

## Aripiprazole-Induced Persistent Hiccups



Nalan Varsak<sup>1</sup>, Osman Kilic<sup>1</sup>, Yasin Kursad Varsak<sup>2</sup>, Ibrahim Eren<sup>3</sup>

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Dear Editor,

'Persistent hiccups' refers to hiccups that continue for more than 48 hours. A number of medical conditions, including idiopathic, psychogenic, and organic causes as well as medications, are known to cause persistent and intractable hiccups. Among the medications reported to induce hiccups, corticosteroids and benzodiazepines are the drug classes most frequently associated with the development of hiccups<sup>1</sup>. Antipsychotic-induced hiccups have rarely been reported in the literature, and to the best of our knowledge, only 8 cases of aripiprazole-induced hiccups have been reported in the literature<sup>2</sup>. Here, an additional case of aripiprazole-induced persistent hiccups is reported with a review of previously reported cases.

A 35-year-old married male patient was brought by his wife to an outpatient clinic in February 2014 for experiencing auditory hallucinations, delusions of being cheated by his wife, and crying without a reason. Mental status examination revealed a normal rate and amount of speech, depressive mood, anxious affect, poor concentration, auditory hallucinations, reference and persecutory delusions, and decreased sleep and appetites. All the routine investigations including hemogram and liver, kidney, and thyroid function tests were within normal limits. The patient was diagnosed with major depressive disorder (MDD) with psychotic features according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth

Edition, and venlafaxine 75 mg/day and aripiprazole 10 mg/day were initiated at the same time. Within 24 hours of taking his medications, the patient started having hiccups continuously. A detailed history and physical examination of the patient did not reveal any signs or symptoms of underlying physical illness. The patient consulted an internist, who after preliminary examination advised to add pantoprazole 40 mg two times daily empirically. Hiccups did not resolve despite a 3-day course of pantoprazole treatment. In order to eliminate underlying possible drug induced adverse effect, we made a decision, based on a literature review, to stop aripiprazole instead of venlafaxine, as there have been eight cases of aripiprazole-induced hiccups reported in the literature, whereas no relationship was reported with venlafaxine. Aripiprazole was discontinued on day 5; hiccups disappeared approximately 36 hours after the last dose of aripiprazole. Aripiprazole rechallenge was planned but the patient did not give consent for rechallenge; therefore, the drug was replaced with olanzapine. The patient was maintaining well on a follow-up one month later.

Hiccups are often associated with gastric distension, sudden changes in temperature and emotion, ingestion of alcohol; they usually resolve spontaneously or with simple measures such as breath holding and rarely necessitate medication. Hiccups continuing longer than 24 hours are rare and may indicate serious underlying diseases<sup>1</sup>. Organic causes should be excluded with adequate evaluation based on history, physical examination, and selected

laboratory tests. Drug-induced hiccups should also be kept in mind while taking history. In this particular case, hiccups started in a patient who was under treatment for MDD with psychotic features and did not resolve spontaneously or with simple measures.

In our patient, aripiprazole represents the key factor in the induction of hiccup. Based on literature review, we made a decision to stop aripiprazole instead of venlafaxine. There have been eight cases of aripiprazole-induced hiccups reported in the literature; three out of eight patients with aripiprazole-induced hiccups reported in the literature were in patients more than sixty-five years old. All reported cases were male except one. In one case, aripiprazole dosage was 5 mg/day; and in another case the dose was 12 mg/day; other cases were 10 mg/day. We also used a 10 mg/day dose of aripiprazole. It may be suggested that hiccup is not related to dosage. Indeed, the fact that rechallenges resulted in re-appearance of hiccup would be considered as a strong indication of causal relationship. When we review the literature, rechallenge produced hiccups in 4 out of 8 cases. Another reported side effect of aripiprazole is a syndrome of inappropriate antidiuretic hormone (SIADH) and associated hyponatremia. Behere et al.<sup>3</sup> have described hiccup and hyponatremia concomitantly induced by aripiprazole; therefore, they suggested that hiccups developed as a result of hyponatremia. There was no hyponatremia

reported in the remaining 4 cases in the literature; the serum electrolyte status was unknown in one case. In our patient, hyponatremia or any other electrolyte imbalance was not developed during aripiprazole treatment.

As both hypo- and hyperdopaminergic states have been associated with the development of hiccups, Ray et al.<sup>4</sup> proposed that the partial agonism of dopamine by aripiprazole could be an underlying mechanism in the development of hiccups. Some studies suggested a relationship between hiccups and dopaminergic agents, showing successful treatment of hiccups with antidopaminergic agents. Olanzapine was found to be successful in a patient who developed intractable hiccups secondary to a traumatic brain injury<sup>5</sup>. The exact mechanism of olanzapine's effectiveness in patients with hiccups is not fully understood. Since olanzapine is a dopamine D<sub>2</sub>-receptor antagonist, this could also have played a role in its effectiveness. In this case, we suggest that the hiccup is possibly related to modulation of neurotransmitter mechanisms due to aripiprazole.

In conclusion, hiccups could be a dose-independent adverse effect of aripiprazole. Despite it being a rarely encountered entity, clinicians should be aware of this adverse effect when administering aripiprazole, particularly in male patients.

**Keywords:** *aripiprazole, hiccups, dopamine*

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<sup>1</sup>M.D., <sup>3</sup>Assoc. Prof., Konya Training and Research Hospital, Department of Psychiatry, Konya - Turkey

<sup>2</sup>M.D., Konya Numune Hospital, Department of Otorhinolaryngology, Konya - Turkey

*Correspondence Address: Dr. Nalan Varsak*

*Konya Eğitim ve Araştırma Hastanesi, Beyhekim Psikiyatri Kliniği,*

*Yazır Mahallesi Turgut Özal Caddesi No:14/C, 42250 Selçuklu, Konya - Türkiye*

*Email address: nalanvarsak@gmail.com*

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**N.V., O.K., Y.K.V., I.E.:** *The author reported no conflict of interest related to this letter.*