

PATHOLOGICAL GAMBLING AND COMPULSIVE EATING ASSOCIATED WITH LONG-ACTING INJECTABLE ARIPIPRAZOLE: A CASE REPORT

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INTRODUCTION

Aripiprazole (ARI) is one of the most frequently used second-generation antipsychotic, first approved for the treatment of schizophrenia by the FDA in 2002 and the European Medicines Agency in 2004. ARI's popularity can be contributed not only to its efficacy and broad therapeutic spectrum, but also to its safe cardiac profile, relatively rare adverse effects, and diverse modes of application, such as capsules, vials, solution and long-acting injectables (LAI). Pharmacologically, ARI acts as a partial agonist of dopamine D2 receptors, D3 receptors and 5-HT7 serotonin receptors (Giri & Peteru 2019, Miuli et al. 2020). Numerous reports describing impulse regulation disorders after treatment with ARI have emerged lately. In 2015 Health Canada and a year later the FDA issued a safety warning. We present a case of pathological gambling (PG) and compulsive eating after therapy with LAI ARI. Written consent was obtained from the patient.

CASE REPORT

A 23-year-old male has been receiving treatment for schizophrenia since he was 16 years old. Before the first episode, he smoked marijuana for about a year. In 2013, at the time of the first hospitalization, he had been receiving risperidone. Due to poor compliance, LAI paliperidone 150 mg monthly was introduced in 2015. After a year and a half, the pharmacotherapy was modified due to hyperprolactinemia with galactorrhoea and weight gain from 100 to 125 kg. LAI paliperidone was discontinued and ARI 15 mg orally was administered. He refused LAI and received oral ARI for a period of 7 months. He did not report any side effects during that time. In 2017 he discontinued the medication but still attended regular outpatient check-ups. After a year, the psychosis worsened and LAI ARI 400 mg monthly was introduced. 6 months later, he reported problematic gambling with gradually increasing frequency (20 to 25 days a month) and bets. Spending his monthly salary in 2 days, he took out several loans. He gained weight up to 155 kg due to compulsive eating and occasional alcohol consumption after losing money. Endocrinological causes were ruled out. The patient refused specialized

treatment for PG. LAI ARI dose was reduced to 300 mg monthly for 3 months without changes in PG before being discontinued. Fluphenazine orally was introduced, but soon switched to risperidone orally due to sedation and leg cramps. No decrease in gambling intensity was observed during the reduction of ARI. However, PG resolved completely within 6 months after the discontinuation and the patient lost roughly 10 kg in one year. He reported no desire to gamble or crisis upon cessation.

DISCUSSION

Impulse control disorders (ICDs) have been well documented with full dopamine agonists, usually in the treatment of Parkinson's disease (Lachance et al. 2019). An Italian pharmacovigilance study found it to be so in more than 80% of therapy associated PG cases, whereas ARI was associated with 5% of cases (Scavone et al. 2020). A similar mechanism of a hyperdopaminergic state in the mesolimbic reward pathways has been postulated, since ARI acts as a partial agonist of dopamine D2 receptors, 5-HT7 serotonin receptors and, most importantly, dopamine D3 receptors (Giri & Peteru 2019). Due to ARI's partial agonism, ICDs may therefore also be dose-related or occur with a longer latency (Mahapatra et al. 2016).

PG and hypersexuality are the most common ICDs associated with ARI, whereas compulsive eating is relatively rare (Lertxundi et al. 2018). Several risk factors have been proposed, including a history of substance abuse, schizophrenia and related disorders, cluster B personality disorder, history of gambling and even genetic polymorphism on the D2 receptor (Lachance et al. 2019). Our patient expressed the first two, whereas polymorphism has not been excluded. Upregulation of dopamine receptor sensitivity after treatment with dopaminergic antagonist antipsychotics has been hypothesized and may also apply to our case (Mahapatra et al. 2016).

Due to its frequency, PG has been the most researched ICD associated with ARI. So far three large pharmacovigilance database reviews found an increased risk of PG after oral ARI, without a definite causality. Two literature reviews were performed in 2019.

