Psychiatria Danubina, 2019; Vol. 31, No. 1, pp 26-31 https://doi.org/10.24869/psyd.2019.26 *Brief review*

ARIPIPRAZOLE-INDUCED PERSISTENT HICCUP: A CASE REPORT AND REVIEW OF THE LITERATURE

Gianluca Serafini[1,2], Giulia Piccinini[1,2], Samantha Visimberga[1,2], Alice Cervetti[1,2], Martino Belvederi Murri[1,2], Fiammetta Monacelli[2,3], Maurizio Pompili[4] & Mario Amore[1,2]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, Genoa, Italy
[2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[3]Department of Internal Medicine and Medical Specialties (DIMI), Section of Geriatrics, University of Genoa, Genoa, Italy
[4]Department of Neurosciences, Mental Health and Sensory Function, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

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SUMMARY

Aripiprazole is an interesting psychoactive compound acting as a dopamine D2 partial agonist, serotonin 5-HT(1A) partial agonist and serotonin 5-HT(2A) antagonist. Aripiprazole possesses a well-documented efficacy in the treatment of both positive and negative psychotic symptoms. However, this medication may be rarely associated with the onset of hiccup. Here, we present the case of aripiprazole-induced hiccup in a young inpatient at his first psychiatric admission together with a review of the current literature about this topic. The possible etiology underlying the emergence of hiccups together with the clinical implications of this adverse event are discussed.

Key words: *words: aripiprazole – hiccup – tolerability - adverse effects*

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INTRODUCTION

Aripiprazole is a psychoactive compound acting as a dopamine D2 partial agonist, serotonin 5-HT(1A) partial agonist and serotonin 5-HT(2A) antagonist. Aripiprazole possesses a well-documented efficacy in the treatment of both positive and negative psychotic symptoms. Generally, it has been associated with modest neurological side effects and no significant adverse effects on serum prolactin levels, weight gain and metabolic alterations (Keck & McElroy 2003), although the possible occurrence of neuroleptic malignant syndrome (Belvederi Murri et al. 2015). However, the onset of hiccups has been rarely reported with the use of therapeutic drugs such as aripiprazole. Hiccup may be considered the product of the simultaneous involuntary spasmodic contraction of the diaphragm and glottic closure determining the suppression of the air entry into the trachea (Alderfer & Arciniegas 2006). Although the exact etiology underlying the emergence of hiccup is poorly understood, the role of dopamine, serotonin and gamma amino butyric acid (GABA) has been well documented.

Here, we present the case of aripiprazole-induced hiccup in a young inpatient at his first psychiatric admission along with a review of the current literature about this specific topic.

CASE PRESENTATION

A 22-year-old male, originated from Albania, has been admitted to our psychiatric inpatient unit (IRCCS San Martino Hospital, Genoa) due to a brief manic episode with psychotic symptoms. The patient had no significant psychiatric episodes in the past. The first mood alterations occurred during the month before his admission, when he presented a brief manic episode, recovered spontaneously with no psychiatric treatment. When he was hospitalized, a bipolar I disorder, manic episode with psychotic features (according to DSM 5 diagnostic criteria) has been diagnosed. The patient signed a regular informed consent.

Specifically, he presented to the Emergency Unit of our hospital with the following psychotic (e.g., persecutory delusions, auditory hallucinations) and mood symptoms (e.g., reduced need for sleep, dysphoria and dissatisfaction, thought and speech acceleration, and psychomotor agitation). These symptoms occurred 3 days earlier, after a car accident during which he did not report any traumatic event. He underwent a brain computed tomography (CT) evaluation that showed no significant alterations before the admission to our psychiatric unit. Toxicological tests resulted negative and the patient did not present a positive history of abuse/dependence behavior as well. The patient's medical history was mute and no concurrent therapy had been prescribed.

The patient was tested at admission (T0) and before discharge (T1) with the following psychometric instruments: Clinical Global Impression (CGI) (Guy 1976) (T0 and T1 disease severity scale score=6 and 3, respectively; T0 and T1 global improving scale score=not evaluated and 1; T0 and T1 index of effectiveness scale=not assessed and 02, respectively) and Young

Mania Rating Scale (YMRS) (Young et al., 1978) (T0 total score=36; T1 total score =2).

