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To cite this article: Hamza Ayaydın & Şermin Bilgen Ulgar (2018) Diurnal enuresis developing in association with risperidone and aripiprazole use in a child with autism spectrum disorder: a case report, *Psychiatry and Clinical Psychopharmacology*, 28:3, 329-331, DOI: [10.1080/24750573.2017.1402497](https://doi.org/10.1080/24750573.2017.1402497)

To link to this article: <https://doi.org/10.1080/24750573.2017.1402497>



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Published online: 20 Nov 2017.



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CASE REPORT



Diurnal enuresis developing in association with risperidone and aripiprazole use in a child with autism spectrum disorder: a case report

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ABSTRACT

Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder. Risperidone and Aripiprazole appear to be effective in associated behavioural problems with ASDs, including irritability, aggressiveness, hyperactivity, self-injurious behaviour, and stereotypies. In our case, new-onset diurnal enuresis was observed as a side effect after risperidone use. New-onset diurnal enuresis improved when risperidone was stopped, but recommenced when aripiprazole was added to treatment. However, all symptoms of enuresis resolved when the aripiprazole dosage was reduced. In contrast to some reports in which aripiprazole was used in the treatment of enuresis, our case is different in that it led to diurnal enuresis.

ARTICLE HISTORY

Received 1 October 2017
Accepted 1 November 2017

KEYWORDS

Autism; diurnal enuresis;
aripiprazole; risperidone;
child

Introduction

Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder. Risperidone and aripiprazole appear to be effective in associated behavioural problems with ASDs, including irritability, aggressiveness, hyperactivity, self-injurious behaviour, and stereotypies [1,2]. Diurnal enuresis is defined as involuntary daytime voiding of urine. Enuresis is a side-effect that adversely affects treatment compliance and quality of life for children and their carers. Various psychotropic agents have been reported to cause nocturnal enuresis. In order of prevalence, these include clozapine, olanzapine, quetiapine, and risperidone [3]. Younger age may also add a greater risk for enuresis [4]. In our case, new-onset diurnal enuresis was observed as a side-effect after risperidone use. Risperidone therapy was stopped, and the patient was started on aripiprazole in the light of reports of the therapeutic effect of aripiprazole in the treatment of clozapine-related enuresis [5].

Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D2 and serotonin type 1A (5HT1A) receptors, and as an antagonist at serotonin type 2A (5HT2A) receptors [6].

New-onset diurnal enuresis improved when risperidone was stopped, but recommenced when aripiprazole was added to treatment. However, all symptoms of enuresis resolved when the aripiprazole dosage was reduced. In contrast to the therapeutic effect of aripiprazole in the treatment of enuresis developing in association with clozapine use, in our case enuresis

developed when the aripiprazole dosage was increased [5]. In contrast to some reports in which aripiprazole was used in the treatment of enuresis [5], our case is different in that it led to diurnal enuresis. Then enuresis subsequently resolved, with no impairment of improvement in behavioural problems, following a mild dose reduction. To the best of our knowledge, ours is the first case that risperidone and aripiprazole-induced diurnal enuresis in a preadolescent with autistic disorder.

Case presentation

A 5-year-old female was referred to our outpatient clinic for her aggressiveness, severe temper tantrums, self-injurious behaviours, stereotypies, and hyperactivity. She was diagnosed with ASD due to his severe impairment in language development and social-emotional reciprocity and repetitive behaviours and restricted interests. Because of her behavioural problems and repetitive behaviours, risperidone was initiated at 0.25 mg/day and then the dose was increased to 0.5 mg/day. Her behavioural problems improved partially, but within the second week of risperidone treatment she developed new-onset diurnal enuresis. Her medical history and workup, including blood biochemistry tests, fasting glucose, ultrasonography, urinalysis, electroencephalography and neurological examination, were all normal. She had urinary bladder control at three years of age, and she and her family had no previous history of urinary incontinence. Because her mother requested the discontinu-

ation of risperidone due to the adverse effect on the fourth week of treatment, we decided to switch to aripiprazole. Enuresis ceased rapidly during the first week of risperidone discontinuation. Because of her behavioural problems, aripiprazole was initiated at 2 mg/day and gradually titrated up to 4 mg/day over two weeks. Within the second week of treatment, she developed diurnal enuresis again. Her medical workup, including blood biochemistry tests, fasting glucose, ultrasonography, urinalysis, electroencephalography and neurological examination, was normal. On the 4th week of treatment, her parents reduced the dose of aripiprazole used from 4 mg/day to 3.5 mg/day due to persistence of enuresis. The patient's enuresis resolved with no adverse effect on the improvement in her behavioural problems within one week after dose reduction.

