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Case Report

A rare adverse effect of aripiprazole: hiccups and dose-dependent tolerance

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ABSTRACT

Hiccups result from sudden, irregular contraction of the diaphragm and intercostal muscles, leading to immediate closure of the larynx. Aripiprazole, a third-generation antipsychotic, functions as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors while antagonizing serotonin 5-HT2A receptors. Hiccup is a rarely reported side effect of aripiprazole. Research indicates that neurotransmitters, especially dopamine, serotonin, and GABAergic transmission are likely central to hiccup development, though specific mechanisms remain unclear. Here we present a 52-year-old male patient with a long-standing psychosis, who developed hiccups after initiation of aripiprazole. A 52-year-old male patient with a long-standing psychotic disorder, characterized by delusions of misidentification, social withdrawal, and impaired self-care. Shortly after initiation of aripiprazole, the patient developed persistent hiccups that continued overnight, prompting hospitalization. Symptomatic treatment with chlorpromazine and metoclopramide resulted in the resolution of hiccups. Aripiprazole was discontinued, and brexpiprazole was initiated. Despite its pharmacological similarity to aripiprazole, brexpiprazole was well tolerated and did not induce hiccups. Interestingly, hiccups did not recur after we re-challenged with aripiprazole starting from ultra-low doses and titrated slowly. With this case report, we concluded that aripiprazole may induce hiccups, particularly during treatment initiation. This effect may be related to its dopaminergic agonism at D2 receptors at low doses, while brexpiprazole's lower agonistic activity at D2 receptors may explain the absence of hiccups. Our case suggests that when aripiprazole is initiated at ultra-low doses and titrated slowly, hiccups may not recur, and discontinuation or switching to an alternative antipsychotic may not be necessary.

Keywords: Aripiprazole, Hiccups, Adverse effects, Brexpiprazole, Rechallenge

INTRODUCTION

A hiccup is a recurring and involuntary sound produced by the sudden closure of the glottis, caused by an involuntary contraction of the diaphragm and respiratory muscles.[1,2]

Hiccups are usually self-limiting and resolve on their own without treatment.[3,4] They are frequently seen in healthy individuals and can be triggered by rapid gastric distension, gastroesophageal reflux, or gastritis.[4,5]

Although hiccups are generally considered a non-serious condition, persistent or intractable hiccups may be associated with serious medical conditions, such as CNS tumors, gastrointestinal disorders, ear, nose, and throat (ENT) problems, infections, or various drug treatments.[4,6] In severe cases, hiccups can cause malnutrition, dehydration, and weight loss.[3]

While the exact cause of hiccups is not fully understood, several neurotransmitters are thought to play an important role in their mechanism, particularly dopamine and serotonin.[6,7]

Aripiprazole is a third-generation antipsychotic with a unique pharmacodynamic profile. It acts as a partial

agonist at dopamine D2, D3, and serotonin 5-HT1A receptors, while serving as an antagonist at the serotonin 5-HT2A receptor.[4,6] Generally, aripiprazole is considered a safe medication due to its favorable metabolic side effect profile, but it has been reported to cause persistent hiccups in patients with bipolar disorder or schizophrenia.[6]

This case describes a 52-year-old male with a longstanding psychotic illness who developed persistent hiccups shortly after aripiprazole was restarted.

CASE REPORT

A 52-year-old male with a long history of psychotic illness presented with persistent hiccups shortly after starting aripiprazole. The patient was first admitted to psychiatric care at the age of 16 with symptoms including delusions that his family was not his own, social withdrawal, and decreased self-care. At that time, he was treated with antipsychotic medications including haloperidol, chlorpromazine, and fluphenazine decanoate.

Over the following years, the patient continued psychiatric follow-up and was treated with several antipsychotic medications. For a long period, he had been maintained on clozapine.

Approximately five years prior to the current presentation, the patient had briefly used aripiprazole. However, the treatment was discontinued within a few months, and its clinical effects were not fully evaluated.

Due to ongoing treatment considerations, aripiprazole therapy was restarted on 03 December 2024. Shortly after initiating the medication, the patient developed persistent hiccups that began soon after drug intake and continued throughout the night. Because of the severity and persistence of the symptoms, the patient was hospitalized.

During hospitalization, the patient was treated with chlorpromazine and metoclopramide injections for symptomatic relief. Following this treatment, the hiccups resolved and the patient was discharged.

Given the suspected association between aripiprazole and the onset of hiccups, aripiprazole was discontinued. Instead, brexpiprazole 2 mg/day was initiated. Although brexpiprazole has a pharmacological mechanism similar to aripiprazole, the patient did not experience recurrence of hiccups during brexpiprazole treatment. However, given that aripiprazole was considered more beneficial for his overall symptoms and clinical presentation, we decided to reintroduce it.

Several weeks later, aripiprazole was cautiously reintroduced using an oral solution formulation (1 mg/ml). Treatment was initiated at a dose of 0.5 ml and gradually increased at five-day intervals. The dose was titrated up to 2.5 ml. Notably, during this gradual titration process, the patient did not develop hiccups.

