LETTERS TO THE EDITOR

False-Positive Methadone Drug Screens During Quetiapine Treatment

To the Editor: Quetiapine is a widely used antipsychotic and mood stabilizing compound. So far, false-positive methadone urine drug screens during quetiapine therapy have been described for 3 adults[1] and 12 adolescents.[2] Here, we report a case series of 10 inpatients, 4 men and 6 women from 22 to 48 years old, suffering from mood or psychotic disorders who tested positive for methadone. Since such false-positive methadone screenings may seriously affect the therapeutic relationship, this potential interaction is highly relevant for clinicians.

Case series. Urine drug screens were performed with the COBAS Integra Methadone II test kit (kinetic interaction of microparticles in solution [KIMS] methodology) by Roche. All serum quetiapine levels were measured in steady-state conditions. In none of our 10 patients who tested positive for methadone was this finding expected, and the patients believably denied intake of this drug. The urine of 4 patients was investigated with gas chromatography–mass spectrometry, which indicated negative results for methadone. All 10 patients received quetiapine, 4 of them in the extended release form. Doses varied between 200 and 800 mg/d. Data were gathered between January 2008 and June 2009.

Two of the 10 patients received quetiapine monotherapy. One of these patients tested negative for methadone in the urine drug screen at a serum quetiapine level of 51 ng/mL (150 mg/d of quetiapine) and then positive 2 weeks later at a quetiapine level of 80 ng/mL (200 mg/d). The other patient receiving monotherapy tested negative for methadone before quetiapine treatment was initiated and then positive at a serum level of 339 ng/mL (200 mg/d of quetiapine extended release).

In a further patient taking extended release quetiapine, a negative screening was obtained at a serum quetiapine level of 28 ng/mL, turning positive at 87 ng/mL. Positive methadone screens were also obtained at serum quetiapine levels of 64 ng/mL and 83 ng/mL, respectively, for 2 patients taking immediate release quetiapine. The patient with a serum level of 83 ng/mL, who was receiving 800 mg/d of quetiapine, later showed both positive and negative screening results at the lower dose of 600 mg/d.

On the basis of these 5 patients' serum quetiapine levels, one could assume a threshold of about 60 ng/mL to yield a false-positive methadone test. In Cherwinski et al,[2] 125 mg/d of quetiapine (no serum level was indicated) was sufficient to yield a false-positive methadone test. A systematic look at 142 methadone urine drug screens from 129 inpatients of our hospital in an 18-month period (January 2008–June 2009) revealed 4 positive methadone tests. Quetiapine was the only drug these 4 patients had in common. For 4 other patients from this group with negative drug screens, serum quetiapine levels have been determined: 87 ng/mL for immediate release quetiapine (1,100 mg/d) and 95, 271, and 391 ng/mL for extended release quetiapine (no trough level; doses were 500, 800, and 600 mg/d, respectively). This shows that in not every case does quetiapine have an effect on methadone screens.

Drugs that have been shown to cross-react with methadone[3] feature a tricyclic structure with a sulfur and a nitrogen atom in the middle ring, which is common to both quetiapine and methadone. Therefore, it is plausible that this structural similarity between quetiapine and methadone could underlie cross-reactivity in the methadone drug screen.

In summary, this report strongly suggests that positive methadone drug screenings be confirmed by a second method such as high-performance liquid chromatography or liquid chromatography–mass spectrometry, especially in patients treated with quetiapine.

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Manic and Psychotic Symptoms Following Subcutaneous Leuprolide in a Male Patient With No Prior Psychiatric History

To the Editor: Leuprolide is a synthetic luteinizing hormone–releasing hormone (LHRH) agonist used in the treatment of advanced prostate cancer. It is available as an immediate-release intramuscular injection, a depot suspension for intramuscular injection, and an extended-release suspension for subcutaneous injection. After a 45-mg dose of subcutaneous leuprolide, 99.1% of patients experience clinical castration by day 28, defined as serum testosterone levels < 50 ng/mL.[1] In addition to this decrease in serum testosterone levels, decreases in sex hormone–binding globulin and estradiol are also seen.[1,2]

Although there have been reports[3,4] of emotional lability, depression, and anxiety with LHRH agonists, the data are not consistent. Furthermore, all published reports on psychiatric side effects of LHRH agonists have been exclusively in female patients. The package insert[1] of leuprolide depot subcutaneous injection does list anxiety, depression, and delusions as occurring in less than 5% of patients. Here, we describe a case of a 65-year-old man with no prior psychiatric history who developed manic and psychotic symptoms after receiving a 45-mg subcutaneous injection of leuprolide. This is the only case available in the literature that describes a male patient experiencing such severe psychiatric symptoms in association with leuprolide.

