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Possible agitation and disruptive behavioural with aripiprazole in prader-willi syndrome: Insights from a case series

Anabela Galiana[a], Maria A.D. Acunti[a], Jorgelina Stegmann[b,*]

[a] Department of Mental Health, Fundación SPINE, Buenos Aires, Argentina
[b] Department of Clinical Medicine, Fundación SPINE, Buenos Aires, Argentina

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ABSTRACT

Prader-Willi Syndrome (PWS) is characterised by a complex behavioural phenotype, including psychiatric disorders. Off-label use of aripiprazole, an atypical third-generation antipsychotic drug, is relatively common amongst patients with PWS given its more favourable profile as regards to possible effects on appetite. We evaluated the clinical behavioural status in relation to treatment with aripiprazole, as well as a possible relationship between the onset of disruptive behaviour and adverse effects of agitation or pharmacological activation with the use of aripiprazole in six patients with PWS. In the largest case series to date exploring the effect of aripiprazole in PWS, we identified that patients under treatment with aripiprazole were prone to worsening and disruptive behaviours. Our hypothesis-generating findings, though not providing evidence of causation, raise concerns about potential harmful effects related to high-risk behaviors involving a relatively common treatment used in clinical practice with limited evidence.

1. Introduction

Prader-willi syndrome (PWS) is characterised by a complex behavioural phenotype. Moreover, psychiatric disorders are also common amongst adults with PWS, particularly psychosis (Sinnema et al., 2011). Antipsychotic medication is commonly used for people with a dual diagnosis of intellectual disability and psychotic illness. In addition, many people with intellectual disability and challenging behaviour are treated with antipsychotic medications (Zuddas et al., 2011; Deb et al., 2014). Aripiprazole use is also associated with lower rate of clinically significant weight gain compared with other atypical antipsychotics (Akhtar and Khan, 2008). Atypical antipsychotic drugs have been used to treat many disorders, and considering this population's propensity to hyperphagia and obesity, aripiprazole has emerged as a promising treatment for patients with PWS (Briegel, 2018).However, to the best of our knowledge only two isolated case reports of its use have been documented to date (Briegel, 2018; Akça and Yilmaz, 2016). Despite such scarce data regarding the safety and efficacy of aripiprazole in PWS, its off-label use is widespread in clinical practice. Hence, the purpose of this case series was to evaluate the use of aripiprazole for the management of irritability and disruptive behavioural episodes in a sample of six patients with PWS and psychosis or behaviour disorder.

2. Material and methods

All PWS patients included in this case series were receiving regular therapy using a transdisciplinary approach in an institution dedicated to the treatment of rare diseases. Such regular transdisciplinary therapy (RTT) involves various areas. Clinical medicine, nutrition, occupational therapy, kinesiology, psychopedagogy, psychology, psychiatry and speech, psychiatry and speech therapy. RTT was defined as a treatment carried out according to a pre-established frequency (weekly, fortnightly, or monthly) and the therapeutic indications determined by the transdisciplinary team, based on the needs and resources of the individual receiving treatment and his/her family.

Of the six patients, the indication of aripiprazole was based on their behaviour in 3 cases and on psychosis or bipolar spectrum disorder in 3 cases. None of these patients were receiving any other concomitant antipsychotic medication.

Behavioural assessment was carried out using qualitative and quantitative criteria based on a Behaviour Rating Scale in PWS (Disruptive Behaviour Scale, DBS), specifically designed by our area of mental health (psychology, psychopedagogy and psychiatry) to classify those with PWS as being at mild, moderate or severe risk for disruptive behaviour based on 8 disruptive behaviour indicators. On this basis, PWS

* Corresponding author. Fundación SPINE, Laprida 2080, C1425EKV, Ciudad Autónoma de Buenos Aires, Argentina.
E-mail address: jstegmann@spine.org.ar (J. Stegmann).

