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Potentiating the Adverse Effects of Zolpidem in a Patient with Alcohol Dependence and SSRI use

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Abstract

Though rare, zolpidem has been implicated in perceptual disturbances. Zolpidem elimination can be reduced with liver or kidney pathology. Concomitant Selective Serotonin Reuptake Inhibitor (SSRI) and alcohol use have increased susceptibility to delirium. This case describes a 63 year old Caucasian male, seen by the consulting service, having depression and alcohol dependence, presenting with auditory and visual hallucinations with paranoid delusions. He was prescribed zolpidem 10mg for several years, but reported doubling his dose recently, until stopping the medication 7 days prior to hospitalization. He was non-compliant with citalopram 40mg daily. He presented with sodium of 130mmol/L, potassium of 2.6mmol/L, and mild transaminitis. Using the Liverpool ADR Causality Assessment Tool, it was deemed possible that his perceptual disturbance was associated with zolpidem. Mental status changes have been seen at zolpidem doses exceeding 10mg. A high proportion of zolpidem is protein-bound, and influenced by age, alcohol consumption, and malnutrition, which can contribute to hemo concentration and toxicity. Pharmadynamic potentiation of zolpidem may result from interactions between zolpidem and SSRIs, with ensuing prolonged zolpidem-associated hallucinations. Sleep disturbance is common in psychiatric patients and the potential for zolpidem associated side effects should be considered when using a pharmaco therapeutic intervention.

Introduction

Visual hallucinations can be defined as a perceptual experience of an object or event in the absence of external stimuli and are frequently encountered in psychiatric consultation. Thorough evaluation is required due to numerous etiologies, some of which are potentially life threatening. Organic causes such as delirium, dementia with Lewy bodies and other brain pathology along with sleep disturbances and drug effects must be ruled out prior to considering a primary psychosis [1]. Though rare, occurring in 0.3% of patients in one study, zolpidem has been implicated in visual hallucinations and illusions [2].

Zolpidem, a short acting imidazopyridine hypnotic agent commonly used to treat insomnia, binds to and agonizes $GABA_A$ receptors. Zolpidem undergoes first-pass metabolism, resulting in a bioavailability of 70%, and is highly bound to plasma proteins [3]. It follows linear kinetics and is eliminated both through the kidneys and liver [4]. Therefore, elimination tends to be reduced in patients with liver or kidney pathology, resulting in the possibility of increased serum levels and subsequent toxicity [3]. In malnourished patients, hypoalbuminemia is common and can result in elevation of unbound drug concentration that may account for, or contribute to, zolpidem toxicity [5]. Others susceptible to toxicity are women, whose zolpidem plasma levels were noted to be 40% higher than men at equivalent doses, and those with concomitant selective serotonin reuptake inhibitor (SSRI) treatment which can displace zolpidem because of competing high protein affinity. Additionally, Kumar et al. noted the role of ethanol in reducing surface expression of the alpha-1 subunit containing $GABA_A$ receptors increasing susceptibility to delirium with even small alterations to zolpidem dose [6].

The following case report takes into account various vulnerabilities such as alcohol dependence, malnutrition and concomitant SSRI use. A 63 year old male was seen in a consultation with the Internal Medicine team for their observation of a psychotic process. This case highlights several risk factors associated with zolpidem toxicity.

Case

Subject

Mr. S is a 63 year old Caucasian male, with a medical history of hypertension and depression, who presented to the emergency department at the request of family members following the development of auditory and visual hallucinations with paranoid delusions. Mr. S was admitted to the medical service with subsequent psychiatric consultation. Subsequent history did not suggest seizure disorder or other neurological illness. The patient did have a history of alcohol dependence with one episode of delirium tremens 4 years prior. Mr. S's spouse confirmed a history of alcohol dependence with an increase in drinking over the past 13 years after the unexpected death of a grandchild. Mr. S reported consuming approximately 1 pint (375ml) to 1 "fifth" (750ml) of vodka daily in 1-2 week blocks with interval periods of abstinence. His last drink of alcohol was 2-3 days prior to this hospitalization. Mr. S reported using chewing tobacco (3 packs every week) but denied any other substance use, including illicit drugs. Stressors identified were financial and marital stress lending to a recent diagnosis of depression treated with citalopram. No family history of depression or psychosis was identified.

On interview, Mr. S denied hallucinations. He went on to state

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that he felt fine and was aware of his surroundings. He was convinced that his coworkers, along with longtime friends, gave a movie crew the key to his house to make an X-rated film. He witnessed various bizarre things including seeing actors dressed as ghosts and demons. He reported attempting to speak with them but could not understand them when they started writing on the floors, walls and ceiling of his house. He was unable to understand the writing and reported the crew used "special effects" which caused the writing to continuously scroll. As Mr. S described, when he approached the people, they once again used a "Hollywood technique" to vanish suddenly. He was convinced the entire cast left within an hour of him calling the police.

