Quetiapine Cross Reactivity With Urine Methadone Immunoassays

TO THE EDITOR: Drug screening through urinalysis is a widely accepted method for rapid detection of potential drug use at a relatively low cost. On the other hand, interferences are not that unusual in these kinds of kit assays because of similarities in compound chemical structures and the often nonspecific ways in which the compounds are detected.

We report a case of three schizophrenia patients with quetiapine monotherapy who underwent urine drug screens in the context of a functional magnetic resonance imaging (fMRI) study. At the time of investigation, the patients did not take other drugs.

Using the Cobas Integra Methadone II testkit by Roche (1), we found methadone-positive results that were unexpected, given the patients' medical histories. The Cobas Integra Methadone II testkit contains an in vitro diagnosticum for semiquantitative and qualitative methadone detection in human urine, with a threshold of 300 ng/ml for methadone positivity. In a second step, we tested blood samples taken on the day after the last quetiapine intake to cross check with mass spectrometry (LC/MS/MS). Chromatographic peaks were confirmed and quantified by tandem mass spectrometry on a Micromass Quattro Ultima, using the mass transitions 384 >253 amu for quetiapine and 310 >265 amu for methadone as described previously (2). Samples (190 microliter) were spiked with 10 microliter d3-methadone internal standard (1 microgram/ml in methanol, mass transition 268 >265) and extracted with 500 microliter –20°C cold acetonitrile. Hundred microliter supernatant were directly injected into the HPLC/MS/MS instrumentation. Chromatographic separation of the analytes was performed on a reverse-phase C18 column (Waters Acquity, 1.7 micrometer, 2.1×50 mm [www.waters.com]), with a mobile phase gradient from 50% acetonitrile and 50% 5 mM formic acid in water (buffer A) to 100% acetontrile (buffer B) over 2.2 over 1.8 minutes at a flow rate of 0.25 ml/minute. The level of quantification was 1 ng/ml for quetiapine and 2 ng/ml for methadone. Quetiapine metabolites were not quantified (determined). In contrast to the rechecked urinalyses (again methadone-positive), the quantitative assay, which was performed at the same time, did not reveal methadone positivity in the patients' plasma.

In summary, in case of clinical doubt, positive drug screenings should always be verified by more specific quantitative tests before confronting patients with results. Given our findings, this could be of special interest in patients treated with quetiapine who show methadone-positive urine drug screens.

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Manic Episode During Treatment With Aripiprazole

TO THE EDITOR: Atypical antipsychotics are being increasingly used for the treatment of bipolar disorder. Olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole received Food and Drug Administration approval for the management of this disorder. We report a case of possible induction of mania with the use of aripiprazole.

A 45-year-old Caucasian woman with a diagnosis of schizoaffective disorder-bipolar type reported stable mood with minimal mood swings while receiving divalproate sodium 1500 mg at bedtime and fluphenazine hydrochloride 5 mg in the morning and 10 mg at bedtime. She complained of grinding teeth at night, being excessively sleepy, and having increased appetite and weight gain. After discussing the potential risks and benefits, a decision was made to add aripiprazole to the current regimen, with a future plan of decreasing fluphenazine.

Aripiprazole was started at 10 mg a day. The patient complained of changes in mood from the third day of starting aripiprazole. She reported decreased need for sleep, racing thoughts, euphoric mood, and grandiose delusions about being a royalty. She was noted to be laughing inappropriately and singing loudly. She scored 31 on the Young Mania Rating Scale (1). She denied abusing alcohol or drugs in the interim. Aripiprazole was discontinued, and she was enrolled in a partial hospital program. Her manic symptoms reduced in intensity within a few days and resolved completely within 2 weeks after discontinuation of aripiprazole. She scored 6 on the Young Mania Rating Scale at 2 weeks.

The temporal relationship of the manic symptoms to the initiation of aripiprazole and their resolution with discontinuation of this medication supports the assumption that the manic episode was induced by aripiprazole. Seven out of the eight criteria proposed by Aubry et al. for a switch into mania secondary to atypical antipsychotics were met, suggesting that aripiprazole was the proximate cause of this patient's manic symptoms (2).

Several possible mechanisms have been proposed for the induction of mania by atypical antipsychotics, including a high ratio of 5-HT_2/D_2 receptor occupancy with risperidone and olanzapine, and monoamine reuptake inhibition antidepressant-like effect of ziprasidone (3). Aripiprazole is a partial agonist at 5-HT_{1A} and partial antagonist at 5-HT_{2A} receptors (4). It is a partial agonist at dopaminergic receptors with high affinity for D_2 and D_3 receptors and moderate affinity for D_4 receptors (4). Combined effect of antagonistic activity at 5-HT_{2A} and partial agonistic activity at D_2 receptors, along with agonistic activity at 5-HT_{1A} receptors, may cause frontal dopamine release contributing to manic symptoms. In addition, the prolonged use of fluphenazine could have resulted in a func-