## *Case Review*

# Diphenhydramine associated Complex Sleep Behaviors in an individual stable on Zolpidem: Case report and literature review

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**Abstract**

Zolpidem, a non-benzodiazepine receptor agonist, prescribed for short-term insomnia, is well known to cause complex sleep-related behaviors (CSB). Diphenhydramine is an antihistaminic most commonly used for allergies, motion sickness, insomnia and anxiety disorders. We describe a case in which a combination of factors, including diphenhydramine precipitated sleep walking and sleep-related eating behavior in an individual who was stable on Zolpidem. Although the mechanism is not clear, several factors are postulated as CSB inducing factors in individuals taking zolpidem including genetic vulnerability, drug-drug interactions, concomitant use of central nervous system (CNS) depressants and co-morbid physical conditions. Based on this case report, we strongly suggest that clinicians should thoroughly review the risk factors for complex sleep behaviors in individuals who are prescribed Zolpidem, avoid medications having the potential for drug-drug interaction, CNS depression; and make patients aware of the risk of using over the counter antihistaminic medications along with Zolpidem.

***Keywords:*** Zolpidem, diphenhydramine, complex sleep behaviors, sleep walking, sleep eating

## Introduction

Diphenhydramine is an over the counter medication in the United States, used widely for its antihistaminic properties. On the other hand, Zolpidem, a non-benzodiazepine receptor agonist (NBRA), belongs to the imidazopyridine class and was approved for the short-term treatment of insomnia by US Food and Drug Administration (FDA) in 2007. The benefits of zolpidem are noteworthy as after its introduction to the market, it was found to be effective in several neurological disorders as well (Wang et al., 2007; Clauss et al., 2004).

Complex sleep behaviors (CSB) are classified as parasomnias in the International Classification of Sleep Disorders, Second Edition. Zolpidem alone, with concomitant medications and with several other factors can increase the risk of CSB. We describe a case in which diphenhydramine precipitated CSB in an individual who was stable on Zolpidem.

## Case

A 52-year-old mildly obese (BMI 32.13), male veteran with a history of major depression and combat-related post-traumatic stress disorder (PTSD) was seen in the mental health clinic (MHC) of a Veterans Affairs Medical Center (VAMC). His medical comorbidities included diabetes mellitus type II (DM II), mild obstructive sleep apnea (OSA), restless leg syndrome (RLS) and chronic neck, back and knee pain secondary to falling from a telephone pole. On MHC intake, the veteran was being prescribed sertraline 100 mg/day for depression, hydroxyzine 25 mg every 6 hours as needed for anxiety and zolpidem 10 mg at night for insomnia. He had been taking the sertraline for 2 years and the zolpidem and hydroxyzine for greater than one year without any adverse effects. His non-psychiatric medications included metformin 500 mg twice a day for DM II and cholecalciferol 1000 mg once a day for calcium replacement. The veteran denied ever having any symptoms of mania, hypomania, psychosis, major anxiety, primary sleep disorders, alcohol or

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substance abuse. He had stopped smoking cigarettes 7 years previously. At presentation, the veteran described continuing symptoms of major depression related to PTSD despite sufficient sleep employing zolpidem 10 mg/day. Consequently, the sertraline was increased up to 200 mg/day which was well tolerated. As his initial iron and ferritin levels were within normal limits, he was prescribed ropinirole 2 mg for RLS.

A polysomnography verified the presence of mild OSA and a continuous positive airway pressure (CPAP) device was ordered. However, the veteran stated that the CPAP face mask made him feel claustrophobic. A sleep clinic referral resulted in the veteran being given education about the CPAP device and OSA in addition to the facemask being changed to a nasal mask. However, the veteran still refused to use the nasal mask. After his RLS improved, he stopped using both the ropinirole and the saline nasal solution.

On his third MHC follow-up visit at 12 weeks, with the increase in sertraline to 200 mg, he endorsed improved PTSD and depressive symptoms. When the side effects of zolpidem were reviewed with the inclusion of CSB, the veteran mentioned that 2 weeks prior he had found a knife, peanut butter and a loaf of bread outside a kitchen cabinet in the morning, as if someone tried to make a sandwich during the night. He remembered that along with his regular medications, he had taken over-the-counter diphenhydramine 50 mg for nasal congestion before going to bed. It was apparent that he had arisen during the night and gone to the kitchen to prepare peanut butter sandwiches and then returned to bed without any memory of these events. He denied any family history CSB and this was his first episode. After providing education about the risk of CSB with zolpidem, he stopped taking diphenhydramine with the zolpidem and the nighttime eating behavior has not returned to date.

