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Aripiprazole Induced Gambling, in Patients with Learning Disabilities

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Abstract

In this paper we explore the potential association between aripiprazole—a partial dopamine agonist and gambling. In December 2023, The Medicines and Healthcare Products Regulatory Agency (MHRA) issued a drug safety alert, highlighting an increasing number of yellow card reports, linking the use of Aripiprazole with impulse control disorders, such as gambling, hypersexuality, increased spending and binge eating. Aripiprazole exerts its therapeutic effects via partial agonistic activity at dopaminergic and serotonergic receptors, particularly within the mesolimbic pathway, commonly referred to as the brain's "reward pathway". It has been hypothesised that partial agonism at the D2 and D3 receptors within these pathways may contribute to the emergence of impulse control disorders in susceptible individuals, although the precise mechanisms remain poorly understood. We reviewed the available literature linking aripiprazole to impulse control disorders and case reports where individuals being treated with this therapeutic agent had either developed or exacerbated existing gambling behaviours, in addition to reviewing 2 cases on the Community Forensic teams (CFT) caseload where patients were exhibiting similar patterns of either excessive or problematic gambling behaviours following initiation of aripiprazole. As a literature review, searches of PubMed, Embase, CINHAL (Ebsco) and Google Scholar were undertaken using the terms "aripiprazole", "gambling", "impulse control disorder" "D2 receptors", "D3 receptors", "mesolimbic system", "reward pathway" and "pathological gambling". English-language publications available up to January 2024 were reviewed. Our findings from searching the existing literature, media reports and our own caseload do find a temporal correlation between problematic gambling and aripiprazole use. The severity of this varies between affected individuals, however; the MHRA update further corroborates this link. We suggest further research into the mechanisms of action of aripiprazole on

mesolimbic system is required to gain a better understanding of why this psychotropic medication appears to potentially upregulate the rewards pathway, and what underlying inherent and environmental factors predispose some individuals to develop impulse control disorders and not others. Review of our clinical caseload demonstrated a temporal association between aripiprazole treatment and the emergence or worsening of gambling behaviours in both cases. In Patient A, initiation of aripiprazole coincided with a marked escalation in gambling behaviour, while Patient B developed problematic gambling following commencement of treatment. However, several potential confounding factors were identified. Patient A was concurrently misusing substances, a recognised risk factor for impulsive behaviours that may have contributed to the reported upregulation of D3 receptors. Both patients also had coexisting learning disabilities and neurodevelopmental disorders, in addition to histories of impulsive behaviours and substance misuse, all of which are recognised risk factors for impaired impulse control. Consequently, although a temporal relationship with aripiprazole was observed, causality cannot be established from these cases alone. We further recommend careful consideration of antipsychotic selection, open dialogue with patients, family and carers, including education regarding this potential adverse effect, in addition to increased pharmacovigilance by clinicians monitoring response to treatment. Vigilance may be warranted in patients with pre-existing addictions or other recognised risk factors for impulsive behaviours.

Keywords

Aripiprazole, Gambling, Impulsivity, MHRA, D2 Receptors, D3 Receptors, Psychotropics, Antipsychotics, Safety Update

1. Introduction

In December 2023, a drug safety update was issued by the Medicines and Healthcare products regulatory agency (MHRA) advising healthcare professionals of an increase in yellow card reports linking aripiprazole with gambling and other impulse control disorders [1]. The update also highlighted an apparent lack of awareness of these risks and advised that this information should be clearly communicated to patients and carers when using this drug.

Between 30 June 2009 and 28 August 2023, the MHRA received 69 Yellow card reports describing gambling or gambling disorder associated with aripiprazole use [1].

There has also been increased media coverage of the issue, with the BBC publishing reports on individuals who have experienced these adverse side effects [2] [3]. Furthermore, a class action lawsuit was initiated in Canada concerning the manufacturers of Abilify and Abilify Maintena, alleging inadequate warning of the potential risks of compulsive gambling, compulsive shopping, hypersexuality and binge eating associated with these medications [4]. This heightened media

focus has contributed to growing awareness of the issue amongst both health care professionals and the general public.

Considering this update, and the increased reporting of the association of Aripiprazole with impulse control disorders we reviewed our caseload, identifying two patients prescribed aripiprazole who subsequently developed or experienced worsening gambling issues. These cases are presented to illustrate the temporal relationship between treatment initiation and gambling behaviours and to explore whether discontinuation of aripiprazole was associated with any change in clinical presentation.