Case report. Mr A, a 65-year-old white man, was brought into the emergency department by the police after they were called by his wife. She reported that he was extremely agitated, shouting profanities, threatening her, and accusing her of being schizophrenic. Over the last 3 to 4 weeks, he had been progressively sleeping less, only sleeping 1 to 2 hours per night immediately prior to admission. He had persecutory delusions regarding the Mafia and FBI. He was hyperverbal, had pressured speech, and was repeatedly quoting the Bible. Over the past several weeks, he had been displaying bizarre behavior, such as impulsively buying objects he had no use for and excessively spending money. He had also been irritable with his wife and using profanity, which was unusual behavior for him. At the time of admission, an accurate history could not be obtained

Table 1. Other Published Cases of Leuprolide-Induced Psychiatric Episodes[5,6]

Age (y)/Sex	Reason for Leuprolide Treatment	Leuprolide Dosing	Psychiatric Side Effects	Treatment/Outcomes
28/F[5]	Endometriosis and premenstrual syndrome	Dose not stated	After fifth injection, developed mania: racing thoughts, pressured speech, and decreased need for sleep	Required hospitalization; improved with lithium 300 mg tid; patient had a history of depression and a questionable history of a prior manic episode
27/F[6]	Endometriosis, stage II	3.75 mg IM monthly	Within 2 weeks of first injection, developed panic attacks, depressive symptoms, and passive suicidal ideations	Symptoms improved with sertraline, monthly leuprolide injections were continued
28/F[6]	Endometriosis, stage III	3.75 mg IM monthly	After second injection, developed severe depressive symptoms, paranoia, and auditory hallucinations	Symptoms improved with sertraline, monthly leuprolide injections were continued
37/F[6]	Endometriosis, stage IV	3.75 mg IM monthly	After second injection, developed extreme irritability, passive suicidal ideation, and decrease in motivation	No pharmacologic treatment, monthly leuprolide injections were continued
22/F[6]	Endometriosis, stage III	3.75 mg IM monthly	Within 2 weeks of first injection, developed decreased sleep, irritability, and paranoia	Symptoms improved with sertraline, monthly leuprolide injections were continued

Abbreviations: F = female, IM = intramuscular.

from the patient, and therefore the majority of the information was obtained from his spouse.

Laboratory test results on admission, including thyroid panel, basic metabolic panel, complete blood count, and urinalysis, were all within normal limits, except the patient's red blood cell count (RBC) was 3.88 M/mm^3 (normal: 4.00–5.30 M/mm^3) and his hematocrit was 35.5% (normal: 38.0%–46.0%). The rapid plasma reagin test result was negative. A toxicology screen was negative for illegal substances. The patient's blood alcohol level was undetectable, and neurologic examination results were unremarkable.

When Mr A arrived in the emergency department, he was agitated and combative. He struck a nurse and threatened to hurt other staff members. At this time, the patient had to be placed in 4-point restraints. He also received haloperidol 5 mg intramuscularly. He was then involuntarily committed to the psychiatric inpatient unit.

The patient's past medical history was significant for prostate cancer, and he had received radiation seed implants 4 years before. However, 3 months prior to this admission, his prostate-specific antigen levels became elevated. Upon the recommendation of his physician, the patient received leuprolide 45 mg subcutaneously approximately 2 months prior to this admission; this dose is intended to be administered once every 6 months. His past medical history was otherwise unremarkable. The patient had no history of psychiatric illness. His wife reported that his current behavior was an extreme deviation from his normal behavior. She reported no other recent medication changes. There was no evidence of metastasis.

Mr A was a college graduate who had a successful career and retired about 5 years ago. He denied tobacco or illicit drug use. He did state that he drank rarely. The patient had no family history of psychiatric illness, but one of his sisters did have Alzheimer's disease. He had been married for 30 years; he had 2 children who lived out of the home and had no psychiatric history of their own. His home medications were loratadine 10 mg/d, aspirin 81 mg/d, multivitamin daily, and fish oil daily. He had no known drug allergies.

Upon admission, he was started on treatment with oral olanzapine 10 mg/d. At day 4 of hospitalization, he began to become less paranoid and guarded. He was still irritable and quick to anger with staff and patients; however, he was not physically assaultive. His speech remained pressured and tangential. A computed tomographic scan and magnetic resonance imaging of the head yielded unremarkable findings. On day 7 of hospitalization, the patient's olanzapine dose was increased to 20 mg/d. By day 9, he began to participate more appropriately in groups and was easier to talk to. He was exhibiting no paranoid or aggressive behaviors. His speech became regular and less tangential. He no longer exhibited any persecutory delusions. He required no other medications during his hospitalization. A repeat complete blood count did show an increase in both RBC and hematocrit to 4.11 M/mm^3 and 38.3%, respectively. He was discharged home with appropriate follow-up after 13 days of inpatient hospital treatment.

A month after discharge, Mr A continued to do well and decided to discontinue olanzapine on his own. After another month off olanzapine treatment, he continued to do well with no psychiatric symptoms. He never received a second shot of leuprolide.

This is the first case report of a male patient with no prior psychiatric history developing manic and psychotic symptoms after receiving a leuprolide injection.

A PubMed/MEDLINE search of publications from 1980–2010 using the terms *leuprolide, goserelin, mania, psychosis, mood disorder,* and *bipolar disorder* revealed 2 publications,[5,6] for a total of 5 cases, describing leuprolide-induced mood disturbances, and only 2 of those cases involved mania and/or psychosis. The rest of the cases described only depressive symptoms. Previous case reports[5,6] have described psychotic symptoms in women after receiving leuprolide, but none have demonstrated this in men (Table 1). In these reports, it was theorized that estrogen's rapid withdrawal following leuprolide therapy was a cause for the psychiatric symptoms.

