Aripiprazole and Impulse-Control Disorders: A Recent FDA Warning and a Case Report

To the Editor: Aripiprazole is a unique antipsychotic with partial dopamine agonist properties increasingly linked to pathological gambling.[1,2] The US Food and Drug Administration (FDA) released in May 2016 a safety announcement[3] in relation to aripiprazole and the induction of impulse-control disorders (ICD), inclusive of pathological gambling, hypersexuality, compulsive shopping, and compulsive eating.

Case report. Mr A, a 35-year-old married man employed as a mechanic, was diagnosed with schizophrenia (as per *DSM-IV* criteria) in 2007 and commenced on aripiprazole 10 mg/d. His past history included attention-deficit/hyperactivity disorder, alcohol abuse, and sporadic use of tetrahydrocannabinol and methamphetamines but no history of significant gambling or compulsive shopping.

Within 4 weeks of commencing aripiprazole, he reported an increased urge to gamble, with weekly spending of US $100 on slot machines. Due to persistent psychosis, Mr A's aripiprazole dose was increased to 15 mg/d, with an increase in gambling to $200 weekly between 2007 and 2015. Aripiprazole was increased to 20 mg/d in 2012 due to a relapse of psychosis, but there was no change in his level of pathological gambling. Following the increase in aripiprazole dose (15 mg/d to 20 mg/d), Mr A began to compulsively shop, purchasing significant amounts of mechanical work tools, which were never used. He also became hypersexual on treatment with aripiprazole 10 mg, with a dose-dependent increase in symptoms with 15 mg/d, contributing to marital tension. Mr A's hypersexuality and accumulated losses of $200,000 due to pathological gambling and compulsive shopping resulted in the breakdown of his marriage.

After Mr A's family discovered that aripiprazole could cause pathological gambling, they informed his general practitioner in 2015, who then ceased aripiprazole treatment. This cessation followed by the commencement of risperidone led to the cessation of his pathological gambling, hypersexuality, and compulsive shopping urges within 2 weeks, without destabilizing his schizophrenia. Importantly, as a result of his ICD resolution, he reunited with his wife with no ongoing relationship or financial difficulties.

Dopamine agonists for patients with Parkinson's disease are associated with an increased risk of developing ICD.[4–6] Of interest, it has been shown that aripiprazole, a partial dopamine agonist, resulted in more severe pathological gambling than full dopamine agonist agents.[6] It has been postulated that dopamine agonists with a higher relative affinity for D_3 than D_2 receptors, such as pramipexole, resulted in significantly higher rates of ICD, thus implicating D_3 receptor agonism more specifically with ICD.[5,7] Aripiprazole is generally thought to be a partial D_2 agonist, but has also been shown to have high affinity for the D_3 receptor.[8] The D_3 receptor is predominantly found in the striatal, prefrontal cortex, and insula limbic circuits involved in key reward pathways, which have been implicated in the development of pathological gambling.[9]

The FDA, through their Adverse Event Reporting System, identified 184 cases of a possible association between ICD and aripiprazole, with 17 cases published in the medical literature.[3] Pathological gambling was the most common, with 164 cases (89%) reported; others included 9 cases of hypersexuality, 4 cases of compulsive buying, 3 cases of compulsive eating, and 4 cases with multiple ICD.[3] This case report adds to the existing literature and is one of the few specifically linking aripiprazole with induction of multiple ICD in a single patient with no history of ICD, with complete resolution of these symptoms following its cessation. The FDA safety warning means that clinicians should specifically screen for ICD before prescribing aripiprazole, educate patients about potential risks, and specifically monitor for ICD following commencement or dose increases. More research is required to specifically identify the dopamine receptor pathway and specific dopamine agonists involved in the induction of ICD, which could then lead to more specific therapeutic targets for pathological gambling and ICD.

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