2. Method

We performed a literature search using the databases PubMed, Embase and Google scholar and included the search terms: aripiprazole, gambling, impulsivity, MHRA, D2 receptors, D3 receptors, psychotropics, antipsychotics, safety update. Only, English language publications available up to January 2024 were included.

As this was a literature review, publications were selected based on their relevance *i.e.* the relationship between aripiprazole and impulse control disorders, rather than a formal review process such as would be for systematic review. Sources that were not directly relevant, or duplicated publications were excluded from our criteria. Search dates for this literature review were from November 2025 to April 2026.

In addition, two cases were identified from the Community Forensic Learning Disability Team (CFT) caseload. Both patients exhibited problematic gambling behaviours that came to clinical attention following the publication of the MHRA Drug Safety Update and were subsequently reviewed for a potential temporal association with aripiprazole treatment.

We used the ICD-11 classification criteria of gambling disorder, to classify the gambling behaviours observed in these patients: "*a pattern of persistent or recurrent gambling behaviour that is not primarily conducted over the internet and is manifested by*: *impaired control over gambling*, *increased priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities and*, *continuation or escalation of gambling despite occurrence of negative consequences. The behaviour pattern is of sufficient severity to result in significant impairment in personal*, *family*, *social*, *educational*, *occupational or other important areas of functioning*." [5]

The ICD-11 classification further specifies that the pattern of the gambling behaviours (6C50.0) can be continuous, episodic or recurrent, and that these behaviour patterns must be present for at least 12 months for the diagnosis to be made, but adds that this duration may be shortened if all of the diagnostic criteria are met and symptoms of the disorder are severe [5]. This diagnosis was applicable as will be discussed further, the patients prioritised their gambling behaviours above all other areas of functioning and needs.

Patient A

Patient A is a 31-year-old-male with a background of mild-moderate learning disability (LD), attention deficit hyperactivity disorder (ADHD) and schizophrenia. He attended mainstream schooling up to the age of 11 and then attended special educational needs (SEN) schools, where he was noted to display disruptive behaviours.

He has a history of substance misuse from childhood and had funded these habits by begging, stealing and at times gambling. In addition, he has a long forensic history dating back to the age of 16 and has a total of 31 convictions for 41 offences.

Patient A has been detained under the mental health act on two occasions, initially to treat a psychotic presentation and subsequently to stabilise his mental health. He was discharged when stable on Zuclopenthixol depot to the care of CFT.

Following a period of stable mental health and increased adherence to treatment, patient A requested a medication review, stating a preference for oral medication over the depot. It was agreed that he could trial Aripiprazole whilst being gradually weaned off Zuclopenthixol. Aripiprazole was chosen due to its lower risk of metabolic adverse effects compared with many other second-generation antipsychotics He was commenced on Aripiprazole 15 mg once daily to treat his psychotic illness (schizophrenia) and initially showed a positive response to this.

His family reported initial concerns about spending long periods of time away from home gambling and had been told that he had been seen begging for money from the public to enable him to continue gambling.

However, over the subsequent 3-month period his family reported a drastic increase in gambling behaviours. They described him as gambling daily for up to 16 hours per day. He would beg when he had run out of money and use his winnings to continue gambling or paying for other personal services. He had been reprimanded by the police on three occasions for begging and he then chose to gamble in other towns where he was not known, to avoid further contact with the police.

Due to the families concerns a medication review was prompted, and he was switched to a paliperidone long-acting depot formulation. He continues to be stable in his mental state, however, after a long period of abstinence from alcohol he is now drinking again. Although gambling behaviours persisted, both the patient and his family described a clinically significant reduction in their frequency and severity. Gambling was no longer reported to dominate his daily activities or take priority over his basic needs to the same extent as during aripiprazole treatment.

Patient B

Patient B is a 41-year-old male with a background of mild-moderate LD and autism. Special educational needs were identified at a pre-school level, and he attended SEN schools from the age of 5 onwards.

Mr B has a history of substance misuse, and a forensic history of violence, sexual violence, harassment and breach of restraining orders.

He had been prescribed Risperidone 0.5 mg daily for the treatment of anxiety symptoms associated with autism.

During an admission on a secure unit, his Risperidone was changed to Aripiprazole 5 mg once daily, after noting that he was experiencing metabolic side effects, namely weight gain and elevated blood sugars. A review a month later showed an improvement of blood glucose levels and no destabilisation of mood.

Mr B was discharged to a supported living facility, where staff raised concerns about patterns of gambling. He would go out daily to use slot machines and gamble his money. He would use winnings to continue gambling and had begun prioritising these over necessities such as food and drink and paying utility bills, leading him to develop arrears due to lack of monies.

