Hiccups Induced by Aripiprazole Combined With Sertraline in an Adolescent With Olfactory Reference Disorder: a Case Report

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Case report

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Abstract

Background

Hiccup can cause significant distress to patients and affect medication compliance. Individuals with olfactory reference disorder (ORD) who might develop persistent hiccups when treated with a combination of antidepressant and antipsychotic, leading to significant distress and impairment.

Case presentation

We report a rare case of an adolescent with ORD who was treated with aripiprazole combined with sertraline and who began to hiccup persistently after 6 days on this treatment. He stopped hiccupping after the aripiprazole had been suspended for 12 h. After discharge, the patient continued on sertraline alone and reported no hiccupping at one-month follow-up.

Conclusions

Clinicians should consider that the combination of aripiprazole and sertraline can induce hiccups during the acute administration period in adolescents with ORD.

Background

Olfactory reference disorder (ORD) is a psychiatric condition characterized by the persistent and erroneous belief that one emits an unpleasant body odor. ORD is included in the International Classification of Diseases 11th Revision (ICD-11) as a subtype of obsessive-compulsive and related disorders [1]. ORD is typically accompanied by repetitive and excessive behaviors, such as checking for body odor repeatedly, showering frequently, and avoiding social situations, leading to significant distress and impairment of quality of life [2].

No standard treatment for ORD has been established, although selective serotonin reuptake inhibitor (SSRI) and atypical antipsychotic have been used together [3]. The antidepressant sertraline selectively inhibits the reuptake of serotonin (5-hydroxytryptamine, 5-HT) by neurons in the central nervous system, and it weakly inhibits reuptake of norepinephrine and dopamine [4]. Sertraline can prevent relapse in patients with obsessive-compulsive disorder [5]. The combination of sertraline or other selective serotonin reuptake inhibitors with the atypical antipsychotic aripiprazole can be effective against refractory obsessive-compulsive disorder [6]. Aripiprazole acts as a partial agonist at dopamine D2 and 5-HT_{1A} receptors, while it acts as a partial antagonist at the 5-HT_{2A} receptor [7]. Its agonism at the 5-HT_{1A} receptor may explain how it can be effective in combination with sertraline [6].

While aripiprazole shows a favorable metabolic profile and few adverse effects, it was reported to cause persistent hiccups in an adolescent with bipolar disorder [8] and in adult patients with bipolar disorder or schizophrenia [9, 10]. Hiccups are caused by involuntary, repetitive contractions of the diaphragm and the intercostal muscles as a result of sudden glottis closure [11]. Hiccups can be induced by tumors in the

central nervous system, inflammatory diseases, gastrointestinal disorders, and different drug therapies [12]. Although the precise etiology of hiccups is unclear, neurotransmitters such as dopamine and serotonin can play an important role [13]. By extension, the use of antipsychotic medications that regulate these neurotransmitters have been associated with hiccups [13].

Here we report a case in which a Chinese adolescent with ORD suffered persistent hiccups as a result of combination therapy of aripiprazole and sertraline.

Case Presentation

In July 2020, a 17-year-old Chinese male was brought to our hospital by his parents. The adolescent reported that since 2018, he had become aware of persistent, unpleasant smell from his body, leading him to spend more than one hour per day bathing his body and feet, to change his shoes frequently and to re-wash his feet every time he went out. He wore each pair of shoes only once and would frequently ask his parents to buy him new shoes. When someone coughed or covered his or her nose around him, he suspected that it was because of his unpleasant body odor. He reported feeling distress and anxiety, and he complained of impaired social functioning. He did not want to go to school or crowded places, and he paid a lot of attention to the expressions and movements of people around him, even counting the frequency of those actions.

The patient had no history of psychiatric illness and no family history of mental disorders. There were no signs of infection, and results were normal for all clinicopathological examinations, including blood and urine tests, blood glucose levels, as well as tests of liver, renal, and thyroid function. Results were also normal for electroencephalography, electrocardiography, transcranial Doppler ultrasonography, and head magnetic resonance imaging. On the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), his sub-score on obsessions was 18, and his sub-score on compulsions was 16. He scored 25 on the 24-item Hamilton Anxiety Scale, 10 on the 14-item Hamilton Depression Scale, and 4 on the 32-item Hypomania Checklist. The patient showed no signs of hypomania.

