Aripiprazole-Induced Hypersexuality

To the Editor: Aripiprazole differs from other antipsychotics because of its unique pharmacologic profile; it acts as a partial agonist of the dopamine D_2 receptors. The literature shows a surge of reports[1–4] describing impulse-control behaviors with dopamine receptor agonist drugs, and the US Food and Drug Administration (FDA)[5] recently issued a warning regarding these behaviors. In this report, we describe the case of a patient with bipolar disorder who developed hypersexuality following aripiprazole treatment.

Case report. Mr A is a 60-year-old man with a history of bipolar II disorder (*DSM-5* criteria) and no significant medical problems, who was being followed in an outpatient practice. He had no prior history of substance abuse, psychiatric hospitalizations, or suicide attempts and was stable for more than 6 months on lamotrigine 300 mg daily, venlafaxine 75 mg daily, risperidone 1.5 mg twice daily, and clonazepam 1 mg twice daily as needed. During a follow-up appointment, he displayed moderate grandiose delusions, and the risperidone was cross-tapered with aripiprazole to address those symptoms. A month later, Mr A presented with elated mood. Aripiprazole was increased to 15 mg daily, risperidone was completely tapered off, and his symptoms disappeared. After a month of treatment with aripiprazole, Mr A became obsessed about engaging in sexual activities and had a very high libido and an uncontrollable urge to masturbate. Besides hypersexuality, he displayed no other manic or hypomanic symptoms; his symptoms at that time were very different from his prior hypomanic states. A complete medical workup was performed, and all of his laboratory values (including thyroid function and HIV) came back within normal limits; his urine toxicology test was positive for benzodiazepines, which was consistent with prior results, and his head computed tomography scan was unchanged from prior scans. Aripiprazole was ultimately discontinued, and all of his hypersexuality symptoms ceased within a few days. After 2 weeks, Mr A was at his baseline level of functioning prior to the cross-taper when he was asymptomatic.

In this case, the hypersexuality symptoms followed a reasonable temporal sequence after aripiprazole was started, and that all of the symptoms disappeared after the cessation of the drug points toward a correlation between both events. Also, Mr A's score of 9 on the Naranjo Adverse Reaction Probability Scale[6] indicates that the hypersexuality was definitely an adverse reaction to aripiprazole.

The majority of antipsychotics cause decreased libido and have negative effects on sexual desire and function.[7] Conversely, aripiprazole acts as a partial agonist of the dopamine D_2 receptor, as a partial agonist at the 5-HT_{1A} receptor, and as an antagonist at the 5-HT_{2A} receptor. Literature[8,9] shows that medication with partial dopaminergic agonistic activity can cause compulsive behaviors, such as pathological gambling, compulsive shopping, and hypersexuality.[4] Reports[9] indicate high prevalence rates of compulsive behaviors from 6% to 24%, and, in the majority of the cases,[1,2] the abnormal behavior ceased after drug discontinuation.

The mesolimbic dopaminergic circuit acts as a reward system for food, sex, and drugs of abuse and may be involved in compulsive disorders. Brain dopamine systems that link the hypothalamus and the limbic system appear to form the core of the excitatory system, while serotonin has clear inhibitory effects on sexuality.[10] There are several hypotheses underlying the possible mechanisms of this association. Moore et al[4] suggested that these behaviors are reward-based and are reinforced by dopaminergic stimulation, specifically by the dopamine D_3 receptor. Others suggest that the combined antagonism of 5-HT_{1A} and partial agonism of D_2 receptors of aripiprazole could cause frontal dopamine release,[11] especially in patients with chronic exposure to D_2 antagonists,[12] which would result in a state of relatively high dopamine activation and could even cause full manic symptoms.

To date, there are many cases[1,3,4] reporting pathological gambling after aripiprazole treatment but very few reporting hypersexuality. Although it is difficult to predict who would develop these behaviors, the literature[4] suggests that patients with personal or family history of obsessive-compulsive disorder, bipolar disorder, impulsive personality, alcoholism, or drug abuse are at highest risk. The FDA recently issued a warning regarding the impulse-control behaviors seen in patients taking aripiprazole and recommended that clinicians should be familiar with this adverse reaction.

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