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were thus divided in 3 levels of behavioural risk: minor (0 to 7 points), moderate (8 to 16 points), and severe (17 or more points), with the aim of quantifying the longitudinal change in behaviour through the use of repeat measures over time.

Information was obtained by interview, the clinical follow-up description of their mental health, the retrospective review of the clinical history, and the report of family members and carers.

Clinical behavioural status in relation to treatment with aripiprazole was analysed, and the existence of a possible association between the onset of disruptive behaviour and adverse effects of agitation or pharmacological activation with the use of aripiprazole in PWS was explored.

3. Results

3.1. Case#1

Nineteen year old male with clinical and confirmed PWS by methylation test. This patient presentes history of severe obstructive sleep apnoea and hypopnea syndrome at 10 years. Tonsillectomy at 10 years. He was admitted at the age of 19 with morbid obesity, weight 96,800 kg, BMI 46 kg/m2. Generalized hypotonia, hypogonadism. Normal thyroid profile. Osteopenia. Diabetes without dyslipidemia.

The patient had problematic behaviours that were very difficult to manage, linked to his condition of intellectual disability and behavioural phenotype of PWS, intense and persistent behavioural outbursts with poor control of impulses, low tolerance to frustration and to limits, showing oppositionalism and a negativistic attitude, reaching heteroaggressiveness towards objects and people. No other indicators have been identified, according to DSM V clinical criteria, of other diagnoses of psychiatric comorbidity.

Upon admission, he had disruptive behaviors (DBS 29) and was receiving treatment with aripiprazole (2.5 mg/day) in another facility for 4 months previously to the admission in our Institution. He underwent RTT for 6 months without improvement, therefore aripiprazole was increased to 5 mg/day. The behaviour disorders persisted and it was considered that the medication dose was too low and therefore ineffective and it was further increased (10 mg/day). Thereafter, impulsive behaviours continued leading to an additional dosing increment up to 20 mg/day. Given the progressive worsening behaviour despite increasing dose, including impulsive and violent outbursts, progressive drug withdrawal was decided. There were significant behaviour improvements after withdrawal (DBS 12).

3.2. Case#2

Twelve year old female with clinical and genetic tests providing evidence of deletion for PWS, with a diagnosis of bipolar spectrum disorder and behaviour disorder. Regarding clinical diagnosis the patient presented osteopenia, hypogonadism, strabismus, skin picking. Weight at admission to treatment 60,200 kg, BMI 33.78 kg/m2. Normal polysomnography. No diagnosis of apnoea, diabetes, or hypertension. Elevated TSH thyroid profile. Subclinical hypothyroidism. No indicators have been identified according to DSM V clinical criteria of other diagnoses of psychiatric comorbidity.

When admitted to our institution the patient was receiving treatment with aripiprazole 5 mg/day due to severe behavioural issues, problems at school, affective lability, irritability, tachypsychia, hyperthymic verbiage, behavioural disinhibition, and negativism. The Family stated that in the previous facility the patient was receiving a baseline treatment of 2.5 mg for two months and irritability worsened once the dose was increased to 5 mg/day, for which it was decided to reduce and withdraw the medication to evaluate baseline behaviour without medication. A decrease in challenging oppositional problem behaviours and irritability was observed. Upon admission, the quantitative assessment of behavioural risk using the disruptive behaviour risk scale revealed a severe disorder (DBS 20). She underwent RTT with no improvement in her disruptive behaviours, leading to drug withdrawal. Significant behaviour improvement was documented after withdrawal (DBS 4).

