Asian Journal of Psychiatry 23 (2016) 128–130

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

Aripiprazole induced Impulse Control Disorders: Where do we stand?

Aripiprazole, known as a third-generation antipsychotic drug due to its unique pharmacological profile, has partial agonist properties at the D2, D3-dopamine and 5-HT7 serotonin receptors. In May 2016, the U.S, Food and Drug Administration (FDA) issued a safety warning with the use of Aripiprazole suggesting its association with uncontrollable urges to gamble, binge eat, shop, and have sex which stopped when the medicine was discontinued or the dose was reduced. A review of the published literature yielded 22 cases in total which reported the onset of impulse control problems after the initiation of pharmacotherapy with Aripiprazole. (Table 1). The average age of the patient was 28 with a range from 19 to 64 years and majority (17 out of 22) being male. 15 patients had a diagnosis of schizophrenia or related disorders like schizoaffective disorder and 6 patients had diagnosis of bipolar disorder whereas only one patient had unipolar depression. The average dose of Aripiprazole used was 25 mg/day however the modal dose was 15 mg. The majority of patients (16, 72%) reported pathological gambling, followed by hyper sexuality. One patient presented with features of compulsive shopping. All the patients who exhibited pathological gambling were male, whereas three out of the four patients who developed hyper sexuality were female. Three patients presented with symptoms suggestive of more than one type of impulse control disorder. In 10 out of the 16 patients with pathological gambling, there was worsening of occasional and recreational gambling behaviour present prior to initiation of Aripiprazole whereas in rest of the patients it was new onset impulse control disorder. In all the patients a reduction of the impulse control related behaviour was observed within a few months after Aripiprazole was stopped.

It is interesting to note that the impulse control related disorder mainly seen in patients treated with aripiprazole can be re-conceptualized under the rubric of behavioural addiction. The most studied prototype of behavioural addiction is pathological gambling which is one of the impulse control disorders. The hallmark of behavioural addictions is the failure to resist an impulse to perform an act that is harmful to the person or to others (APA, 2000). Additionally it is also characterized by a recurrent pattern of behaviour, and repetitive engagement in these behaviours which ultimately interferes with functioning in other domains. Dopamine agonists used in the treatment of Parkinson's disease have also been shown to stimulate pathways that govern reward behaviour, pleasure, and addiction through D3 receptors and lead to impulse control disorders (Ahlskog, 2011). D3 receptors have been demonstrated to mediate motor responses, but are also located in limbic nuclei and their stimulation has been implicated in the addiction process. Some authors reported that Aripiprazole has an agonist action at the D3 receptor (Roxanas, 2010) – which is mainly present in the limbic system. This is purported to lead to a stimulation of the reward system (Ahlskog, 2011) hence implicating its role in emergence of impulse control problems. The hyper-stimulation is proposed to be particularly enhanced in cases of a previous treatment by antipsychotics acting as a dopaminergic receptors antagonist, owing to the up-regulation and the dopaminergic receptor hypersensitivity processes. The partial agonist action Aripiprazole then causes stronger effects. Moreover, the partial agonist activity of Aripiprazole imparts less action than a complete agonist, which could explain why the occurrence of behaviours like pathological gambling is sometimes late or due to increase in dosage (Gaboriau et al., 2014).

Another finding from the analysis of available reports show that the impulse control related behaviour emerged or exacerbated only on Aripiprazole dosage of higher side i.e. 15–30 mg. In animal models of cocaine self-administration, low doses of Aripiprazole administered daily before each self-administration and reinstatement sessions were demonstrated to reduce, yet not prevent, cocaine self-administration, although blocking the reinstatement of cocaine-seeking behaviour (Feltenstein et al., 2007). In contrast, when continuously infused, Aripiprazole seems to have no significant effects on cocaine self-administration or cocaine choice, whereas acute injection rapidly induces a reduction in seeking behaviour, although only at low-intermediate doses (Thomsen et al., 2008). These experiments demonstrated the effect of Aripiprazole in both acute and chronic paradigms, with different effects at different doses.

It is important to distinguish the potential role of Aripiprazole on neural pathway underlying impulse control and behavioural addiction as they have major implications in treatment consequences. Low dose Aripiprazole has been successfully used in the treatment of trichotillomania, one of the classical impulse control disorders. (Sasaki and Iyo, 2015). Similarly, a meta-analyses found that Aripiprazole had a much larger effect-size than other antipsychotics in controlling impulsivity and anger related symptoms (Mercer et al., 2009). Such findings suggest efficacy of Aripiprazole in reducing impulsivity not related to psychosis and comes in clear conflict with reports of worsening or causing emergence of impulse control disorders.

From a pharmacodynamics perspective Aripiprazole is a unique molecule. Its properties and interactions with various receptor systems needs to be further explored in order to delineate its effects on pathways underlying impulse control and addictive behaviour. Based on available literature, we recommend that Aripiprazole should be used with caution in individuals with a prior history or co-morbid impulse control disorder. As this symptom has been characteristically seen with higher dosages, a

http://dx.doi.org/10.1016/j.ajp.2016.08.001

Table 1
Characteristics of patients on Aripiprazole having impulse control disorder.