Consequently, his medication was reviewed, and it was felt that due to stability and good functioning Aripiprazole could be discontinued, later monitoring showed no disturbance of mental health, and he is currently not prescribed any psychotropic medications.

Although gambling behaviours persisted following cessation of aripiprazole, staff initially reported a reduction in their intensity. However, this improvement was not sustained, and he continues to gamble regularly. This suggests that while aripiprazole may have contributed to the emergence or escalation of gambling behaviours, other biological, psychological or environmental factors are also likely to have influenced their persistence.

As with Patient A, several recognised risk factors for impulsive behaviours were present, including learning disability, autism and a history of substance misuse. Consequently, it is not possible to attribute the observed gambling behaviours solely to aripiprazole treatment. Nevertheless, the temporal relationship between medication initiation and the emergence of gambling prompted clinical concern and supported review of his treatment.

3. Discussion

The primary mode of action for most antipsychotics is through the modulation of the dopamine receptors particularly D2 receptors, although many antipsychotic agents also demonstrate activity at the D3 receptors and other neurotransmitter systems. Within the central nervous system, the dopamine system is a pivotal neurotransmitter involved in the regulation of cognition, emotions, motivation, mobility and affect [6]. Disruption of the dopamine system has long been implicated in several psychiatric disorders, making dopamine receptors key targets for antipsychotic treatment [6]. Historically, the D2 receptor were considered the principal therapeutic target; however, increasing evidence has suggests that D3 receptors may also help in regulating reward processing, motivation and addictive behaviours [6].

The D2 receptor has been found to be widespread throughout the central nervous system, whereas D3 receptor are concentrated predominantly within the mesolimbic and the cortical areas [6] [7]. These areas of the brain are associated

with executive functions, emotion, goal directed behaviours and rewards [6] [7]. D3 receptors appear to demonstrate higher affinity for dopamine than D2 receptors, estimated to be one to two orders of magnitude greater, making them an area of increasing pharmacological interest [6].

Aripiprazole is an atypical, second-generation antipsychotic drug, it is a partial agonist at dopamine D2 and D3 receptors, a partial agonist at 5-HT1A receptors and an antagonist at 5-HT2A receptors [8]. It was the first antipsychotic marketed with partial agonist activity at the dopamine receptors [9]. It is licensed for the treatment and maintenance of schizophrenia, bipolar affective disorder and as an adjunct in major depressive disorder [10] [11]. Its receptor profile is associated with a relatively low risk of extrapyramidal symptoms and metabolic adverse effects when compared with many alternative antipsychotic agents.

Common side effects of this drug listed in the BNF include "anxiety; appetite abnormal; diabetes mellitus; gastrointestinal discomfort; headache; musculoskeletal stiffness; nausea; vision disorders; weight decreased" [8]. However, following the MHRA Drug Safety Update published in December 2023, clinicians are now advised to remain alert to the possibility of impulse control disorders—including pathological gambling, compulsive shopping, binge eating and hypersexuality—in patients receiving aripiprazole [1]. These adverse effects receive comparatively limited emphasis within standard prescribing references, highlighting the importance of clinician awareness and patient education.

Impulse control disorders are well recognised in patients receiving full dopamine agonist for Parkinson's disease, an effect thought to relate to dopaminergic stimulation of the mesolimbic reward pathways, particularly through D3 receptor activation, although the precise mechanisms remain incompletely understood [9] [10]. Increasing evidence suggests that partial dopamine agonists such as aripiprazole may produce similar effects. Because of its affinity for D3 receptors, aripiprazole has attracted increasing attention as a possible contributor to reward-seeking behaviours, including pathological gambling [11]-[16].

Reports of gambling associated with aripiprazole have appeared since approximately 2010, leading to the FDA issuing a drug safety warning in May 2016 highlighting gambling, increased spending, hypersexuality and binge eating as potential adverse effects [10]. Etiman *et al.* found that patients taking aripiprazole were 5 times more likely to develop and be diagnosed with gambling disorder, and an 8 fold increase in those with bipolar disorder compared to those not using aripiprazole [14]. Similarly Williams *et al.*, in a systematic review and meta-analysis concluded that third generation antipsychotic medications, including aripiprazole appear to increase the risk of impulse control disorders and concluded that there does appear an increased risk of the development of impulse control disorders [15]. The European pharmacovigilance database also reported issues with impulse control disorders arising in individuals prescribed this medication [10].

