OMCR

*Oxford Medical Case Reports*, 2016;4, 66–67

doi: 10.1093/omcr/omw017

Case Report



CASE REPORT

# Persistent hiccups due to aripiprazole in an adolescent with obsessive compulsive disorder responding to dose reduction and rechallenge

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## Abstract

Our case involves persistent hiccup arising in an adolescent with obsessive compulsive disorder (OCD) who was using aripiprazole as an augmentation to fluoxetine and whose hiccups remitted with dose reduction and rechallenge. Treatment suggested that aripiprazole might lead to hiccups. Antipsychotics are also used for the treatment of hiccups, but recent case reports suggest that they cause hiccups as well. Within 12 h of taking 5 mg aripiprazole, the 13-year-old girl began having continuous hiccups, which lasted for 3–4 h. The hiccups resolved when the dose of aripiprazole was reduced to 2.5 mg. To achieve augmentation, aripiprazole was replaced with risperidone 0.5 mg/day for 1 month, but excess sedation was observed. As a result, aripiprazole was restarted at a dose of 2.5 mg/day, and 1 week later, it was increased to 5 mg/every other day. No hiccups were observed.

## INTRODUCTION

'Hiccup' is a repetitive, involuntary, spasmodic and characteristic sound that appears with sudden closure of the glottis as a consequence of involuntary contraction of the diaphragm and respiratory muscles [1]. Although the pathophysiological processes that cause hiccups have not been fully determined, central nervous system disorders, gastrointestinal disorders such as gastric distension and reflux, head and neck diseases, metabolic disorders, electrolyte disorders and some drugs are posited as causes of hiccups [1].

Among drug-induced hiccups, aripiprazole, a dopaminergic stabilizing agent, is often cited, both for transient and persistent hiccups among adult and adolescent patients [2–6]. As far as we are aware, hiccups in these patients arose while switching treatments and did not involve dose titration and rechallenge. Here, we present persistent hiccups arising in adolescent with obsessive compulsive disorder (OCD) who was using aripiprazole as an augmentation to fluoxetine and whose hiccups remitted with dose reduction and rechallenge.

## CASE REPORT

The patient was a 13-year-old girl who was referred to the outpatient clinic with complaints of controlling, counting, a need

**Received:** December 30, 2015. **Revised:** March 1, 2016. **Accepted:** March 2, 2016

for symmetry and excessive washing. She was diagnosed with OCD 4 years ago by a child and adolescent psychiatrist and has received sertraline up to 200 mg/day along with intermittent exposure response prevention for 4 years, with no significant benefit. Mental status examination revealed obsessions of doubt, symmetry, ordering, contamination and religiosity, checking, ordering and mental compulsions along with depressive symptoms. Developmental milestones were normal with no evidence of tics. Family history revealed maternal OCD with a positive response to fluoxetine. Baseline psychometric evaluations revealed C-YBOCS and CGI-S scores of 35 and 6, respectively. Accordingly, the diagnosis of OCD was confirmed, and sertraline was cross-tapered with fluoxetine up to 60 mg/day on the 16th week of treatment. Evaluation at the 4th month revealed C-YBOCS and CGI-S scores of 31 and 5, respectively, which suggests minimal benefit. Aripiprazole 5 mg/day was added therefore, for augmentation. The patient and her family reported that persistent hiccups started 12 h after the initial dose and continued for a week. After this, the parents immediately reduced the dose to 2.5 mg/day, leading to the cessation of hiccups. To achieve augmentation, aripiprazole was replaced with risperidone 0.5 mg/day for 1 month, but excess sedation was observed. Consequently, aripiprazole was restarted at 2.5 mg/day. One week later, the dose was increased to 5 mg/every other day with no occurrence of hiccups. She was followed for 8 weeks without hiccups, and her C-YBOCS and CGI-S scores were found to be 15 and 3, respectively, denoting treatment response. Evaluation with the Naranjo algorithm revealed a score of 7 (probably adverse drug reaction) [7].

## DISCUSSION

Here, we report a female adolescent with OCD who developed persistent hiccups with aripiprazole augmentation of fluoxetine treatment, whose hiccups remitted with dose reduction and did not appear with a rechallenge. Although previous reports of persistent and transient hiccups with aripiprazole exist, our case is unique in that the adverse reaction responded to dose reduction and did not appear with rechallenge [2–6]. Although the exact roles of neurotransmitters within the reflex arc of hiccups are not known, antipsychotics are used in the management of hiccups [8]. Existing data suggest that both dopamine and serotonin may play a role in the generation of hiccups [2–6,8]. Previous reports posited that both hypo- and hyper-dopaminergic states may lead to hiccups [2–6,8]. However, there are several other alternative explanations in our case. First, elimination of aripiprazole involves two cytochrome P450 isoenzymes (CYP2D6 and CYP3A4) and fluoxetine, which is a potent inhibitor of CYP2D6, can block the metabolism of aripiprazole and increase its blood levels [9]. Second, partial agonistic at 5-HT1A and antagonistic effects at 5-HT2A receptors of aripiprazole within the spinal cord at the level of the phrenic nerve, perhaps potentiated by fluoxetine, may have caused the hiccups [10]. Lastly, as posited before, either hypo- or hyper-dopaminergic states may cause hiccups as shown before [2–6]. The temporal profiles of hiccups in our patient, their remission with dose reduction and their lack of re-occurrence with challenge, suggest, however, a mechanism of potentiation of its effects probably via CYP450. Regardless of exact etiology, it may be prudent for the clinicians to be aware of this rare adverse effect.

## CONFLICT OF INTEREST STATEMENT

None declared.

## FUNDING

There were no sources of funding.

## ETHICAL APPROVAL

No approval is required.

## CONSENT

The patient's parent signed consent was obtained.

## GUARANTOR

M.O.K. is the guarantor of this paper.

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