The patient has been treated with the following psychoactive treatments. At day 1, aripiprazole 14.6 mg and delorazepam 3 mg daily were administered by intramuscular formulation. After approximately 12 hours by the first aripiprazole injection, the patient started complaining about the onset of hiccup that was persistent even during the night. At day 2, psychoactive drugs were orally converted in 30 mg of aripiprazole and 1.5 mg of delorazepam daily, respectively. Lansoprazole 15 mg daily has been administered after 36 hours of continuous hiccup, with no relief. Thus, hypothesizing that the hiccup may be induced by aripiprazole, we suspended it after 48 hours, and asenapine was introduced at the initial daily dose of 20 mg. Interestingly, the hiccup spontaneously stopped 12 hours after the last aripiprazole ingestion. Using the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al. 1981), we found a probable relation between the titration of aripiprazole and the occurrence of persistent hiccup in our patient (Score 8). The psychotic and mood symptoms recovered completely at day 6 when the patient was discharged with asenapine 20 mg daily, delorazepam 0.5 mg, and lansoprazole 15 mg daily. The patient was then evaluated after 4 weeks from his discharge and the presence of hiccup has never been observed.

DISCUSSION

Hiccup is a spontaneous, myoclonic contraction of the diaphragm and intercostal muscles with closure of the glottis (Steger et al. 2015, Chang et al. 2012). Kolodzik and Eilers (1991) reported that, based on their duration, hiccups may be classified in: acute attacks (less than 48 hours), persistent hiccups (more than 48 hours), and intractable hiccups (more than 1 month according to Steger and colleagues (2015) or more than 2 months based on Chang et al. (2012)). They are generated by a "reflex arc" (Chang & Lu 2012) which includes vagus and sympathetic nerves conveying somatic and visceral sensory signals, a central processing unit in the midbrain and motor fibers transmitting efferent stimulus by phrenic nerves to diaphragm and accessory nerves to the intercostal muscles, respectively (Chang & Lu 2012). Dopamine, serotonin and gabaergic transmission (Ray et al. 2009) are presumably involved in the occurrence of hiccups, although the exact mechanisms underlying this adverse effect remain unclear. Any physical and chemicals irritants, inflammatory and neoplastic conditions evoking the hiccup reflex, are associated with the emergence of hiccup. Hiccup often occurs during gastroenteric and specific neurological diseases but it can be even related to multiple factors as well as specific medications (Steger et al. 2015). Both first- and second-generation antipsychotics are often used to treat hiccup although this symptom may be also associated with the occurrence of similar adverse effects (Shapiro et al. 2003). Specifically, olanzapine, haloperidol, and chlorpromazine demonstrated efficacy in treating hiccup, while aripiprazole, clozapine, perphenazine, and risperidone have been reported to be involved in its occurrence (Silverman et al. 2014).

To our knowledge there are, overall, 8 case reports and 1 retrospective study describing the link between aripiprazole administration and the onset of hiccup, and a total of 21 cases of aripiprazole–induced hiccup, with any apparent relation to the way of administration or the dosage, neither to patients' diagnosis.

CRITICAL REVIEW OF THE LITERATURE: MAIN IMPLICATIONS AND FUTURE PERSPECTIVES

First, Behere et al. (2007) described the case of a man presenting hiccup two days after the administration of aripiprazole 10 mg daily in add on to sodium valproate, oral antidiabetic drugs, and thyroxine supplement. Here, the emergence of this symptom seemed to be related to aripiprazole-induced hyponatremia. Indeed, after aripiprazole discontinuation and switching to quetiapine, sodium levels have been stabilized during the course of one week and hiccup spontaneously stopped. Another similar case about this topic (Ginsberg 2007) has been carefully summarized by Silverman et al. (2015).

Other evidence suggested that hiccup may be related to the occurrence of hyponatremia (for more details, see George et al. (1996)) although premarketing studies together with two other case reports (Behere et al. 2007, Ginsberg 2007) have shown the infrequent occurrence of hyponatremia associated with aripiprazole use (Aripiprazole Mosby's Drug Consult 2006; Bachu and colleagues (2006)). Conversely, in our case sodium levels were not altered before and after aripiprazole administration and other laboratory tests (complete blood count, electrolytes, renal, hepatic, pancreatic, thyroid, metabolic functions, and urinalysis) also resulted in a normal range.

Moreover, Ray et al. (2009) reported a case of a young male with a history of head injury who experienced the occurrence of hiccup some hours after the oral administration of aripiprazole 10 mg in addition to carbamazepine.