Discussion

We report a female patient with ASD developing new-onset diurnal enuresis following both risperidone and aripiprazole use. Enuresis resolved entirely following a slight reduction in aripiprazole dosage from 4 mg/day to 3.5 mg/day, while the effectiveness of treatment was maintained.

Although it is difficult to state risperidone or aripiprazole definitively as the causes of new-onset diurnal enuresis in the case, the chronological process and dramatic response to risperidone discontinuation and aripiprazole dose reduction in the absence of an identifiable medical cause are suggestive of the causal effect. Several reports have described enuresis developing in association with antipsychotics [3,5,7,8]. In some reports, enuresis resolved spontaneously during the therapeutic process, while in other reports, enuresis improved with the addition of another antipsychotic (such as aripiprazole) [5]. Other reports described no recurrence of enuresis when one drug was stopped and the patient started on another antipsychotic [7]. In our case, risperidone was stopped because it caused enuresis, but enuresis recurred when the patient was started on aripiprazole. Two consecutive antipsychotics causing enuresis, and that enuresis improving following a slight aripiprazole dose reduction of 0.5 mg/day, and the effectiveness of treatment being maintained, suggested that the drug dosage should be reduced to the lowest level needed to maintain clinical effectiveness in order to resolve the enuresis, before adding another drug or stopping one drug and immediately switching to another.

While the pathophysiology of antipsychotic-induced enuresis remains unclear, a number of mechanisms have been described, including: (1) reduced dopamine transmission in the basal ganglia [9]; (2) decreased tone of the internal bladder sphincter due

to α 1-adrenergic blockade [10]; (3) blockade of pudendal reflexes via antagonism of 5-HT₂ or 3 [11]; and (4) urinary retention and subsequent overflow incontinence due to antimuscarinic properties of antipsychotics [12].

Risperidone acts as an antagonist on the 5HT_{2A} and D₂ receptors, also it has a strong blockade effect for α -1 and α -2 adrenergic receptors. Adrenergic blockade effect is suggested to urinary incontinence by decreasing the tonus of internal urethral sphincter [10]. One study showed an association between 5HTR_{2A} gene polymorphisms and polysymptomatic nocturnal enuresis [13]. The antagonist activity of aripiprazole at α 1 and 5HT_{2A} receptors on internal bladder sphincter and detrusor muscle, respectively, might have caused to enuresis in this case. In addition, possible reduced dopamine transmission due to partial agonist activity of aripiprazole at D₂ receptors might also cause enuresis in our case. The sedative effects of antipsychotics may lead to inability to wake up during sleep and might cause nocturnal enuresis. Because our case experienced enuresis only during the day time, and her parents reported no difficulty of the patients in waking up during risperidone or aripiprazole treatment, enuresis does not seem to be related to sedation. In contrast to one case report describing nocturnal enuresis developing in association with aripiprazole [14] and another adolescent case report of diurnal enuresis developing [8], the therapeutic effect of aripiprazole has been shown in clozapine-related enuresis [5]. Early identification of this side effect combined with early prevention may increase medication adherence. In this case, aripiprazole first caused dose-dependent enuresis in a preadolescent child, which then resolved with a mild reduction in dosage. From that perspective, this case report shows, in the light of the current literature, that two different antipsychotics are able to cause diurnal enuresis and that aripiprazole can be used in the aetiology and treatment of enuresis in a dose-dependent manner. Her Naranjo adverse drug reaction probability scale score was 8 for each drug [15].

However, the use of risperidone and aripiprazole has become widely common in treating behavioural problems (such as aggressiveness, self-injurious behaviours) associated with ASDs, thus, this case report indicate that the need to monitor the possibility of enuresis precipitated by antipsychotics is increasingly important.

Disclosure statement

No potential conflict of interest was reported by the authors.

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