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Case Report

A Case Report of Iloperidone-induced Sleep-related Eating Disorder

Hani Raoul Khouzam*

Department of Psychiatry, Sacramento VA Medical Center and UC Davis Health, Sacramento, California, USA

***Corresponding Author:** Hani Raoul Khouzam, MD;MPH. Staff Psychiatrist Department of Psychiatry, Sacramento VA Medical Center Clinical professor of Psychiatry and Medicine, UC Davis Health, Sacramento, California USA.

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Abstract

Sleep-related eating disorder is a Non-Rapid Eye Movement Sleep Arousal Disorders characterized by recurrent episodes of nocturnal eating or drinking after an arousal from the Non-Rapid Eye Movement (NREM) sleep stage. Several medications, including atypical antipsychotics, have been reported to induce sleep-related eating disorder. This case report illustrates the development of sleep -related eating disorder during treatment with the atypical antipsychotic Iloperidone. It also reviews Iloperidone core mechanisms of action and propose a possible link between its effects on 5-hydroxytryptamine-2A and 2C (5-HT2A) and (5-HT2C) neuroreceptors and the development of Sleep-related eating disorder.

Keywords: Schizophrenia; Sleep-related Eating Disorder; Atypical Antipsychotics; Iloperidone; Treatment.

Introduction

Sleep-related eating disorder (SRED) is a Non–Rapid Eye Movement Sleep Arousal Disorders characterized by recurrent episodes of eating or drinking that occur after an arousal from the NREM period of sleep with partial or complete amnesia for the event [1]. Various injuries could also occur during SRED, due to consumption of inedible or toxic items or because of hazardous behaviors performed while searching, cooking, or baking of food [2]. Adverse health effects could also occur due to the intake of high calorie foods and subsequent weight gain [2,3]. Individuals with SRED typically have full or almost complete amnesia for these events [4]. SRED is distinct and different from night eating syndrome in which patients wake up during their nighttime sleep to eat while fully aware of their awakening and consuming approximately at least one-third of their daily calories [5]. SRED could be idiopathic or commonly associated with other primary sleep disorders such as sleepwalking, restless legs syndrome (RLS), obstructive sleep apnea (OSA), other medical conditions or could be induced by medications. Several medications could induce SRED-like behaviors including sedative hypnotics such as the benzodiazepine receptor agonists [6] and Zolpidem [7,8]. The atypical or second-generation antipsychotics (SGAs), Olanzapine [9], Risperidone [10], Quetiapine [11] and Aripiprazole [12] also have been reported to induce SRED. This case report describes a patient who developed SRED during treatment with the SGA Iloperidone.

Case Report

Mr. L is a 33-year-old single gentleman who was diagnosed and treated for schizophrenia since he was 21-year-old. His condition was described as having treatment resistant schizophrenia (TRS) due to his unresponsiveness to several antipsychotic medications. He was then treated with clozapine. He was stable while maintained

on 750mg daily dose of clozapine. He did not develop any adverse effects to clozapine except for a moderate weight gain, which he accepted and counteracted further increase by eating a healthy diet and daily physical exercise. For the past 4 years he remained employed as a part time clerk in a local warehouse. He was admitted to the hospital due to symptoms suggesting (SARS-CoV-2) COVID-19 infection which included fever with chills, cough, difficulty breathing, fatigue, muscle aches, headache, sore throat and runny nose. His diagnosis was also confirmed by a positive COVID-19 testing. His physical examination did not reveal any abnormal findings, other infections, head injury, bone fractures or joint problems. A medical work-up including complete blood count (CBC), chemistry profile, urine analysis, urine screen for illicit drugs and thyroid function test were all normal. Given his pre-COVID-19 relatively good health status, he was discharged after receiving 5 days of medical support and oxygen therapy. Mr.L recovered from COVID-19 infection without any medical complications and was scheduled to be vaccinated in about 90 days from the time of his infection. Inadvertently he did not receive clozapine during his hospital stay. He also did not want to resume clozapine therapy because of his weight gain. His current weight was 177 lb., and he felt that given his 56" height, his weight should not exceed 150 lb. He began to experience paranoid thoughts and delusions about his neighbors using their mobile phones to spy on him. He also began to hallucinate and was hearing his deceased grandfather telling him to join him in the afterlife. His co-workers were concerned about his welfare because he stopped going to his place of employment and was refusing to eat for fears of being poisoned. He neglected his hygiene and looked disheveled with a gaunt appearance. Fortunately, he called his case manager at the local community mental health clinic and requested assistance because he "could no more bear" the fears of being poisoned and of hearing the voices of the dead.

