CLINICAL VIGNETTE

Zolpidem-induced Somnambulism and Sleep-related Eating

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Introduction

Somnambulism and sleep-related eating disorder are non-rapid eye movement (NREM) sleep-related parasomnias, considered to be disorders of arousals.[1] They occur in the first third of the night when NREM sleep dominates. Patients are typically aroused from slow-wave sleep, part of NREM, and engage in primitive behaviors such as eating, ambulation, sex and aggression, all devoid of cortical planning. During these episodes, the patient is neither conscious nor deliberate in their behavior and has partial or complete amnesia of the event the following morning.

While both somnambulism and sleep-related eating disorder can be primary in etiology, in this vignette, the condition is induced by zolpidem. This case highlights the importance of providers being aware of medication induced behaviors, their potential of affecting patient's other health conditions and general safety.

Case Presentation

The patient is a 49-year-old female with history of poorly controlled Diabetes Mellitus type II referred to Sleep Medicine for management of insomnia.

She has a long-standing history of both sleep onset and maintenance insomnia and has been on chronic zolpidem for 3-4 years, prescribed by an outside doctor. She had a polysomnogram which did not show evidence of sleep disordered breathing nor sleep movement disorders.

She was initially on zolpidem 5 mg, which eventually lost efficacy, and at which point her dose was subsequently increased to 10 mg. She then started exhibiting behaviors such as sleep walking and sleep eating, with no recollection of the events, but were witnessed by her daughter. She brought to her office visit a video showing her eating a tub of ice cream while sitting in bed, not responsive to, nor aware of her surroundings. In another situation, she was witnessed eating a stick of butter. As a result of these events, she herself decreased her zolpidem dose to 5mg. Despite this, however, the sleep related behaviors continued to occur.

Patient was given bedroom safety precautions and recommended to stop taking zolpidem. On a subsequent visit she reported complete cessation of the parasomnias.

Pertinent labs include: POC glucose 428 mg/dL, HgbA1C 12.9%.

Discussion

Parasomnias are thought to be precipitated by an arousal which leads to an incomplete dissociation from sleep.[1] The resulting state is a composite of both NREM and wake, with characteristics resembling both. In this case, the parasomnias exhibited were not primary but were induced by zolpidem.

Of the medications which can trigger parasomnias, zolpidem is most commonly reported.[2] The incidence of zolpidem-induced somnambulism in studies have been 0.5%[3] in post-marketing surveillance and 5.1%[4] in psychiatric patients. Other medications which have been found to be associated with sleep walking include the Z drugs (zolpidem, zopiclone, zaleplon), sodium oxybate, tricyclic antidepressants (topiramate), selective serotonin re-uptake inhibitors (paroxetine, fluoxetine, sertraline), selective norepinephrine reuptake inhibitors (mirtazapine), lithium, bupropion, atypical antipsychotics (olanzapine, quetiapine), older generation antipsychotics (chlorprothixene, perphenazine, and thioridazine), and beta blockers (propranolol, metoprolol).[2] It is important for practitioners to be aware of these other drugs which could possibly trigger parasomnias, especially when a patient is on more than one of the above listed drugs.

The pathophysiology of parasomnias remains unclear. Those with tendency for parasomnias have been found to have unstable NREM sleep characterized by an EEG marker called cyclic alternative pattern.[5] In other instances, medical disorders like obstructive sleep apnea, or periodic limb movements of sleep can lead to arousals during NREM sleep creating an opportunity for a parasomnia to develop. Tassinari proposes that during these arousals, central pattern generators are activated which allows for the automatic behavior to be exhibited. Central pattern generators are networks of neurons located in the pons and spinal cord, programmed to activate certain motor neurons which then generate a particular motor pattern without control from higher brain centers.[6] The result is a person within the confines of sleep, who has the ability to carry out automatic behaviors without need of cortical input.

At a cellular level, serotonin has been implicated in parasomnias due to its known involvement in activation of motor

neurons.[7] Cape et al demonstrated the effect of serotonin on muscle by injecting serotonin in the basal forebrains of rats during sleep.[8] They found that serotonin induced slow wave sleep and increased muscle tone, suggesting a role in the perpetuation of parasomnias.

Further expounding on the serotonin model to provide a possible mechanism for zolpidem-induced parasomnias, Juszczak proposes that the desensitization of GABAergic receptors by zolpidem leads to an increase in serotonin levels and consequently increased muscle activity.[9] Zolpidem is known to bind to the benzodiazepine receptor located specifically between the α_1 and γ_2 subunits of the GABA-benzodiazepine-chloride ionophore complex, and upon activetion, produces inhibition of neuronal excitation.[10] Juszczak theorizes that when zolpidem binds to its receptor, the potentiation subsequently leads to receptor desensitization. This then results in decreased inhibition, allowing increased serotoninergic neuron activity and hence, subsequent activation of motor neuron complexes. The probability of a parasomnia occurring in Juszczak's model depends also on the half-life of the medication in question, drug pharmacokinetics and each individual's degree of response in receptor desensitization and serotonin release. Perhaps it is at this juncture, central pattern generators, as proposed by Tassinari, come into play.

While the mechanism of zolpidem-induced parasomnias is not fully understood, notorious side effect of zolpidem are well known. In 2013, the United States Food and Drug Administration (FDA) released a safety announcement to lower the recommended dose of several zolpidem medications for women.[11] For zolpidem, the recommended dose was decreased from 10 mg to 5 mg. This change was mainly secondary to studies demonstrating high blood levels of these medications the morning after intake, resulting in impaired cognitive ability. Due to differences in drug metabolism, women were more likely than men to exhibit these higher levels. In our patient, despite lowering her dose to the recommended level of 5 mg, her parasomnias persisted. It was only after the patient completely stopped taking zolpidem was there cessation of the parasomnias. There have been cases in literature demonstrating that when a patient is switched to a different drug of even the same class, the unwanted sleep behaviors can sometimes disappear. The reason for this is unknown.

This case illustrates the importance of communicating to other providers regarding pertinent patient history. I was able to discuss this finding with the patient's Endocrinologist, who was not aware of the parasomnias. This provided one possible explanation for the patient's poor glucose control. Those who exhibit sleep-related eating disorder tend to consume high carbohydrate foods (cookies, ice cream, potato chips), toxic and inedible items.[1] While the sleep-related eating disorder cannot fully explain the patient's HgbA1c, being able to curtail her parasomnias gave the patient a better chance in improving control of her diabetes mellitus.

In summary, zolpidem-induced parasomnias while rare, can have detrimental effect on patient safety and other medical conditions. The mechanism of medication-induced parasomnias may be associated with desensitization of GABAergic receptors and further research in this area can be beneficial. While using any medication which has been associated with parasomnias, it is crucial to use as low a dose as possible and to stop the medication should any sleep-related complex behavior occur.

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