3.3. Case#3

Eleven year-old female with clinical diagnosis of PWS. The Weight at admission to treatment was 37.900 kg and height was 130.5 cm. Patient presented mild scoliosis, hypogonadism, osteopenia and skin picking. No diagnosis of hypertension or diabetes. Normal polysomnography. Furthermore, the patient presented a diagnosis of psychosis and behaviour disorder, received treatment with aripiprazole for 6 months. Admitted due to behaviour problems, affective lability, anguish, hyperactivity, anxiety, hyperalertness, suspicious attitude, distrust, strange look, paranoid references of feeling observed. Disorganized thinking at times. Severe skin picking, ideas of death and self-injury. Upon admission, the quantitative assessment of behavioural risk using the disruptive behaviour risk scale demonstrated a severe condition (DBS 25). The patient was medicated at the beginning with aripiprazole 2.5 mg/day and the dose was increased to 5 mg/day, noticing greater irritability, nervousness, and increase of self-injury. As well as an increase in anxiety and insomnia. When it was decided to reduce and suspend medication to rotate to another pharmacological plan, the patient showed improvement, with decreased irritability and self-harm due to skin picking. Upon RTT onset, the family suggested a relationship between aripiprazole treatment onset and the presence of severe behaviours including sleeplessness and self-aggression, thus leading to drug progressive withdrawal. Stable after withdrawal, without pharmacological treatment (DBS 10).

3.4. Case#4

Eighteen-year-old male with clinical and genetic diagnosis of PWS. Regarding the clinical report, the patient presented morbid obesity, with a weight at admission of 96,200 kg, BMI 39.29 kg/m2. Type-2 diabetes with insulin requirement and dyslipidemia with elevated triglycerides. Acanthosis nigricans, hypogonadism, lesions due to skin picking were also stated. However, there are no signs of hypertension. The polysomnography and thyroid profile were also normal. Moreover, this patient presented a diagnosis of behavioural disorder, receiving baseline treatment with aripiprazole 10 mg/day. Regarding the diagnosis of "conduct disorder", this case presents positive indicators since the age of 13 years including transgression of social norms and rules, unacceptance of limits, and damage to objects and people. He has violently attacked his mother, causing injuries with a fracture of his arm. He has had violent behaviour attacking health professionals when they have assisted him in medical check-ups. He has stolen money and objects, has run away from home and spent hours wandering and looking for food. He has shown no signs of remorse or guilt in the face of the pain caused. He impresses with little empathy. Intimacy through shouting and threats. He has been suspended from his day centre for misconduct with peers and teachers. He has had episodes referred to in previous years as episodes of psychomotor excitement that could perhaps be understood today as episodes of an intermittent explosive disorder associated with his underlying condition.

Aripiprazol treatment started with the appearance of positive indicators at the age of 13 years old and the family stated that through these years they observed behavioural conduct worsening with the increase of dosage. These behaviours include outbursts, tantrums, oppositionalism, violation of rules or limits, running away from home, stealing money, violence towards his mother and health professionals with crises of psychomotor arousal. Upon admission, he showed a severe disruptive behaviour risk score (DBS 28). After the onset of RTT with a simultaneous dose increase to 15 mg/day, the behavioural disorder persisted even after psychotherapeutic treatment; including episodes of escape from home, violence (aggressiveness and disinhibition) and oppositional be-

Table 1
Individual quantitative assessment of behavioural risk using the disruptive behaviour risk scale (DBS) in individuals with Prader-Willi syndrome. Relationship with treatment with aripiprazole.

Case	PWS Diagnosis Method	Aripiprazole	After Withdrawal	Ba Baseline diagnosis	Maximum dose
#1	Clinical and Genectic	Severe (DBS 29)	Moderate (dbs 12)	Behaviour Disorder	Aripiprazole 20 mg/d
#2	Clinical and Genectic	Severe (DBS 20)	Mild (DBS 4)	Bipolar Spectrum Disorder and Behaviour Disorder	Aripiprazole 5 mg/d
#3	Clinical	Severe (DBS 25)	Moderate (DBS 10)	Basel Psychosis and Behaviour Disorder	Aripiprazole 5 mg/d
#4	Clinical and Genectic	Severe (DBS 28)	-	Basel Psychosis and Behaviour Disorder	Aripiprazole 15 mg/d
#5	Clinical and Genectic	Severe (DBS 27)	Mild (dbs 6)	Behaviour Disorder	Aripiprazole 20 mg/d
#6	Clinical and Genectic	Severe (DBS 29)	Moderate(DBS 19)	Base Psychosis and severe Behaviour Disorder	Aripiprazole 5 mg/d

(-) No report.

haviour, and accumulation of garbage. The patient, immersed in complex socio-economic conditions of the family, discontinued treatment.

