at least some of the concentrations studied in vitro would be toxic in vivo.

On the other hand, 3 factors could increase the concentration of free drug in patients with AIDS and expose them to greater risk. First, chronic illness may reduce plasma protein level and, thereby, increase the percent of free drug. Second, the protein binding of valproate is concentration dependent so that free fraction will increase as blood level increases. Third, protein binding of valproate may decrease as a result of drug interactions (e.g., with aspirin).

Although the observation that valproate, in vitro, stimulates replication of HIV-1 and cytomegaloviruses should not be cause for clinical alarm, further study is clearly indicated. As Witvrouw et al. conclude: "In particular, it would seem appropriate to monitor viral load (i.e., plasma viral RNA titers) in HIV-positive individuals when being treated with VPA [valproate]."[3]

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Attacks of Jealousy That Responded to Clomipramine

Sir: Pathologic jealousy can be a manifestation of several psychiatric disorders. The patient described here suffered from an atypical form of obsessive-compulsive disorder, had a strong family history of emotional disturbance and relationship difficulties, and responded dramatically to treatment with low-dose clomipramine.

Case report. Ms. A, a 33-year-old woman, was referred with a 9-month history of "jealousy attacks." These consisted of episodes of uncontrollable rage, lasting about 30 minutes, during which she would accuse her boyfriend of "every possible sort of infidelity under the sun" and occasionally attack him physically. Such episodes typically occurred weekly and were precipitated by pictures of partially dressed women in newspapers or on television programs. She experienced intrusive thoughts about his infidelity every day, which she recognized as excessive and senseless and attempted to control but found the buildup of tension unbearable. She felt that similar thoughts and attacks had been responsible for her previous divorce and were jeopardizing the future of her current relationship. Ms. A had been free of jealous thoughts and rage for an intervening 10-year period during which she had no romantic relationships.

Ms. A's mother had received inpatient treatment for depression associated with her husband's infidelity; a maternal aunt committed suicide after several attempts; a paternal aunt and grandfather committed suicide after the breakup of their marriages; and a cousin (who had some cleaning rituals) and the patient's brother are currently receiving treatment for affective disorders associated with marital problems. Ms. A has been troubled with premenstrual symptoms, but there was no apparent relationship between the attacks and her menstrual cycle. There was no evidence of epileptic phenomena. She had not seen a psychiatrist previously and denied alcohol or drug abuse.

When interviewed, Ms. A did not appear anxious or depressed. Although she described occasional feelings of low mood, initial insomnia, and social anxiety, these did not meet duration or severity criteria for an affective disorder or anxiety state. She denied ever suffering a panic attack. She did have re-

current, intrusive, excessive, and unwanted concerns about her son's health, but no other obsessional thoughts and no compulsive acts. There were no psychotic phenomena, and cognitive function was intact.

A diagnosis of obsessive-compulsive disorder with obsessional jealous sexual thoughts was made, previously described as morbid jealousy of obsessional type,[1] and she was prescribed clomipramine. After taking 40–60 mg daily for 3 weeks, she reported no further episodes, but a reduction to 30 mg daily because of side effects led to 2 attacks. Clomipramine was therefore increased to 50 mg daily, and the patient has had no further attacks since, other than when she was admitted for psittacosis and the clomipramine was inadvertently stopped. She is now married and has not been troubled at all by obsessional thoughts for 2 years. At her last appointment, she said, "I can't remember what it feels like to be jealous.…Rage is a distant memory."

Obsessional jealousy is increasingly recognized and can be successfully treated with a variety of antidepressant drugs.[2,3] The unusual presentation in this patient could have prevented accurate diagnosis and effective treatment. Similar patients may also benefit from treatment, especially if they have a family history of similar complaints.[3]

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Olanzapine-Induced Manic-Like Syndrome

Sir: Olanzapine is a new atypical antipsychotic with antidopaminergic and antiserotonergic blocking activity that results in antipsychotic efficacy with an extrapyramidal side effect profile superior to that of conventional neuroleptics.[1] This beneficial side effect profile may make olanzapine particularly suitable for schizophrenic patients who have developed HIV infection. We report 2 HIV-positive chronic schizophrenic patients in whom olanzapine was used and who developed a manic-like psychomotor activation syndrome.