DISCUSSION

Several mechanisms may explain aripiprazole-induced hiccups in this case. Aripiprazole acts as a partial agonist at dopamine D2 and D3 receptors and at serotonin 5-HT1A receptors, while antagonizing 5-HT2A receptors.[4] Its partial stimulation of D2 receptors can alter dopaminergic activity, potentially triggering hiccups.[7] At lower doses (up to 7.5 mg/day), it likely acts as a dopamine agonist by activating D2 and D3 receptors in the brainstem's "hiccup center".[4,6] Through its partial agonism at the 5-HT1A receptor, aripiprazole may also enhance serotonergic activity affecting the phrenic nerves, and by antagonizing 5-HT2A receptors, it may further contribute to hiccup development.[6,7] Additionally, aripiprazole has been reported to increase the expression of the GABAA (β-1) receptor.[6]

An important consideration in this case is the patient's prior treatment history. The patient had been maintained on clozapine — a potent D2 antagonist — for a prolonged period before aripiprazole was reintroduced. Prolonged treatment with a strong D2 antagonist may cause upregulation of postsynaptic D2 receptors. Therefore, the hiccups that appeared after starting aripiprazole could be due to its stimulating effect on these upregulated receptors, rendering the patient particularly susceptible to dopaminergic stimulation at the brainstem level.[7] This is consistent with reports of hiccups occurring in patients who were switched from potent D2 antagonists such as olanzapine or risperidone to aripiprazole.[7]

Some studies have reported cases where patients developed hiccups when aripiprazole was combined with other medications such as benzodiazepines or methylphenidate. In these cases, hiccups resolved after one of the drugs was discontinued, suggesting that co-administration may elevate the risk of hiccups.[6]

Based on reported cases, aripiprazole induced hiccups occur most frequently in adolescent and middle-aged males. In terms of psychiatric diagnosis, a hiccup can be seen across a range of psychiatric conditions. The most common reported conditions are: bipolar disorder, schizophrenia, depression, substance abuse, and obsessive-compulsive disorder.[7] While aripiprazole induced hiccups are seen most commonly in male patients, psychogenic hiccups are more frequently observed in female patients.[7] The patient's age and sex are consistent with this epidemiological pattern, as persistent and intractable hiccups tend to occur more often in men, especially those aged 50 and above.[4,7]

For the management of aripiprazole-induced hiccups, the most common approach is stopping the medication, which has been successful in most cases.[7]

Other interventions include switching to a different antipsychotic, such as haloperidol, risperidone, or olanzapine. Initiating adjunctive agents like gabapentin,

pregabalin, or metoclopramide may also help manage aripiprazole-induced hiccups.[3,7] Among these medications, Chlorpromazine is the only medication approved by the FDA specifically for the treatment of hiccups.[2] In this case, the patient was treated with chlorpromazine and metoclopramide injections during hospitalization, which led to resolution of symptoms.

Although brexpiprazole shares a similar pharmacological mechanism to aripiprazole, acting as a partial agonist at D2, D3, and 5-HT1A receptors and as an antagonist at 5-HT2A receptors, the patient did not experience hiccups during brexpiprazole treatment.[2] This may suggest that subtle differences in receptor binding affinities between the two agents could influence the likelihood of hiccup induction, though further research is needed to clarify this.

A distinctive aspect of our case report is the successful reintroduction of aripiprazole using an oral solution formulation, achieved through gradual titration. Starting at a very low dose (0.5 ml of 1 mg/ml) and titrating gradually at five-day intervals up to 2.5 ml, hiccups were avoided entirely. This supports the hypothesis that low-dose aripiprazole functions as a dopamine agonist at the brainstem hiccup center, and that gradual titration may allow receptor adaptation, thereby preventing hiccup induction.[4] This approach may be a useful option for patients who require aripiprazole but have previously experienced this side effect. To further assess the causal relationship between aripiprazole and the hiccups, we applied the Naranjo adverse drug reaction probability scale.[9] The scale yielded a total score of 6, indicating a probable adverse drug reaction. The detailed scoring is presented in Table 1.

Table 1: Naranjo adverse drug reaction probability scale.

Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was readministered?	+2	-1	0	-1
Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score (probable: 5–8)				6

CONCLUSION

In conclusion, aripiprazole-induced hiccups may be rare, but this case is a good reminder that it can happen, especially when starting aripiprazole for the first time or switching from a potent D2 receptor antagonist like clozapine. In this patient, prolonged clozapine use may have upregulated D2 receptors, making him more vulnerable to hiccups once aripiprazole was introduced. What makes this case particularly valuable is that it shows discontinuation of aripiprazole is not the only option. By reintroducing the medication slowly, starting from a very low dose and titrating gradually, the patient tolerated aripiprazole without any recurrence of hiccups, suggesting a dose-dependent tolerance. When faced with this side effect, clinicians may want to consider symptomatic treatment alongside a careful, slow titration rather than immediately stopping the medication.

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