There are reports about the positive past history of head injury in patients who presented aripiprazole-induced hiccup (Ray et al. 2009, Silverman et al. 2014, Kattura & Shet 2013, Yeh 2011). For example, Silverman et al. (2014) reported the case of a 21 year-old man, with a history of head trauma, who presented hiccup after the administration of aripiprazole 10 mg daily. The patient swallowed aripiprazole in add on to valproate 1500 mg and lorazepam 2 mg daily. Hiccup suddenly occurred at the dosage of 15 mg daily, exactly at day 6.

Thus, aripiprazole was increased to 25 mg daily and metoclopramide was initiated. Hiccup did not remit with metoclopramide neither with chlorpromazine treatment. Indeed, it stopped 24 hours after aripiprazole discontinuation and switching to risperidone. Although it is not possible to suppose a specific link between aripiprazole-induced hiccup and the positive history of head injury, the frequent occurrence of this association is clinically interesting. However, our patient presented a car accident the day before his hospitalization, but he and his parents denied any traumatic events or signs of neurological impairment that were even excluded by the brain CT.

There are three case reports showing the occurrence of hiccup after switching from other antipsychotics to aripiprazole (Yeh 2011, Duvarci & Yilmaz 2013, Hori & Nakamura 2014). Yeh and colleagues (2011) reported the occurrence of persistent hiccup in a 19 year-old patient presenting a mild mental retardation due to premature birth and congenital cytomegalovirus infection. The hiccup with a duration of approximately 72 hours, presented after switching from risperidone 4 mg/day to aripiprazole 10 mg/day, and did not improve with a single dose of metoclopramide 5 mg. Duvarci and Yilmaz (2013) also reported the occurrence of hiccup after switching from zuclopenthixol 5 mg/day to aripiprazole 10 mg/day whereas Hori and Nakamura (2014) reported the case of a female presenting hiccup after switching from olanzapine 5 mg/day to aripiprazole 12 mg/day. Importantly, in all these cases hiccup stopped just after aripiprazole discontinuation and switching to risperidone (Yeh 2011, Duvarci & Yilmaz 2013) or paliperidone (Hori & Nakamura 2014). When a high potency D2 antagonist has been prescribed, a D2 postsynaptic receptors upregulation is supposed, thus the hiccup associated with the subsequent use of aripiprazole could be explained evoking the agonistic effect of this compound on upregulated D2 receptors (Yeh 2011, Duvarci & Yilmaz 2013). The 5HT(1A) agonistic and 5HT(2A) receptors antagonistic effects of this drug may further enhance hiccup stimulating the activity of the phrenic nerve (Yeh 2011, Duvarci & Yilmaz 2013).

In our report, the patient was drug naïve, and hiccup stopped after switching to asenapine, which possesses an antagonistic action on 5HT(1A) receptors as well as high affinity for D2 receptors (Correll 2010), and this seems to be related with the hiccup improvement. Recently, De Filippis et al. (2015) presented four case reports of hiccup during aripiprazole and benzodiazepine combined treatment. In these cases, hiccup stopped after benzodiazepine discontinuation or add on with pregabalin. Indeed, hiccup arc reflex can be activated by GABA(a) receptors (benzodiazepine facilitating GABA(a) activation) in combination with voltage-gated calcium ions, whereas it can be inhibited by GABA(b) receptors and calcium ion channel blockers such as pregabalin or gabapentin (alpha-2-delta ligands).

These findings seem to be confirmed by a retrospective study on 354 inpatients which were recruited during the course of 2013 at the Psychiatric Unit of Sant'Andrea Hospital, in Rome (Caloro et al. 2016). Here, 8 cases of hiccup were identified, with each case related to benzodiazepine treatment, 7 cases related to aripiprazole-benzodiazepine combination, and one case related to only benzodiazepine treatment. In three cases, hiccup resolution has been achieved through aripiprazole discontinuation and switching to other antipsychotics while in the remaining cases due to benzodiazepine discontinuation (in two of these cases through pregabalin addition and benzodiazepines discontinuation). Caloro et al. (2016) found an increased risk for developing hiccup in patients exposed to aripiprazole-benzodiazepine (in particular delorazepam) compared with those who were not exposed to this combination (OR= 68.69, 95% CI, 0.82 to 27.6). The risk was exclusive to the male sex, as no females presented a drug-related hiccup (OR=6.56, 95% CI from 1.61 to 26.73) and females were more exposed to the combination when compared to males indicating that the increased risk in male population was not related to a major exposure to the combination. Sex-related factors are likely to be involved in the pathophysiology of hiccup (Caloro et al. 2016) as protracted hiccup appears predominant in males. To our knowledge, the only case of aripiprazole-related hiccup in a female patient was that presented by Hori and Nakamura (2014). The authors hypothesized a neurochemical interaction between dopaminergic and gabaergic transmissions, with a possible intermediation of the endocannabinoid system for this case. This may explain the increasing risk of hiccup in the patient treated with benzodiazepine–aripiprazole combination (Caloro et al. 2016).