Prior to clozapine therapy Mr. L was treated for multiple episodes of acute schizophrenia with several antipsychotic medications including Chlorpromazine, Haloperidol, Perphenazine, Fluphenazine, Risperidone, Quetiapine, and Olanzapine. He did not want to reinitiate Clozapine or any of his previously prescribed antipsychotic medications, but consented to a trial of Iloperidone, based on its relatively low potential for causing weight gain. He was started on Iloperidone 1 mg bid for one day, then increased to 2 mg bid on day 2, on day 3 the dose was raised to 4mg bid, and on the 4th day, Iloperidone was raised to 6mg bid. He did not develop adverse effects to the total daily dose of Iloperidone 6mg twice a day which he continued to take for the following 21 days.

Mr. L was satisfied with Iloperidone effects in leading to the remission of the paranoid suspiciousness regarding his neighbors. He also experienced a relief from not hearing anymore voices. He began to care for his basic needs and resumed his employment at the warehouse where he was kindly welcomed back by his co-workers and his supervisor. He reported enjoying cleaning up his bedroom, grooming, buying his groceries and exercising. He was surprised to wake up tired every morning and to find his refrigerator almost empty from a week worth of food. The grocery store manager also commented that he has been buying extra food and was shopping for food almost daily and was wondering if his appetite has dramatically and unexpectedly increased. Mr. L clarified that he has not had an increased appetite but that he was gaining weight and did not know why his refrigerator was always empty in the morning. One of his co-worker suggested that he leaves his mobile telephone camera facing the refrigerator so it can record the nighttime events. He accepted the suggestion, and was astonished to see himself waking up at night and ravenously eating all the food that was in his refrigerator. He became distressed, overwhelmed, and experienced intense feelings of self-disgust toward his gluttonous behavior. He called his case manager and announced that "he may be losing his mind", and blamed Iloperidone for causing him to wake up and eat at night and also for causing him to gain 10 extra pounds and he wanted to stop taking it. He was afraid that without taking an antipsychotic medication, he will experience recurrence of paranoia, suspiciousness and hearing voices. He refused to reinitiate Clozapine therapy but accepted Ziprasidone as an alternative to Iloperidone. At the time of writing this report he has taken Ziprasidone for 12 days and has not been engaged in any SRED.

Discussion

Schizophrenia is a severe, lifelong mental disorder affecting around 1% of the world's population [13]. The disease is characterized by positive, negative, and cognitive symptoms, and can lead to significant functional impairment [1]. It is estimated that approximately one-fifth to one-half of patients have TRS [14]. While defining TRS has been a subject of debates and controversies, it is generally agreed by various clinical practice guidelines, that the lack of response to two different antipsychotics would qualify pa-

tients of being classified as having TRS [15]. Clozapine when appropriately prescribed and, when well tolerated is considered the antipsychotic of first choice for TRS.

Mr. L had history of TRS that favorably responded to Clozapine until it was inadvertently interrupted during an episode of COVID-19 hospitalization and then his refusal of its initiation due to its effects on weight gain. The reemergence of an acute episode of TRS warranted treatment with the antipsychotic Iloperidone based on Mr. L choice, despite the lack of sufficient evidence about its effectiveness in TRS treatment. It is not yet determined if ongoing Ziprasidone treatment would also induce SRED and thus warranting ongoing monitoring for the development of this adverse event.

Iloperidone is an atypical SGA medication which was approved in May 2009 by the US Food and Drug Administration (FDA) for the acute treatment of schizophrenia in adults. It is a piperidinyl-benzisoxazole derivative with its core mechanism of actions that are like other SGAs. It differs from other SGAs in that it affects a variety of 5-hydroxytryptamine-2A (5-HT2A), 2C(5-HT2C), HT6 (5-HT6) serotonergic and D3, D4 dopaminergic receptors [16,17]. It also affects neurotransmission of norepinephrine with effects on α1-adrenergic receptors, with secondary effects on α1-2C noradrenergic receptors. It is believed that because of Iloperidone varied mechanism of actions, it can play a role in improving the negative and cognitive symptoms of schizophrenia and could provide the possibility of a unique and favorable side effects profile that may make it an alternative option for patients who have previously not tolerated or adequately responded to other available SGAs [15]. Iloperidone efficacy is like Haloperidol, Risperidone and Ziprasidone and seems to have minimal extrapyramidal side effects, weight gain and prolactin level elevation. Its drug to drug interactions through the CYP3A4 and CYP2D6 enzymes, along with its potential for QT prolongation, may limit its use in certain patients who are at risk of developing these potential adverse effects [15-17]. When slowly titrated to the desired therapeutic dose, Iloperidone is generally well tolerated, with a favorable safety profile, and could be an effective treatment option in patients with schizophrenia [15-17]. Its place in therapy and performance in TRS has not been established. The recommended target dose of Iloperidone is 12 to 24 mg/d, administered twice daily. The dose should be titrated over 4 days to reach a dose of 12 mg/d to minimize dizziness and/or orthostatic hypotension (starting with 1 mg bid, then 2 mg bid, 4 mg bid, and 6 mg bid). Slower titration may be necessary for patients who have history or are at risk for orthostatic hypotension. Iloperidone can be administered without regard to meals. The optimal efficacious dose for Iloperidone is unclear but, given dose-related tolerability concerns, a dose of 12 mg/d may be best for most patients. The slow initial titration schedule and twice-daily dosing are considered potential disadvantages which could sway clinicians from considering Iloperidone as their first option for the treatment of schizophrenia [18].