Case 1. Mr. A, a 38-year-old black man who has the DSM-IV diagnoses of schizophrenia, chronic undifferentiated type, and polysubstance dependence in remission, was admitted to our hospital approximately 16 years ago. He has been hospitalized continuously since that time, as his disorder has remained resistant to a variety of conventional antipsychotic medications (at dosages of at least 1000 mg/day of chlorpromazine equivalents trifluoperazine, haloperidol, thioridazine, and loxapine) given for what are normally adequate periods of time. His schizophrenia recently also failed to respond to risperidone of up to 8 mg/day. His medical history included seizure disorder, probably related to drug abuse and withdrawal. Four years ago, Mr. A was found to be HIV-positive. At that time, he was prepared for a clozapine trial, which was, however, not initiated due to his HIV-positive status. For the last 4 years, he has been seizure free and has not been treated with anticonvulsants. Mr. A is somatically stable and is currently being treated with didanosine and zalcitabine; his CD4 cell count is in the 600–700/mm^3 range. There has been no evidence of HIV-related dementia.

Mr. A's major psychiatric symptoms consist of severe thought disorder, auditory hallucinations, grandiose and persecutory delusions, as well as behavioral abnormalities: impulsivity, assaultiveness, and hypersexuality. About 1 year ago, Mr. A was started on olanzapine 10 mg/day, while loxapine 250 mg/day was tapered over 2 weeks. After 2 weeks, the dose of olanzapine was increased to 15 mg/day and after 3 weeks to 20 mg/day. During this time, Mr. A was less withdrawn, less socially isolated, and more interested in ward activities; his grooming improved, and he was better able to handle his family visits.

After 3 weeks of olanzapine treatment, however, Mr. A became restless and mildly agitated, and he started pacing and posturing. This behavior escalated to manic excitement associated with reduced sleep, severe agitation, and threatening attitude. In addition, he became grossly psychotic, which he had never been in the past. His sensorium remained clear as evidenced by full alertness and orientation with good short- and long-term memory function on mental status examination. Vital signs, complete blood cell count (CBC), and Sequential Multiple Analyzer (SMA 12/60) results were unchanged as compared with baseline. No extrapyramidal symptoms were noted. The dose of olanzapine was decreased to 15 mg/day and then to 10 mg/day. Currently, Mr. A is less behaviorally activated and shows no manic symptoms, but continues to be floridly psychotic.

Case 2. Mr. B, a 43-year-old Panamanian man with the DSM-IV diagnoses of schizophrenia, chronic undifferentiated type, and polysubstance dependence in remission, was admitted to our hospital approximately 5 years ago from a shelter for the homeless. He was incoherent, paranoid, and disheveled. His first psychiatric hospitalization occurred about 30 years ago at the age of 15, and he spent nearly all of his life in institutions. The presenting symptoms have remained constant over the years: auditory hallucinations, persecutory and grandiose delusions, severe disorganization of thinking, and behavior characterized by promiscuity, suicidality, and assaultiveness. He was found to be HIV-positive in 1990. Currently, he is treated with zidovudine and lamivudine. There is no evidence of HIV-related CNS involvement, as evidenced by the absence of organic signs.

During his current hospitalization, Mr. B's schizophrenia has responded poorly to conventional antipsychotics used at dosages of at least 1000 mg/day of chlorpromazine equivalents (trifluoperazine, chlorpromazine, and thioridazine augmented with valproate) given for adequate periods of time. A trial with clozapine was not considered due to his HIV-positive status.

About 1 year ago, olanzapine treatment was started, while Mr. B's thioridazine dosage was gradually tapered over 2 weeks. The olanzapine dosage was gradually raised from 5 mg/day to 20 mg/day over 4 weeks. Treatment with clonazepam, 1 mg t.i.d., was started during this time. He remained very disorganized and thought disordered during this time, and he developed manic behavior, such as restlessness, agitation, impulsivity, bizarre posturing, and twisting of his body. There was no evidence of extrapyramidal symptoms, including dystonia or rigidity. Vital signs were stable, and laboratory values remained unchanged as compared with baseline. Sensorium remained clear, and there were no signs of organicity. With gradual decrease of olanzapine to 10 mg/day, some improvement in his excitement symptoms was seen, although they still

necessitated discontinuation of olanzapine 4 months later. Subsequently, Mr. B was started on risperidone up to 16 mg/day, which led to stabilization of his behavior. After 4 weeks, olanzapine was added again and was gradually titrated to 10 mg/day, which led to development of another episode of manic activation. Olanzapine was discontinued, and manic symptoms subsequently resolved.

After the start of olanzapine treatment, both patients experienced a manic-like activation, which they had never experienced before during their multiple failed neuroleptic trials that had also necessitated switches from one neuroleptic drug to another. They also had not shown manic-like symptoms during the natural course of their psychosis before the start of antipsychotic treatment. As olanzapine was reduced or discontinued, this syndrome subsided. The second patient showed a recurrence of it as olanzapine was reintroduced.

