

# Aripiprazole induced hiccups

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## ABSTRACT

Hiccups are a product of involuntary, intermittent spasmodic contraction of the diaphragm and inspiratory intercostal muscles that results in sudden inspiration and abrupt closure of the glottis. The exact pathophysiology of hiccups remains unknown. However, certain neurotransmitters, medications, and other factors have been implicated.

We report a case of a 38 year old patient who developed hiccups three days after adding aripiprazole 5 mg once a day to his medication regimen. Medical and environmental causes were ruled out and aripiprazole was discontinued. One day later, the hiccups resolved.

Several case reports have described patients who developed hiccups when treated with aripiprazole and related this to changes in neurotransmitter concentrations. However, due to limited literature, it was difficult to determine rate of occurrence of this adverse event with aripiprazole.

A temporal but not a causal relationship was observed between initiating aripiprazole and development of hiccups in this patient. A causal relationship cannot be established since the patient was not re-challenged with aripiprazole. Nonetheless, clinicians should be cognizant that use of aripiprazole may be associated with hiccups.

## KEYWORDS

aripiprazole, hiccups, adverse effect

## BACKGROUND

Hiccups are a benign and transient phenomenon that can affect anyone. They are a product of involuntary contraction of the diaphragm and the intercostal muscles resulting in closure of the glottis and preventing entry of air into the trachea.<sup>1</sup> The exact mechanism by which hiccups are provoked remains unknown. However, it has been postulated that an interaction among the brain stem, respiratory centers, phrenic nerve nuclei, reticular formation in the brain stem, and hypothalamus occurs resulting in the development of hiccups.

Dopamine, serotonin, and gamma amino butyric acid (GABA) have been implicated in the generation of hiccups.<sup>2</sup> There were reports relating the cause of hiccups to dopaminergic agents and their successful treatment with antidopaminergic agents.<sup>3,4</sup> There were also reports attributing hiccups to exposure to antidopaminergic agents.<sup>5</sup> The use of sertraline and olanzapine to treat hiccups appears to associate serotonin in the development of hiccups. Clozapine has been reported to cause and treat hiccups which may further implicate serotonin.<sup>1,6,7</sup> The evidence supporting the role of GABA in hiccups was demonstrated by the use of GABA agonists

such as baclofen and pregabalin in its management.<sup>8,9</sup> Other causes of hiccups can be idiopathic, psychogenic and organic. Medications such as barbiturates, benzodiazepines, corticosteroids, methyldopa, methohexital, and dexamethasone have been identified as common pharmacologic causes for hiccups.<sup>10</sup> We report a case of a 38 year old male who developed hiccups three days after the addition of aripiprazole to his medication regimen.

## PATIENT CASE

The patient was a 38 year old Hispanic male with a history significant for major depressive disorder, sleep apnea, hypertension, cardiac arrhythmia, gastroesophageal reflux disease (GERD), knee pain, and hyperlipidemia. The patient was hospitalized secondary to suicidal ideations and auditory and visual hallucinations. On admission, his laboratory measures were within normal limits and his outpatient oral medications were continued. His medication regimen included esomeprazole 20 mg daily, clonazepam 1 mg twice daily and 2 mg at bedtime, citalopram 40 mg daily, metoprolol 25 mg daily, aspirin 81 mg daily by mouth, trazodone 50 mg at bedtime, KCl 20 mEq daily, telmisartan/hydrochlorothiazide 40/12.5 mg

daily, and ibuprofen 800 mg three times daily as needed. On hospital day two, he was initiated on aripiprazole 5 mg daily for hallucinations and citalopram was increased from 40 mg daily to 60 mg daily (This was prior to the FDA's warning and updated maximum doses for citalopram). Three days later, hiccups developed and were not relieved by any conventional treatments such as breathing into a bag, drinking water, or holding his breath. After ruling out medical and environmental causes for the hiccups, the treating physician discontinued aripiprazole. One day later, the hiccups resolved but the patient continued to experience hallucinations. Consequently, risperidone 0.5 mg twice daily was initiated and titrated to 1 mg twice daily without resurgence of hiccups. Throughout his hospitalization, additional medication changes occurred, but there was no recurrence of hiccups. Four weeks later, he was discharged from the hospital in stable condition with improvement in depression, hallucinations, and sleep symptoms. Since his hospital discharge, the patient remained on the same medication regimen without return of the hiccups.

## REVIEW OF THE LITERATURE

Aripiprazole stabilizes dopamine and serotonin concentrations through actions on the D<sub>2</sub>, 5HT<sub>1A</sub>, and 5HT<sub>2</sub> receptors.<sup>11</sup> Unlike other antipsychotics, aripiprazole has a favorable metabolic profile with minimal risk for development of extrapyramidal side effects. Review of the literature revealed several case reports relating the development of hiccups with aripiprazole. Two case reports had similar findings in which hiccups may have been associated to hyponatremia induced by aripiprazole.<sup>12-13</sup> This was not the case in our patient. During admission and a week after hospitalization, our patient's serum sodium levels remained within normal limits, therefore eliminating the possibility of hyponatremia induced hiccups.

As reported by Ray et al., the likely cause of hiccups in our patient was aripiprazole's neurotransmitter modulation.<sup>2</sup> As a partial agonist at the D<sub>2</sub> and D<sub>3</sub> dopamine receptors, aripiprazole can result in both hypo and hyperdopaminergic states, both of which have been implicated in hiccups. It was possible that a dystonic reaction of the diaphragm due to D<sub>2</sub> blockade resulted in hiccups in this patient. Alternatively, aripiprazole's partial agonistic activity at the 5-HT<sub>1A</sub> receptor may have facilitated phrenic neuronal activity at the spinal cord level and therefore resulted in hiccups.<sup>3</sup> On the contrary, risperidone is an antagonist at both dopaminergic (D<sub>2</sub>) and serotonergic (5-HT<sub>2A</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>1C</sub>, 5-HT<sub>1D</sub>)

receptors which could explain why this patient tolerated risperidone better than aripiprazole.<sup>14</sup> There was a report relating risperidone to cause hiccups in a 16 year old male with Down Syndrome one day after initiation of therapy.<sup>15</sup> It was plausible that demographic and genetic differences explain why the patient reported here did not develop hiccups on risperidone while that of Cheng did; however, more data are needed to confirm this. Similar to our patient, Yeh reported on a 19 year old patient with schizophrenia who developed hiccups 36 hours after being switched from risperidone to aripiprazole with hiccups resolving after discontinuation of aripiprazole and reinitiation of risperidone.<sup>16</sup> The difference in mechanism of action between the two agents may explain why our patient developed hiccups with aripiprazole but not with risperidone. According to the Naranjo scale, the probability score for the adverse reaction our patient experienced was 7 (probable);<sup>17</sup> nonetheless, the exact mechanism of development of hiccups remained unknown.

## CONCLUSION

Given the lack of evidence for medical causes of hiccups in our patient, a temporal but not a causal relationship between the initiation of aripiprazole and the development of hiccups can be established. A causal relationship cannot be established with certainty in our patient because he was not re-challenged; instead he was switched to another atypical antipsychotic. Nonetheless, clinicians should be cognizant that use of aripiprazole may be associated with hiccups. Additionally, due to the limited availability of literature describing occurrence of hiccups with aripiprazole, it was difficult to establish the rate of occurrence of this adverse event. Further studies and case reports will be needed in order to determine the rate and severity of aripiprazole induced hiccups as well as the exact mechanism for antipsychotic induced hiccups.

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