3.5. Case#5

Seventeen year-old male with PWS Clinically and genetically diagnosed. Moreover, this patient presents a diagnosis of behaviour disorder and ADHD.Concerning clinical evaluation: Weight: 85.8 kg; Height: 160 cm; BMI: 33.5 kg/m2 (obesity). Increased TSH (subclinical hypothyroidism), hypercholesterolaemia, hypertriglyceridemia and hepatic steatosis. Polysomnography showing partially impaired sleep architecture (limited deep sleep). No apneas or hypopneas and no pathological respiratory events. Lumbar bone densitometry: Osteopenia. This patient was diagnosed at age 9 with attention-deficit hyperactivity disorder (ADHD) and was medicated with extended-release methylphenidate 20 mg/day, with a good initial response for 2 years. The parents reported that the behaviour worsened, becoming more impulsive, aggressive and irritable. Which led to adding aripiprazole to the plan. Medicated with aripiprazole for 2 years with dose increases up to 20 mg/day. As his behaviour continued to worsen, expressing irritability, tantrums, aggressiveness, escape from home, and accumulation of garbage, methylphenidate was suspended and the dose of aripiprazole was increased. Upon admission, he had a high disruptive behaviour risk score (DBS 27). RTT along with downtitration to 10 mg/day of aripiprazole was decided, with significant improvement, leading to progressive drug withdrawal. The patient showed significant progress thereafter with stable behaviour after withdrawal (DBS 6).

3.6. Case#6

Twelve-year-old male with PWS Clinically and genetically diagnosed, in addition to a diagnosis of psychosis and severe behaviour disorder, was under treatment with aripiprazole for 8 months, reaching a dose of 5 mg/day, previous admission to our institution. This patient was admitted to our institution at 12 weighing 55 kg, BMI 25.9 kg/m2. Presenting obesity, hypothyroidism, scoliosis and dyslipidemia with elevated cholesterol. No diagnosis of diabetes nor hypertension. Cardiac Doppler ultrasound: Tricuspid insufficiency and pulmonary physiology. He presented problematic behaviours at home and school, leading to suspension. He showed aggressive reactions, with alterations in the perception of reality with paranoid thought content. With self-referential ideas of prejudice and distrust, the patient referred that his colleagues spoked bad things to him, that they looked at him badly, and this provoked anger in him. He reported that they said ugly things to him or insulted him, when this was not the case. He became distressed, his behaviour and thoughts became disorganized with increased anxiety, discomfort and affective lability. No other clinical criteria indicators have been identified according to DSM-V or other diagnoses of psychiatric comorbidity. He showed severe disruptive behaviours (DBS 29). One year after RTT onset, it was decided to decrease medication to 2.5 mg/day. Fifteen days after dosage reduction the patient showed a good therapeutic response thus it was decided to undergo progressive reduction and finally drug withdrawal due to the behavioural improvement. The patient showed improvement in conduct thereafter (DBS 19).

4. Discussion

In this case series involving patients with PWS, we observed a possible relationship between aripiprazole and the occurrence of agitation and behavioural activation. After drug discontinuation, a consistent significant reduction in disruptive behaviours such as agitation, irritability, impulsiveness, and even behaviours constituting a risk to physical integrity or life was noticed. In addition, the characteristics of the typical behavioural phenotype of PWS were significantly exacerbated upon treatment onset.