It could be argued that this manic-like syndrome represents a withdrawal reaction from previous antipsychotic treatment. However, we believe that this is unlikely because of the cross-taper used in these 2 patients, the prolonged persistence of this syndrome, and its reduction once olanzapine was either discontinued or decreased in dose. Other differential diagnostic considerations include akathisia, anticholinergic delirium due to olanzapine's antimuscarinic profile, and HIV-related dementia. We ruled out delirium and dementia in both patients given their clear sensorium and absence of organic signs during these episodes. Akathisia cannot be completely ruled out for the first patient, whereas the concomitant use of clonazepam in the second patient mitigated against akathisia. A final consideration could be manic-like symptoms associated with the use of zidoyudine, lamivudine, didanosine, or zalcitabine. However, none of these drugs has been reported to be associated with manic-like symptoms. We speculate that this response may be related to olanzapine's reported antidepressant response in schizophrenic and schizoaffective patients.[2] Tollefson et al.[2] reason that olanzapine's potent anti-5-HT_{2A} profile may mediate this response in a way that is similar to the action of certain antidepressants.

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Sexual Dysfunction Associated With Mirtazapine: A Case Report

Sir: The recently released antidepressant mirtazapine has a unique pharmacologic action that makes it unlike any other antidepressant on the U.S. market today.[1] It is purported to assert its antidepressant effects by antagonizing the presynaptic α_2-adrenergic autoreceptors and heteroreceptors on norepinephrine and serotonin presynaptic axons as well as acting as a postsynaptic antagonist of 5-HT_2 and 5-HT_3.[2] By virtue of this 5-HT_2 and 5-HT_3 blockade, the side effects typically associated with the SSRIs such as nausea, vomiting, diarrhea, insomnia, and sexual dysfunction tend to occur less often with mirtazapine than with placebo.[3] A case is presented in which a patient treated with mirtazapine for depression developed sexual dysfunction.

Case report. Mr. A, a 30-year-old white man, was referred to the mental health clinic by his gastroenterologist to whom he had expressed feelings of depression and hopelessness. On further evaluation, the patient admitted to loss of appetite resulting in a 10-pound (4.54 kg) weight loss in 1 month's time, an inner state of anxiety, early morning awakening, and an inability to concentrate. He was treated for irritable bowel syndrome with omeprazole, 20 mg day, as his only medication. Mr. A was in a stable relationship with his girlfriend of 3 years, reported sexual function as satisfactory, and denied a decreased interest in sexual activity or difficulties with ejaculation. He did not drink alcohol or use illicit substances, tobacco, or caffeine. He agreed to a trial of an antidepressant, and, given his constellation of depressive symptoms combined with a history of irritable bowel syndrome, a choice of mirtazapine was made. Mirtazapine was started at 7.5 mg/day and was titrated up to 30 mg/day after 3 weeks. He reported an overall improved condition and denied any problems with gastrointestinal side effects. After about 1 week of treatment, however, he noted that he began to experience an inability to ejaculate, despite full sexual interest and no difficulties with erection. There had been no changes in his physical health or new medications taken. Without consulting his psychiatrist, Mr. A discontinued mirtazapine treatment abruptly, but denied any problems associated with discontinuation. Within 5 days, he was again able to achieve full orgasm at a level equal to that experienced before initiation of mirtazapine.

Patients treated with mirtazapine have been reported to have comparable or lower sexual dysfunction than that in placebo-treated patients as well as fewer of the other side effects commonly associated with SSRI use,[2,4–6] and the manufacturer of mirtazapine reports sexual dysfunction as a rare event (less than 1 in 1000).[7] Sexual dysfunction is a complicated problem because of the various neurotransmitters involved[8]; in this case, mirtazapine, with properties as a weak peripheral α_1-antagonist,[6] may have altered the concentration of norepinephrine at the end organ site, thus causing this dysfunction. Clinicians should be aware of the complexities of the neurotransmitters involved in sexual function and that any psychotropic agent may play a role in sexual dysfunction.

Conclusions and opinions expressed are those of the authors and do not necessarily reflect the position or policy of the U.S. Government, the Department of Defense, the Department of the Army, the U.S. Army Medical Command, or the 82D Airborne Division.

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Hypomania Associated With Mirtazapine Augmentation of Sertraline

Sir: Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). Its novel mechanism of action involves α_2-adrenergic autoreceptor and heteroreceptor blockade, enhancing serotonin (5-HT) and norepinephrine release; and 5-HT_2, 5-HT_3, and histamine H_1 antagonism.[1] Because mirtazapine blocks 5-HT_2 and 5-HT_3 receptors, 5-HT_1-mediated transmission is enhanced.[1] In initial clinical trials, mirtazapine treatment was associated with manic symptoms in 3 (0.25%) of 1299 patients.[2] We report hypomania associated with the addition of mirtazapine, 15 mg/day, to sertraline, 250 mg/day, in an outpatient with DSM-IV major depressive disorder.