The widespread mechanism of action of Iloperidone inferred its possible association with weight neutrality and made it a viable alternative for patients who are concerned about gaining weight with SGAs, such as it was the case with Mr. L. It is important for clinicians to recognize that certain patients will experience weight gain which occurs within the first weeks of treatment; therefore, awareness of this adverse event is essential when prescribing Iloperidone [19].

SRED is classified as an NREM- Sleep Arousal Disorders that is characterized by recurrent episodes of dysfunctional eating that occur after an arousal from the NREM sleep stage with partial or complete amnesia for the event [1,4]. SRED can be idiopathic or commonly associated with other primary sleep disorders such as sleepwalking, RLS, OSA, other clinical conditions, or use of certain medications such as benzodiazepine receptor agonists [6] Zolpidem [7,8] and the antipsychotics Olanzapine [9], Risperidone [10], Quetiapine [11] and Aripiprazole [12]. At the time of submitting this report it is not known if there are any published reports regarding Iloperidone induced SRED.

It is presumed that Mr. L developed SRED secondary to Iloperidone treatment since he did not have any other co-occurring NREM- Sleep Arousal Disorders such as sleepwalking, RLS, OSAS, other clinical conditions that could have caused his nocturnal overeating episodes. The mechanism of Iloperidone inducing SERD is not fully understood. It is proposed that its action on 5HT-2A and dopamine D2 receptors could have led to increased cortical dopamine release and influencing the serotonergic neurons of the dorsal raphe nucleus (DRN) in the brain stem which constitute an integral component for generation of NREM slow wave sleep (SWS) [20,21]. The maintenance of SWS is well coordinated with motor inhibition so that motor activity does not happen without arousal. The effects of Iloperidone on dopamine and serotonergic receptors

could have prevented the motor inhibition, thus enabling the person to perform motor activities such as walking or eating during NREM without a complete arousal [19,20]. Another proposed effects could be related to Iloperidone effects on 5HT-2C neuroreceptors in the hypothalamus in regulating mood, anxiety, feeding, and reproductive behavior [22]. These effects could have also played a role in increasing appetite, food intake and subsequent weight gain [23]. Additionally, some patients treated with SGAs were also found to have elevated leptin levels [24]. Iloperidone effects on 5HT-2C, may cause leptin resistance in the hypothalamus, contributing to increased food intake and weight gain.

The proposed effects of Iloperidone on inducing SRED through its mechanisms of action on dopaminergic and serotonergic neuroreceptors have not been fully explored or confirmed in large scale randomized placebo control clinical trials and could only be admissible as hypothetical explanations of Mr. L development of SRED.

Conclusion

In this case report a patient with TRS who had a good response and freedom from psychotic symptoms over a 4 years span while maintained on a daily 750 mg dose of clozapine relapsed and experienced recurrence of psychotic symptoms due to the inadvertent interruption of clozapine during a COVID-19 infection hospitalization. He was then treated with Iloperidone as an alternative to clozapine due to his refusal to initiate clozapine in the context of his concerns about gaining weight. Although Iloperidone lead to remission of the psychotic symptoms ;it was found to precipitate SRED which was presumed to be related to its effects on dopaminergic and serotonergic neuroreceptors. The atypical SGAs are frequently prescribed treatment of schizophrenia and other psychotic disorders due to their effectiveness and lack of cumbersome adverse effects, particularly with respect to their low incidence of inducing extrapyramidal symptoms. However, SGAs can induce other adverse effects including metabolic dysregulations and the possibility of developing SRED. Clinicians are thus encouraged and strongly advised to discuss the possibility of SRED as a potential adverse effect of the SGAs which could contribute to a slew of medical complications including increase in metabolic syndrome, weight gain, obesity, diabetes type 2, hyperlipidemia, cardiovascular events, and hypertension [25]. Knowledge of these risks is of crucial clinical importance for further monitoring and the institution of counteractive measures to reverse and minimize the impact of these adverse effects on the overall health and the general well-being of patients. Although it is presumed that SRED was induced by Iloperidone ; randomized double blind placebo controlled clinical trials are needed to determine and confirm this causal correlation.

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Disclaimers

- The views described in this manuscript are those of the author and do not reflect the official policy of the The Sacramento VA Medical Center or The Department of Veterans Affairs or UC Davis Health.
- The demographic characteristics described in this case report do not reveal the patient's true identity, and they have been changed in compliance with the clinical guidelines of protecting patients' rights to confidentiality and for maintaining the integrity and accountability of medical records.

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Volume 2 Issue 9 September 2021