Table 1. Case reports of pathological gambling associated with LAI aripiprazole

Authors, year of publication	Case No.	Age	Sex	Diagnosis	Therapy before ARI	ARI dosage (mode)	Prior gambling	Other risk factors	Side effects	Time of gambling onset after ARI initiation	Money spent on gambling	Decrease/resolution after ARI discontinuation (time)	Management of ICD
Corbeil et al. 2020	1	24	M	SCZ	Risperidone 1 mg/d	20 mg/d (oral), 300 mg monthly (LAI), reduced to 150 mg monthly (LAI) over 18 months	No	History of SUD	Daily gambling	Shortly	Whole paycheck	Yes (immediately)	Therapy changed to Lurasidone 60 mg/d
	2	28	M	SCZ	Risperidone 3 mg/d	1st time: 6 mg/d (oral) 2nd time: 200 mg monthly, increased to 300 mg monthly (LAI)	Yes	History of SUD, Cluster B personality traits	Gambling recurrence	1st time: 1 year 2nd time: Early	1st time: CAD 10.000 2nd time: CAD 20.000	1st time: Yes (n/a) 2nd time: No ARI discontinuation	1st time: ARI discontinuation and specialized care 2nd time: specialized care
	3	24	M	SCZ	Risperidone 1.5 mg/d Paliperidone palmitate 78 mg monthly (LAI) Olanzapine up to 20 mg Lisdexamfetamine 50 mg/d	Introductory dose n/a, 120 mg monthly at the time of gambling (LAI)	Yes (diagnosed retrospectively)	History of SUD, cluster B personality traits	Ocasional gambling with fast emerging EPS	18 months	CAD 1250/week	Yes (n/a)	Therapy changed to Clozapine up to 275 mg/d and community treatment team care
	4	24	M	Psychosis, ADD	None	15 mg/d (oral)	Yes (diagnosed gambling disorder leading to bankruptcy)	History of SUD, cluster B personality traits	Gambling	7 months	Hundreds of CAD	No ARI discontinuation	Lisdexamfetamine replaced with Methylphenidate and specialized care
Scavone et al. 2020	5	32	F	Mood disorder	None	5-10 mg/d (oral) n/a mg monthly (LAI)	n/a	n/a	Gambling	4 months	n/a	n/a	n/a

ADD - attention deficit disorder; ARI - aripiprazole; CAD - canadian dollar; F - female; ICD - impulse control disorder; LAI - long-acting injectable; M - male; n/a - not available; SCZ - schizophrenia; SUD - substance use disorder

One focused on the schizophrenic population but got stifled by several limitations (Lachance et al. 2019). The second found 23 reported cases of ARI associated PG (Giri & Peteru 2019), yet only one described concurrent compulsive eating (Roxanas 2010). Additionally, all patients were treated with oral ARI. LAI may comparably increase the risk almost two-fold, though this could be explained with LAI being more often used to treat severe patients, already more prone to PG (Lertxundi et al. 2018).

PubMed search revealed 9 newly published cases, 5 of them on the LAI formulation, none with concurrent compulsive eating (Chen et al. 2019, Corbeil et al. 2020, Scavone et al. 2020). Non-LAI patients were excluded. The patients were predominantly male with a modal age of 24 years, a history of substance abuse, and primary diagnosis schizophrenia. Three also expressed cluster B personality traits and prior gambling. The emergence of PG after LAI ARI initiation varied considerably, from early to up to 18 months later. Interestingly, one of the patients first developed PG after 1 year of oral ARI but relapsed much faster with LAI formulation. He was one of the two cases where PG has been successfully managed with specialized care without ARI discontinuation.

Besides concurrent compulsive eating, our patient's case is curious due to PG developing only with LAI formulation. Firstly, this could have been dose- or duration-related, though no improvement of PG was reported later during a 3-month decrease of LAI ARI dosage. Secondly, the patient may have been taking ARI inconsistently, even before reporting the discontinuation. LAI ARI, on the other hand, ensured a sustained agonist activity.

CONCLUSION

Despite emerging evidence of ARI induced PG, more studies and thorough reports are required to better understand the relationship between ARI and ICDs, the roles of dose, formulation, treatment duration, schizophrenia, genetics and other risk factors. It remains hard to determine patients' proneness to ARI mediated ICDs. We therefore strongly recommend careful consideration before treatment initiation and vigorous monitoring afterwards.

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Contribution of individual authors:

Both authors performed literature research and partook equally in writing.

Valentin Golouh collected new case data and summarized them in a table.

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