SN	Author	Age (Yrs.)	Sex	Primary diagnosis	Dosage per day (mg)	Impulse control problem	Other	Decrease in symptoms when dosage reduced	Remarks
1	Schlachetzki and Langosch (2008)	24	F	Schizoaffective Disorder	30	Hypersexuality	Compulsive Masturbation	Not studied	New Onset
2	Gavaudan (2011)	46	M	Paranoid Schizophrenia	15	Pathological Gambling	Aggressive Behaviour/ Criminality	Yes	Worsening Of Recreational Gambling
3	Gavaudan (2011)	19	M	Paranoid Schizophrenia	10	Pathological Gambling	Theft/ Criminality	Yes	New Onset
4	Roxanas (2010)	64	F	Schizophrenia	15	Pathological Gambling	Compulsive Eating	Yes	New Onset
5	Kodama and Hamamura (2010)	57	M	Bipolar 1	3	Compulsive Masturbation	Hypersexuality	Yes	New Onset
6	Kodama and Hamamura (2010)	53	F	Bipolar Spectrum Disorder	12	Compulsive Shopping	–	Yes	New Onset
7	Cohen et al. (2011)	30	M	Schizoaffective Disorder	15	Pathological Gambling	Internet Gambling	Yes	New Onset
8	Cohen et al. (2011)	20	M	Paranoid Schizophrenia	15	Pathological Gambling	–	Yes	New Onset
9	Cohen et al. (2011)	19	M	Residual Schizophrenia	10	Pathological Gambling	–	Yes	New Onset
10	Smith et al. (2011)	29	M	Paranoid Schizophrenia	15	Pathological Gambling	–	Yes	Worsening Of Previous Gambling
11	Smith et al. (2011)	28	M	Schizoaffective Disorder	15	Pathological Gambling	–	Yes	Worsening Of Previous Gambling
12	Smith et al. (2011)	27	M	Paranoid Schizophrenia	15	Pathological Gambling	–	Yes	New Onset Gambling
13	Cheon et al. (2013)	37	F	Schizophrenia	20	Hypersexuality	–	Yes	New Onset
14	Cheon et al. (2013)	36	F	Schizophrenia	20	Hypersexuality	Compulsive Masturbation	Yes	New Onset
15	Gaboriau et al. (2014)	55	M	Major Depression	20	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
16	Gaboriau et al. (2014)	24	M	Bipolar Disorder	30	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
17	Gaboriau et al. (2014)	25	M	Bipolar Disorder	5	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
18	Gaboriau et al. (2014)	42	F	Schizophrenia	20	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
19	Gaboriau et al. (2014)	38	M	Bipolar Disorder	20	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
20	Gaboriau et al. (2014)	46	M	Bipolar Disorder	15	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
21	Gaboriau et al. (2014)	29	M	Schizophrenia	10	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling
22	Gaboriau et al. (2014)	32	M	Schizoaffective Disorder	20	Pathological Gambling	–	Yes	Worsening Of Recreational Gambling

slow and judicious dose titration may help in identifying its emergence. Aripiprazole should be stopped in patients who develop these symptoms and alternative pharmacological agents should be considered.

References

Ahlskog, J.E., 2011. Pathological behaviors provoked by dopamine agonist therapy of Parkinson's disease. Physiol. Behav. 104, 168–172.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (text Revision), Fourth edition American Psychiatric Association.

Cheon, E., Koo, B.-H., Seo, S.S., Lee, J.-Y., 2013. Two cases of hypersexuality probably associated with aripiprazole. Psychiatry Investig. 10, 200–202.

Cohen, J., Magalon, D., Boyer, L., Simon, N., Lançon, C., 2011. Aripiprazole-induced pathological gambling: a report of 3 cases. Curr. Drug Saf. 6 (1), 51–53.

Feltenstein, M.W., Altar, C.A., See, R.E., 2007. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. Biol. Psychiatry 61, 582–590.

Gaboriau, L., Victorri-Vigneau, C., Gérardin, M., Allain-Veyrac, G., Jolliet-Evin, P., Grall-Bronnec, M., 2014. Aripiprazole: a new risk factor for pathological gambling? A report of 8 case reports. Addict. Behav. 39, 562–565.

Gavaudan, G., 2011. Pathological gambling: 2 case reports. Reactions 1351, 14. Aripiprazole-induced pathological gambling: a report of 3 cases. Curr. Drug Saf. 6, 51–53.

Kodama, M., Hamamura, T., 2010. Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting. Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. CINP 13, 549–551.

Mercer, D., Douglass, A.B., Links, P.S., 2009. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J. Personal. Disord. 23, 156–174.

Roxanas, M.G., 2010. Pathological gambling and compulsive eating associated with aripiprazole. Aust. N. Z. J Psychiatry 44, 291.

Sasaki, T., Iyo, M., 2015. Treatment of puberty trichotillomania with low-dose aripiprazole. Ann. Gen Psychiatry 14, 18.

Schlachetzki, J.C.M., Langosch, J.M., 2008. Aripiprazole induced hypersexuality in a 24-year-old female patient with schizoaffective disorder? J. Clin. Psychopharmacol. 28, 567–568.

Smith, N., Kitchenham, N., Bowden-Jones, H., 2011. Pathological gambling and the treatment of psychosis with aripiprazole: case reports. Br. J. Psychiatry J. Ment. Sci. 199, 158–159.

Thomsen, M., Fink-Jensen, A., Woldbye, D.P.D., Wörtwein, G., Sager, T.N., Holm, R., Pepe, L.M., Caine, S.B., 2008. Effects of acute and chronic aripiprazole treatment on choice between cocaine self-administration and food under a concurrent schedule of reinforcement in rats. Psychopharmacology (Berl.) 201, 43–53.

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Received in revised form 6 August 2016

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