Although the exact biological mechanism remains unproven, it has been proposed that the partial agnostic activity on the meso-cortico-limbic dopamine sys-

tem alters reward processing and reinforces impulsive or reward seeking behaviours in susceptible individuals [11] [12] [16]. Emerging evidence also suggests that D3 receptor expression may be increased in individuals with substance misuse, potentially increasing vulnerability to these adverse effects [13] [16]. Consequently several authors and the MHRA recommend that clinicians routinely enquire about new or worsening compulsive behaviours during treatment, as patients may not volunteer this information [16].

We believed that documenting our observations of increased gambling behaviours among patients following the initiation of aripiprazole would contribute to the growing evidence describing this potential adverse effect.

In the first case, our patient pre-existing impulsive traits, which included gambling and had a history of substance misuse, ADHD and schizophrenia, all recognised risk factors for impulsive behaviours. Nevertheless, our review suggested that gambling behaviours worsened following initiation of aripiprazole, consistent with the hypothesis that Aripiprazole may exacerbate impulsive behaviours in susceptible individuals.

The second case demonstrated clearer temporal relationship between the initiation of aripiprazole and the onset of problematic gambling. Although gambling persisted following discontinuation, the initial reduction in the severity suggests that the aripiprazole may have contributed, while biological, psychological and environmental factors likely influenced its persistence. As in the first case, a history of substance misuse, mental health and neurodevelopment disorder may have increased vulnerability.

Alternative explanations should also be considered. Substance misuse may have motivated gambling to fund drug use, whilst longstanding impulsive traits neurodevelopmental disorders and the social reinforcement associated with gambling venues may all have contributed. These confounding factors emphasise the multifactorial nature of gambling behaviour and prevent attribution of casualty to aripiprazole alone.

Overall, our findings are consistent with published case reports suggesting that aripiprazole may be associated with the emergence or exacerbation of gambling behaviours in a small proportion of susceptible individuals. However, because both cases contained multiple confounding factors, a causal relationship cannot be established from observational evidence alone. Nevertheless, given the potentially serious consequences, including financial loss, relationship breakdown, legal difficulties and deterioration in quality of life and the widespread use of aripiprazole across psychiatric practice, maintaining awareness of this potential adverse effect remains clinically important.

4. Conclusions

In conclusion, Aripiprazole is an effective, widely used, second-generation antipsychotic medication for the treatment of psychotic disorders. In our cases, it was selected due to its relatively low rate of causing metabolic side effects compared

to other antipsychotic agents. The publication of the drug safety alerts has highlighted the potential association of aripiprazole with either developing or worsening pre-existing impulse control disorders, particularly gambling.

The MHRA's safety update highlights an apparent lack of clinician awareness of these adverse effects and has thus recommended that patients being treated with aripiprazole, should receive education about the potential of this adverse effect developing and regular monitoring when prescribing this medication. However, the underlying neurobiological mechanisms responsible for some individuals developing these behaviours, whilst others do not remain unclear. Current theories support the hypothesis that involvement of the D3 receptors within the mesolimbic pathway may be a contributory factor; however further research is required to clarify the contribution of dopamine receptors (particularly D3 receptor activity), together with the influence of patient-specific vulnerability factors such as substance misuse, learning disabilities, neurodevelopmental disorders and environmental influences.

Following our review of the Community Forensic Learning Disability Team caseload, we identified two patients in whom the initiation of aripiprazole temporally coincided with the emergence or marked escalation of gambling behaviours. Although these observations are consistent with findings reported in the existing literature, they do not establish a causal relationship and should be interpreted within the context of the multiple confounding factors present in both cases.

Despite these limitations, our findings reinforce the importance of clinician awareness of this recognised adverse effect. We recommend exercising increased caution when initiating treatment with aripiprazole, particularly in individuals with a history of substance misuse, pre-existing impulsive behaviours or other recognised vulnerability factors. Clinicians should engage in open dialogue with patients, families and carers to ensure they are aware of the potential emergence of impulsive behaviours, including problematic gambling, compulsive spending, binge eating and hypersexuality. Routine enquiry regarding these behaviours should form part of ongoing clinical reviews, as patients may not readily disclose them unless specifically asked.

Finally, further prospective research is warranted to determine the incidence of aripiprazole-associated impulse control disorders, identify patient groups at greatest risk, explore potential dose-response relationships and better understand the neurobiological mechanisms and other confounding factors that may increase the risk of developing these behaviours. Such work may ultimately support safer prescribing practices and earlier identification of patients who develop these potentially life-changing adverse effects.

Author Contributions

F. N and F. A conceived the proposal for this paper. S. K designed the methodology, collected the data for patient A, performed the formal analysis and wrote the original draft. N. Y collected the data for patient B.

All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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