The association with benzodiazepines has been observed even in our case, and was reported in other three reports as well (Silverman et al. 2014, Kattura & Shet 2013, De Filippis et al. 2015). For instance, Kattura and Shet (2013) reported the case of a 38-year old male who presented hiccup 3 days after the administration of aripiprazole 5 mg in add on to additional medications including clonazepam 2 mg daily.

The hiccup occurrence after a first drug administration varied from few hours (Ray et al. 2009, De Filippis et al. 2015, Sakalli Kani et al. 2015) to 48 hours (Silverman et al. 2014, Behere et al. 2007, Duvarci & Yilmaz 2013) but in the majority of cases it stopped only after aripiprazole interruption (Ray et al. 2009, Silverman et al. 2014, Behere et al. 2007, Yeh 2011, Duvarci & Yilmaz 2013, Hori & Nakamura 2014). Moreover, no specific treatment seems to be effective in improving hiccup except for pregabalin, presumably due to its potential to block α2δ calcium channel (De Filippis et al. 2015, Caloro et al. 2016). According to the current literature, other failing treatment attempts have been reported with metoclopramide (Silverman et al. 2014, Yeh 2011) and chlorpromazine (Silverman et al. 2014). In line with these observations, hiccup did not improve with lansoprazole in our patient although we did not introduce other psychoactive compounds such as metoclopramide

Table 1. Most relevant studies about the association between aripiprazole use and hiccup

Author(s) year	Daily dosage of aripiprazole at hiccup onset	Type of study	Socio-demographic information and psychiatric diagnosis	Psychometric instruments used to evaluate hiccup	Main findings and implications
Behere et al. 2007	10 mg oral	Case report	1 M 69-year old; BD I	None	Discontinuation, 1 week for sodium level and consequent hiccup disappearance; second aripiprazole attempt failed; switch to quetiapine.
Ray et al. 2009	10 mg oral	Case report	1 M 28-year old; history for head injury; BD I	None	Disappearance in 30 h after discontinuation; second aripiprazole attempt failed; switch to quetiapine.
Silverman et al. 2014		Letter to the Editor	1 M 21-year old; history for head injury	None	Disappearance 72 h after discontinuation, not with metoclopramide and chlorpromazine treatment.
Yeh 2011	10 mg oral	Case report	1 M 19-year old; mental retardation, schizophrenia, cerebral palsy	Naranjo score 7; probable drug reaction	Disappearance 36 h after discontinuation, not with metoclopramide 5 mg/d, switch to risperidone.
Duvarci & Yilmaz 2013	10 mg oral	Case report	1 M 66-year old; schizophrenia diabetes mellitus coronary artery by-pass in 2005	None	Disappearance after discontinuation, re-administration of risperidone.
Hori & Nakamura 2014	12 mg oral	Case report	1 F 29-year old; schizophrenia	None	Disappearance 56 h after discontinuation, second attempt failed; switch to paliperidone 6 mg daily.
De Filippis et al. 2015	Oral 20 mg; IM 19.5 mg; IM 29.25 mg	4 case reports	1 M 24-year old; hypomanic episode; 1 M 16-year old; substance-medical induced psychotic disorder; 1 M 23-year old; borderline personality disorder, Substance use disorder (severe) 1 M 41-year old	None None None	Disappearance after 2 days of pregabalin 150 mg daily introduction; Disappearance after delorazepam (3.5 mg/d oral) discontinuation; Disappearance the day after delorazepam (2.5 mg/d oral) discontinuation; Disappearance the day after diazepam (10 mg/d oral) discontinuation and introduction of pregabalin 75 mg/d.
Caloro et al. 2016	IM 30 mg; IM 20 mg; Oral 20 mg; Oral 30 mg; Oral 20 mg; Oral 15 mg; Oral 10 mg	Retrospective study	M 20-year old DB I; M 30-year old DB II; M 30-year old; schizophrenia; M 29-year old; schizophrenia; M 54-year old; BD I; M 43-year old; BD II; M 23-year old; DB I	None	Disappearance after discontinuation, 1 patient switch to olanzapine, 2 patients to quetiapine, 3 subjects to delorazepam 5 mg/d IV and 1 individual to pregabalin.
Sakalli Kani et al. 2015	Oral 5 mg	Case report	M 62-year old; major depression	None	Disappearance in 30 h after discontinuation, Second attempt: hiccup restarted for a few minutes/d and disappeared on day 6.