An estrogen protection hypothesis has been postulated in the literature[7]; according to this hypothesis, estrogen exerts a protective effect on psychotic symptoms in susceptible patients. This hypothesis is supported by an average age of schizophrenia onset that is 5 years later in women than men; an increase in rates of admissions for schizophrenia in women on the days that estrogen levels are lowest in the menstrual cycle; and lower rates of acute psychosis during pregnancy, when estrogen levels are high, and higher rates of acute psychosis in the postpartum period, when estrogen levels suddenly decrease. Further, the incidence of late-onset schizophrenia in women is double that seen in men, and the combination of estrogen and neuroleptics leads to more rapid symptomatic improvement than neuroleptics alone.[7]

Initial research in men experiencing new-onset and/or acute psychosis has demonstrated decreased levels of total testosterone, free testosterone, estradiol, and estrone in men with schizophrenia compared to age- and weight-matched control patients.[8] It is possible that the decreased levels of estradiol following an

LHRH agonist injection may have left our patient vulnerable to the psychotic symptoms that he demonstrated, similar to the case reports in women. Unfortunately, measurements of testosterone and estradiol levels were not ordered for this patient. In retrospect, it would have been extremely helpful to have those levels. However, due to the mechanism of action of leuprolide and the timing of the injection, one would expect the patient to be in a state of chemical castration.

Although this level of severity in psychiatric adverse events with leuprolide is rare, clinicians should be aware of the possibility. A shorter-acting leuprolide formulation may be used if the patient has a history of psychiatric illness or if the clinician is concerned about psychiatric side effects.

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Anticholinergic Mechanisms: A Forgotten Cause of the Switch Process in Bipolar Disorder

To the Editor: In their review of the neurobiology of the switch process in bipolar disorder, Salvadore et al[1] discuss such neurobiological factors as abnormalities in catecholamine levels, up-regulation of neurotrophic and neuroplastic factors, hypothalamic-pituitary-adrenal axis hyperactivity, and circadian rhythms. However, they have ignored anticholinergic enhancement as a possible factor in mood switch. Such a mechanism has long been postulated, on the basis of evidence of anticholinergic activity of tricyclic antidepressants (TCAs)[2] and within the context of a cholinergic-adrenergic hypothesis of mania and depression put forth nearly 40 years ago.[3]

There is a clear relationship between the mechanisms of the switch process and antidepressant activity and efficacy. A role of the cholinergic system in the mechanism of antidepressant action has been well documented on both the experimental and the clinical levels. In 1979, Browne[4] demonstrated that anticholinergic agents such as scopolamine are active in the behavioral despair test, which had previously been asserted to detect antidepressant activity. The results of neurobiological studies provided evidence of a central cholinergic receptor hypersensitivity in mood disorders.[5,6] A possible role of the muscarinic cholinergic receptor in mood disorders was subsequently demonstrated in molecular-genetic studies.[7,8] In 2006, the results of a randomized, placebo-controlled clinical trial conducted at the National Institute of Mental Health showed that the muscarinic cholinergic receptor antagonist scopolamine exerted an antidepressant effect in depressed patients with either major depressive disorder or bipolar disorder.[9] These results have been replicated and are reported in an article published this year.[10]

In 1991, Koszewska and Puzynski,[11] on the basis of an analysis of 869 depressed episodes, suggested an important role of the cholinergic system in the pathophysiology of mood switching: they observed switching into mania/hypomania most frequently during treatment with amitriptyline, the drug showing highest anticholinergic activity. In our recent retrospective analysis of antidepressant-induced mood conversion to mania/hypomania in patients treated from 1972–1996 in the Affective Disorder Unit, Institute of Psychiatry and Neurology, in Warsaw, Poland, we have demonstrated a significantly higher percentage of the switch in patients treated with TCAs than with non-TCA antidepressants.[12] Furthermore, within TCA drugs, the frequency of switch showed some correlation with the affinity of the drug to muscarinic receptors. The frequency of switch in our study was highest in patients who received amitriptyline (42%), the drug with a Kd (equilibrium dissociation constant for muscarinic acetycholine receptors in human brain) of about 18,[2] and lowest in those who received desipramine (18%), which has a Kd of about 198.[2]

Tricyclic antidepressants were the gold standard for the treatment of depression until the early 1990s. Both the distinct therapeutic efficacy in depression and the anticholinergic properties of these drugs have been widely acknowledged. However, their effect on the cholinergic system has been in recent years nearly exclusively linked to unfavorable somatic and cognitive side effect profiles, in contrast to the lack of such effects with new-generation antidepressants (mostly selective serotonin reuptake inhibitors). The possibility of a contribution of their anticholinergic effect to therapeutic action has barely been noticed. On the basis of the evidence described in this letter, we believe that a meaningful role of anticholinergic mechanisms operating in antidepressant activity, and consequently in switch processes, deserves to be strongly mentioned.

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