Collateral data from family noted that family and police could not substantiate Mr. S's claims. Mr. S reported another episode later the same day. When he and his wife were sitting together at home, 7-8 men came into his house and removed the hard drive out of his computer and cut the phone lines after which Mr. S broke into a neighbor's house to call the police once again. The following day, at the behest of coworkers, friends and family, Mr. S presented to the emergency room. A coworker and friend for over 20 years described Mr. S as a dependable, agreeable person with some "OCD tendencies" including refusing to eat out and only eating food he has prepared or out of a sealed package.

An extensive medical work-up was conducted, including urinalysis, chest x-ray and CT imaging of the head without contrast, all of which were noncontributory. A hepatitis panel, serum HIV, acetaminophen level and RPR were also negative. Ammonia, TSH, B12, folate, and iron levels were within normal range. Urine drug screen was positive for a benzodiazepine which was given in the emergency room. At admission, there were some electrolyte abnormalities, including sodium of 130mmol/L and potassium of 2.6mmol/L. Vitamin D deficiency (16ng/ml), thrombocytopenia (137k/ul) in addition to mild transaminitis and an albumin level on the lower end of normal range. These abnormalities were believed to be consistent with poor nutrition associated with Mr.S's alcohol abuse.

They reported taking zolpidem 10mg at bedtime for sleep for the past 3 years prior to admission. Mr. S reported doubling his dose recently but then stopped taking the medication 7 days prior to hospitalization. Delusions started 5 days following the last dose based on self-report and collateral data. Mr. S has a questionable history of compliance but, at admission, he was re-started on his home dose of 40mg of citalopram. The zolpidem was held at admission and was not re-started throughout his three day hospitalization. He was treated with folic acid, thiamine and intravenous fluids along with 5mg of diazepam in the emergency room. His electrolytes were replenished. He subsequently received 5mg of diazepam three times on day one of admission. He did not report subjective complaints of withdrawal and remained hemodynamically stable. The scheduled diazepam was discontinued and diazepam was not required throughout the remainder of his hospitalization. His home antihypertensive agents, including atenolol 50mg daily, lisinopril 20mg daily, and hydrochlorothiazide 12.5mg daily, were continued. Throughout hospitalization, Mr. S was alert and oriented, reality based, and thought processes were linear without hallucinations. He was not observed to be responding to internal stimuli. However, he vehemently continued to believe his recollection of events to be real and vividly recounted these to members of the primary and consulting psychiatry team.

ADR scale

Using the Liverpool ADR Causality Assessment Tool [7], it was deemed possible that the patient's perceptual disturbance was potentiated by zolpidem in a patient with concomitant SSRI and alcohol use.

Discussion

The initial differential comprised of delirium secondary to substance-related withdrawal or other organic causes of delirium, substance-related psychotic disorders, and a primary psychotic disorder. His age did make him susceptible to altered mental status that is often seen with electrolyte abnormalities, and in such instances, a clinician should be cognoscente of delirium [8]. Other than his fixed, persistent delusion, there were no additional disturbances in his attention, orientation, or awareness. Moreover, his work-up for infectious processes or structural changes that precipitate altered mental status changes was unremarkable. His presentation was not consistent with alcohol withdrawal delirium which typically present as perceptual distortions, most frequently visual or tactile hallucinations, in the presence of autonomic hyperactivity manifesting as tachycardia, diaphoresis, fever, anxiety, insomnia, and hypertension [9]. Moreover, Mr. S did report previously experiencing delirium tremens and was able to differentiate this presentation, with accuracy, as being different from his prior experience. Although Mr. S has a significant history of alcohol dependence for which he was monitored with sedative-hypnotic withdrawal checks, the time frame during which the delusions occurred was inconsistent with that typically seen in alcohol withdrawal. Drugs that temper noradrenergic activity either by stimulating presynaptic autoreceptors or by blocking postsynaptic receptors have been shown to ameliorate withdrawal symptoms related to heightened autonomic activity [10]. Mr. S's anti-hypertensive regimen may have accounted for the disappearance of autonomic hyperactivities. Nonetheless, continued monitoring is advised because CNS withdrawal symptoms may rarely occur after autonomic hyperactivities have disappeared. His speech was coherent and organized, inconsistent with confabulation that may be seen with pathology related to alcohol dependence, for example Wernicke Korsakoff syndrome. So, while Mr. S did experience some withdrawal, this was not the sole explanation for his delusions. Based on the history provided by Mr. S and through confirmation via collateral, he did not have a history of previous primary psychiatric diagnosis, nor was there a family history positive for a psychotic disorder. Given these factors, a person at this age is unlikely to have a new onset of a primary psychotic disorder. Alternately, complex behavior disturbances, for example sleep-driving, preparing and eating food, making phone calls, or having sex, have been seen in both sedative-hypnotic naïve and experienced patients [11]. The use of alcohol and other CNS depressants, as seen with Mr. S, has been found to increase the risk of such behaviors. Despite the frequency of prescription of zolpidem, zolpidem-induced complex behaviors are still understudied. Wu-Chou and Shen suggest that complex behaviors of zolpidem may be similar to those caused by benzodiazepines with higher affinity to alpha subunits. In the case of Mr. S, the use of diazepam may have reduced the duration and severity of his perceptual disturbances [11].