Note: d= daily; h=hours; IM= intramuscular; M=Male; BD=Bipolar Disorder

and chlorpromazine, because we preferred to avoid the use of further additional medications in our young, drug naïve patient. Interestingly, in some cases aripiprazole cessation was not necessary as hiccup disappeared simply after benzodiazepine cessation (De Filippis et al. 2015, Caloro et al. 2016).

After aripiprazole interruption, hiccough disappeared after a variable period ranging from 1 (Kattura & Shet 2013) to 4 days (Duvarci & Yilmaz 2013) in accordance with aripiprazole half-life of 54-75 hours (Sakalli Kani et al. 2015). Surprisingly, in our case the hiccup stopped just after 12 hours from the last drug administration, perhaps due to the individual rapid metabolism or other individual factors but this may be only indirectly hypothesized.

There are other additional case-reports in which a reintroduction of aripiprazole after hiccup improvement (Behere et al. 2007, Hori & Nakamura 2014, Sakalli Kani et al. 2015) has been attempted but only in one case aripiprazole resulted well tolerated (Sakalli Kani et al. 2015). In most cases, aripirazole interruption has been switched to another antipsychotic agent such as quetiapine (Ray et al. 2009, Behere et al. 2007, Caloro et al. 2016), risperidone (Silverman et al. 2014, Kattura & Shet 2013, Yeh 2011, Duvarci & Yilmaz 2013), paliperidone (Hori & Nakamura 2014), and olanzapine (Caloro et al. 2016) whereas we successfully switched to asenapine. Table 1 summarizes the most relevant studies about the association between aripiprazole use and hiccup.

CONCLUSIONS

In conclusion, hiccup is described, based on most of the reported evidence, not only as a common but a well described adverse effect related to aripiprazole treatment. However, other additional risk factors have been hypothesized to explain its occurrence. For instance, the association with hyponatremia (Ginsberg 2007), brain injuries (Ray et al. 2009, Silverman et al. 2014, Kattura & Shet 2013, Yeh 2011), male sex (Caloro et al. 2016), and a particular link to other drugs have been reported. In particular, switching from a D2 high potency blocker to aripiprazole seems to increase the risk of hiccup occurrence, although other mechanisms, involving gabaergic and serotoninergic transmission, are presumably implicated (Yeh 2011, Duvarci & Yilmaz 2013). The importance of the interaction between aripiprazole and benzodiazepine in hiccup occurrence needs to be taken into consideration as well.

Clinicians should carefully monitor the relevance of concomitant treatments in case of aripiprazole-induced hiccup. In case of concurrent benzodiazepine consumption, a benzodiazepine suspension, where possible, should be considered and, alternatively, pregabalin may be considered for hiccup treatment. Otherwise, when aripiprazole suspension seems necessary, switching to another antipsychotic with D2 high potency profile may be provided.

More research is needed to better understand the mechanisms underlying aripiprazole-related hiccup, and exactly identify all the potential concurrent risk factors related to this complex phenomenon.

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Contribution of individual authors:

Gianluca Serafini managed the literature searches and wrote the first draft of the manuscript.

Maurizio Pompili & Mario Amore provided the intellectual impetuous and supervised the search strategy.

Martino Belvederi Murri, Fiammetta Monacelli & *Alice Cervetti* revised the manuscript.

Giulia Piccinini & Samantha Visimberga provided help in selecting and drafting the papers.

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Correspondence:

Gianluca Serafini, MD. PhD
Department of Neuroscience, Rehabilitation, Ophthalmology,
Genetics, Maternal and Child Health (DINOGMI),
Section of Psychiatry, University of Genoa, IRCCS Ospedale Policlinico San Martino
Largo Rosanna Benzi 10, 16 132, Genoa, Italy
E-mail: gianluca.serafini@unige.it