To the best of our knowledge, there are only two case reports addressing the usefulness of aripiprazole in PWS (Briegel, 2018; Akça and Yilmaz, 2016). In parallel, a previous study comprising patients without PWS identified agitation as the most common cause of discontinuing treatment with aripiprazole (Shajahan et al., 2008).

Our hypothesis-generating findings should be interpreted with caution given the small number of patients and the observational nature of the study. Furthermore, since all PWS were immersed in a transdisciplinary approach, we cannot infer a direct cause-effect mechanism despite the observation of a possible association between behavioural activation and aripiprazole. However, we would like to acknowledge that a recent publication regarding PWS treatment update, mentioned that some medications can produce iatrogenic mood and behavioural activation in PWS. These include SSRIs, NSSRIs, aripiprazole, modafinil, gonadal steroids, and rarely stimulants or alpha-adrenergic agonists. Symptoms include increased intensity of phenotypic behaviors, followed by increased impulsivity, mood lability, and possibly psychosis. (Butler et al., 2019)

Additionally, we recognize that confirmation of the diagnosis of PWS requires molecular genetic tests, however patient #3 does not present genetic confirmation of PWS. Nevertheless, the clinic diagnosis of this patient was clearly compatible with the PWS phenotype. We understand that it is a limitation of the work and that without a doubt having the certification and genetic subtype would be very valuable to deepen the analysis of this case. Furthermore, we recognize that the agitation observed in the patients in terms of behaviours of restlessness, nervousness, agitation could be a consequence of akathisia. Nevertheless, all our patients undergo regular clinical physical examination and when they were under our treatment we did not observe akathisia or extrapyramidal symptoms. However, we cannot rule out that they did not have them prior to entering our device.

This is the largest series to date addressing the effect of aripiprazole in PWS, therefore our findings are potentially clinically relevant due to the potential incremental risk of agitation and behavioural activation associated with this medication in PWS. It should be noted that in this case series the decision to discontinue the treatment with aripiprazole was determined as no benefits were seen with the treatment. On the contrary with time we considered that the behavioural impairment and agitation were related to this drug. It should be acknowledged that

the genotype of PWS might result in different pharmacogenetic, pharmacokinetic, and behavioural phenotype characteristics with atypical pharmacological responses. Future studies are warranted to explore this in detail.

Also, we recognize that the disruptive behaviour could have persisted with aripiprazole because this drug was not the appropriate treatment, although consistent behaviour improvement was documented in all patients at decreasing doses and with drug withdrawal. However, standard criteria are often difficult to apply in diagnosing psychopathology in individuals with intellectual disabilities. Additionally, psychiatric illnesses in people with PWS have been found to be atypical, resembling an atypical affective disorder with or without psychotic symptoms (Sinnema et al., 2011; Soni et al., 2008).

5. Conclusion

Although preliminary, our findings could warn of possible harmful effects of medication related to risky behaviors, given that it is a relatively common indication in clinical practice despite the limited evidence. Such off-label use is possibly related to the fact that aripiprazole is an atypical third-generation antipsychotic with pharmacological properties differentiating it from other drugs of this category, with a more favourable profile as regards to possible effects on appetite and increased weight (Table 1).

Informed consent

All procedures were performed in accordance with the ethical standards of the Helsinki declaration of 1964 and subsequent addenda, and all patients signed the informed consent (habeas data).

Ethics approval, consent to participate, and consent for publication

All procedures were performed in accordance with the ethical standards of the declaration of Helsinki of 1964 and its subsequent addenda, and all patients or tutors signed the informed consent for their participation and publication.

Availability of data and material

All datasets on which the conclusions of this paper rely are available to readers. Data used are presented in the main manuscript.

Moreover, all materials described in this manuscript, including all relevant raw data, will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Code availability

Not applicable.

Authors' contributions

All authors made substantial contributions to the conception and design of the work, acquired and analysed the data, drafted, reviewed, and approved the final manuscript.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psycr.2022.100033.

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Further-reading

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