Based on the patient's reported symptoms and our tests, we diagnosed him with ORD in accordance with ICD-11 criteria [1]. He was treated with sertraline hydrochloride at 50 mg/day, which was increased gradually to 100 mg/d. On day 5 of hospitalization, he reported feeling less distress and anxiety, but he still reported perceiving an unpleasant smell from his body. Therefore, aripiprazole 10 mg/d taken at night was added to his treatment.

After one day on this combination therapy, he began to hiccup occasionally; after two days, the hiccup was persistent, even during the night. The patient reported being concerned that the hiccups were a side effect of the drug. After three days on combination therapy, aripiprazole was discontinued, and the hiccups stopped at 12 h thereafter. After another seven days on sertraline alone, the patient reported not perceiving any unpleasant smell from his body, and he said that he paid less attention to others' expressions and movements around him. After a total of two weeks' hospitalization, he was discharged

on sertraline at 150 mg/d. The patient reported no persistent hiccupping at a follow-up visit at one month after discharge.

Discussion And Conclusions

To our knowledge, this is the first report of an adolescent with ORD who developed persistent hiccups when treated with a combination of aripiprazole and sertraline, which then disappeared upon discontinuation of aripiprazole.

Aripiprazole may induce hiccups through multiple pathways. It binds strongly to the D3 receptor, which has been shown to play a role in hiccups [14]. Aripiprazole acts as a partial agonist at the 5-HT_{1A} receptor, and its binding can lead to serotonergic facilitation of phrenic motoneuronal activity, inducing hiccups [14]. Aripiprazole acts as an antagonist of 5-HT_{2A} receptors, which may also induce hiccups [15]. In previous studies of patients with major depressive disorder in whom aripiprazole induced hiccupping, the hiccups stopped at 1–4 days after discontinuing the drug [16, 17], which probably reflects its half-life of 54–75 h in the blood [18]. Surprisingly, our patient's hiccupping stopped just 12 h after the last drug administration, which may reflect particularly rapid metabolism or other individual factors.

Whether sertraline can induce or inhibit persistent hiccupping is unclear. It was linked to hiccupping in a patient with obsessive-compulsive disorder and attention-deficit/ hyperactivity disorder [19], but it has also been proposed to suppress hiccupping through its effects on 5HT_{1A} and 5HT₂ receptors as well as on the autonomic nervous system [20]. Future research should examine whether and how sertraline affects risk of persistent hiccupping.

The members of the cytochrome P450 protein family mediate the metabolism of antipsychotics and antidepressants [21]. This may reflect that sertraline inhibits cytochrome P450 protein CYP2D6, which degrades aripiprazole [22]. Thus, the combination therapy may prolong the half-life of aripiprazole, increasing its hiccup-inducing effects on the central nervous system. Genotyping of cytochrome P450 isoenzymes may be advisable in order to avoid this adverse effect of combination therapy.

It is also possible that the our patient's persistent hiccupping reflects that men are at intrinsically higher risk of this condition [23]. Hyponatremia and brain injury may also increase risk of hiccups [24, 25], but our patient did not have a history of electrolyte disturbance or brain injury.

Our case highlights the need for clinicians to be aware of the possibility that aripiprazole combined sertraline may induce hiccups in the acute administration period in adolescents with ORD. Genotyping of cytochrome P450 isoenzymes may be useful for detecting potential contraindications to such combination therapy. Further studies are required to clarify the role of sertraline alone and combined with aripiprazole in triggering persistent hiccupping in patients with ORD, as well as obsessive-compulsive and related disorders.

Abbreviations

ORD: olfactory reference disorder; ICD-11: the International Classification of Diseases 11th Revision; SSRI: selective serotonin reuptake inhibitor; 5-HT: 5-hydroxytryptamine; Y-BOCS: the Yale-Brown Obsessive-Compulsive Scale.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from his parents for the case report. West China Hospital Ethics Committee approved the study.

Consent for publication

The patient's parents received a complete description of the report and provided written informed consent. A copy of the written consent is available for review by the editor of this journal.

Availability of data and materials

This is a single-patient case report. Data sharing is not applicable to this article as no datasets besides those mentioned in the article were generated or analysed.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

ZL and YL completed the paper and contributed equally to this work. ZZX and ZXL conducted follow-up of this patient. YWY and JFD treated this patient. XL critically reviewed the diagnostic results and contributed to the preparation and revision of the manuscript. All authors read and approved the final version of the manuscript.

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