While there is not clear cut explanation for his hallucinations and psychosis we have to consider that the following factors contributed toward a vulnerability to an altered mental state secondary to zolpidem [12]:

Zolpidem dose: the adverse reactions that develop are dose dependent

Mr. S had been taking 10mg of zolpidem. While there have been several reports of minimal neuropsychiatric reactions with doses of 5mg or less, there have been reports of altered mental status at doses of 10mg or greater [4,12-14]. One case described the reactions after a 10mg dose as "similar but less intense compared with a previous experience that involved the use of LSD" [4]. One can postulate that this presentation may be accounted for by acute zolpidem hemoconcentration/toxicity.

Protein binding affinity: a high proportion of zolpidem is protein-bound

The patient's alcohol and malnutrition were believed to account for his abnormal lab findings at initial presentation. These, combined with his age, are suspected to influence protein binding affinity. Since a high proportion of zolpidem is protein-bound, Mr. S had a clinical presentation that could contribute to zolpidem hemoconcentration/toxicity.

Pharmacodynamic Potentiation and Drug Interactions:

Several case reports have suggested that interactions between zolpidem and SSRIs may result in prolonged zolpidem-associated hallucinations [12]. Antidepressants reported to have hallucinations associated with zolpidem treatment include paroxetine, trazodone, fluoxetine, fluvoxamine, venlafaxine, and desipramine [3]. Elko et al. have looked at the interaction between zolpidem and SSRIs and, in their review, found that patients taking both agents were more likely to require hospitalization than those using zolpidem alone. They suggested that a pharmacodynamic potentiation occurs, likely involving serotonin and omega receptors, though a precise mechanism of this potentiation was unclear [15]. The majority of cases involved younger individuals [12]. There is a paucity of reports on the effect of zolpidem in the aged. Elderly patients may be susceptible to neuropsychiatric manifestations resulting from sudden changes in their zolpidem as is seen with benzodiazepines.

While his withdrawal from alcohol, electrolyte disturbance, nutritional status, or use of SSRIs may not individually account for his delusions, these factors are speculated to have made Mr. S vulnerable to zolpidem toxicity, which we suggest might be associated with Mr. S's perceptual experience.

Conclusions

We present a case of a 63 year old man seen on our consultation service to evaluate a perceptual disturbance that is consistent with, if not similar to, cases of zolpidem associated side effects reported elsewhere in the scientific literature. The current case, however, highlights the role of concomitant SSRI therapy along with alcohol dependence and associated malnutrition as modifiable factors potentiating zolpidem toxicity. As Elko et al. [15] observed prolonged hallucinations were seen in those taking anti-depressants with zolpidem. This, however, would not account for such symptomology occurring 5 days after last use of zolpidem. Its rapid absorption, short half-life and absence of an active metabolite would suggest complete elimination. However, in an older patient with malnutrition and alcohol dependence and mixed compliance to treatment, supposedly taking an antidepressant and a supra-therapeutic dose of zolpidem, concern for potentiating zolpidem toxicity and adverse reactions over days from last dose is being considered. Evidence based guidance is limited to case reports with none reporting symptoms after several days. Though limited by over reliance on self-report, lack of MR imaging and possible delirium from an unidentified cause, further study into the pharmacodynamics, pharmacokinetics and drug-drug interactions of zolpidem in medically complicated patients would aid clinicians in cautious consideration of such agents in psychiatric patients. Given that sleep disturbance is a common complaint in psychiatric patients with depression [16] and alcohol use disorders [17], the potential for zolpidem associated side effects should be considered when using a pharmaco therapeutic intervention for sleep disturbance. Persistent sleep disturbance may be an indication of failure to remission of depression. Mr. S had been treated with citalopram 40mg daily, which was found to have a 28% remission rate when treated for 10-12 weeks, per the STAR*D study [18]. A trial of an alternate anti-depressant may have resulted in better resolution of symptom burden. At present, a comprehensive history, including home medications, compliance to medication and medical follow up, substance use history along with collateral information can elucidate an otherwise complex presentation on a medical ward.

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Declaration of Interest

No commercial organizations had any role in the completion or publication of this article. Drs. Chopra, Rayapati and Patel declare no competing interest during the last 36 months.

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