Case report. Ms. A, a 45-year-old white woman, had a history of dysthymia since childhood and had undergone 10 psychiatric hospitalizations in the last 6 years for major depressive disorder. She was previously treated with trazodone, imipramine, nortriptyline, bupropion, fluoxetine, and electroconvulsive therapy. She had no history of mania or hypomania. Her family history was notable for major depressive disorder in her mother and alcohol dependence in her sister. Ms. A had no history of medical problems, and she was taking no other medications. Results from her laboratory work-up were normal. She presented to our clinic with a history of a 3-month major depressive episode. She responded to venlafaxine 300 mg/day and remained euthymic for 3 months. A recurrence of her depressive symptoms after 3 months, however, did not respond to a subsequent dose increase to 375 mg/day. Venlafaxine was discontinued, and sertraline was started and increased to a dose of 200 mg/day. Owing to a lack of a clinically significant response, the dose was increased to 250 mg/day with moderate to marked improvement. After 6 weeks of sertraline treatment, however, Ms. A reported a recurrence of her symptoms. Methylphenidate was added to her regimen (5 mg/day, increased to 10 mg/day after 1 week), but she developed irritability and psychomotor agitation within 2 weeks, and discontinued this drug. These symptoms resolved in 4 days, but she remained depressed. One week later, mirtazapine 15 mg/day was added. Within 4 days, Ms. A displayed hypomanic symptoms, stopped mirtazapine treatment, but continued sertraline treatment. Symptoms of hypomania lasted 3 days and included euphoric and irritable mood, mild grandiosity, decreased need for sleep, rapid and pressured speech, racing thoughts, increased energy, increased goal-directed activity, psychomotor agitation, and extreme physical discomfort ("feeling hyper"). No changes in other medications occurred, and no evidence of substance abuse, physical illness, or psychosocial stress was found to explain this sudden onset of symptoms. After Ms. A's hypomanic symptoms remitted, her depression recurred.

The development of Ms. A's hypomanic symptoms was clearly after the addition of mirtazapine to sertraline. These symptoms quickly resolved after mirtazapine was discontinued. Although it is unclear what role methylphenidate and sertraline played in the onset of Ms. A's hypomanic symptoms, this case suggests that mirtazapine, like other antidepressants, may induce manic symptoms in some patients.

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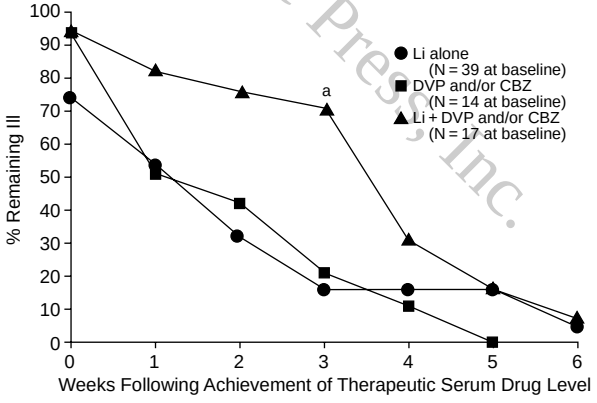
Corrections

In the article "Rapid Titration of Mood Stabilizers Predicts Remission From Mixed or Pure Mania in Bipolar Patients" by Joseph F. Goldberg, M.D., et al. (J Clin Psychiatry 1998;59: 151–158), on page 154, the second sentence under the heading "Pure Mania" should have read: "The most dramatic rate of improvement was seen after 1 week among patients taking lithium combined with divalproex and/or carbamazepine." In addition, the symbols for the "Li alone" group and the "Li + DVP and/or CBZ" group in Figure 2 on page 155 were reversed. The corrected Figure 2 is printed below.

The staff regrets these errors.

Figure 2. Mixed Mania and CGI-Improvement: Proportions Remaining Ill After Achieving Therapeutic Serum Level of Mood Stabilizer*



*Baseline is the time at which a therapeutic serum level was achieved for at least 1 antimanic agent. Patients taking Li + DVP and/or CBZ had a significantly slower time course to remission compared with the other 2 medication groups (log-rank statistic = 6.54, df = 2, $p < .04$). [a]Indicates time point at which a significant difference ($p < .05$) was observed between lithium alone and lithium + DVP and/or CBZ.