**Discussion**

Zolpidem is well known to cause a wide range of CSB or automatism, such as somnambulism, sleep eating, sleep writing, sleep cleaning, sleep driving, sleep sex, sleep shopping, self-intoxication, object manipulation, para-suicidal attempts, homicidal attempts followed by amnesia with or without complaints of visual hallucinations and acute psychotic episodes (Paulke et al., 2014; Chopra et al., 2013; Paradis et al., 2012). Due to increased reports of hypno-sedative-induced CSB, in March 2007, the FDA requested safety label changes of 13 medications (FDA 2016). The incidence of CSB related to zolpidem use ranges from 0.3 to 5.0 % (Sauvanet et al., 1988; Ingaki et al., 2010). However, in persons with psychiatric diagnoses, the range increases to 24.5% in adults and 17.2% in the elderly (Hwang et al., 2010). Based on a review of the literature, it appears that the risk of CSB for hypno-sedatives is highest during initiation or dose increase however, CSB may occur at any time during medication administration (Dolder and Nelson, 2008).

***Role of GABA receptors and slow wave sleep in CSB***

CSB due to benzodiazepines (BZDs) has been well documented although the exact mechanism or mechanisms are unclear. Both BZDs and NBRAs induce their sedative effects by interacting with the $GABA_A$ receptor complex. In contrast to BZDs, NBRAs act selectively on the $\alpha_1 GABA_A$ subunit. While $\alpha_1$ $GABA_A$ agonists induce sedative, amnestic and motor-impairing effects, activation of $\alpha_{2-5}$ $GABA_A$ agonists has anxiolytic, anticonvulsant and muscle relaxant properties (Derry et al., 2004). Moreover, the biokinetic changes when NBRA blood levels increase as NBRAs lose their selectivity and interact with other GABA subunits as well as with the $GABA_A$ receptor complex (Huang et al., 2007). This promotes an increased risk of BZD related side effects such as impairing explicit or implicit memory selectively depending on the BZD variants' unique chemical properties (Morris, 2002).

Any event or substance that decreases sleep latency may interfere with the memory consolidation phase of sleep. Without adequate memory storage, deficits of retrieval and long-term storage are created. Theoretically, sleep-related memory impairment and CSB arises from slow wave sleep. It follows that medications like zolpidem, which decrease REM sleep and increase NREM duration, might increase the risk of somnambulism and other CSB behaviors.

***Role of the serotonergic system***

In addition to the BZDs and NBRAs, sodium oxybate and quetiapine are reported to cause sleep-related eating and sleep-related driving episodes (Wallace et al., 2011; Tamanna et al., 2012). Brainstem serotonergic neurons which project to the ventrolateral preoptic nucleus play an important role in slow wave sleep which modulates the central nervous system (CNS) motor system and maintains the hypotonia of antigravity muscles (Tamanna et al., 2012; Seeman 2010; Ichikawa et al., 2002). Extrapolating from these relationships, when serotonergic inhibition is dampened due to blockage of 5HT-2A by quetiapine, sleep walking without arousal may occur. Similarly, leptin resistance may result from quetiapine blocking the 5HT-2C receptors in the hypothalamus resulting in food craving during sleep (Nonogaki et al., 1998). At this time, it is not clear whether zolpidem or other NBRAs increase food craving with eating during sleep in the same manner as quetiapine.

***Neurobiological changes***

Cerebral pattern generators (CPGs) are genetically

determined neuronal circuits present in the mesencephalon, brainstem and spinal cord which control innate motor behavior necessary for survival such as feeding, locomotion, and reproduction in addition to producing motor activities without any sensory input (Tassinari et al., 2005; Mackay-Lyons 2002; Yuste et al., 2005). CPGs are under the control of the neocortex and may represent inborn fixed movement patterns seen when neocortical dominance is lost such as in parasomnias and epilepsy. Possibly due to the diffuse cortical binding of zolpidem, CPGs release cortical control of learned behaviors and initiates organized behaviors such as driving and cooking.

***Co-morbid medical problems, role of nocturnal hypoglycemia***

Before diagnosing a CSB disorder or REM sleep disorder, medical contributors like OSA, nocturnal seizures, nocturnal hypoglycemia, micro-sleeps secondary to fatigue, confusional arousals, and dissociative states should be ruled out. Conceptually, the CPAP which is a mainstay in the treatment of OSA increases the risk of insulin sensitivity (Harsch et al., 2004). Hypoglycemia selectively affects the basal ganglia and may induce complex body movements. CSB following early morning hypoglycemia secondary to undiagnosed insulinoma or dream-enacting behaviors at the end of apneic spells in OSA are not uncommon phenomena (Lysenko et al., 2012).

***Drug interaction may increase zolpidem levels***

Drug-drug interactions are considered to be a major contributing factor to zolpidem-associated CSB as zolpidem is commonly employed concurrently with multiple psychotropic and non-psychotropic medications. Among the NBRAs, zolpidem, zopiclone, and eszopiclone are primarily metabolized by Cytochrome P450 3A4 (CYP 3A4) while zaleplon is primarily metabolized by aldehyde oxidase (Moltke et al., 1999; Drover et al., 2000). Hence, CSB and cognitive deficits have been reported when employing zolpidem concurrently with valproic acid, fluoxetine, fluvoxamine and trazodone as all of these medications are also metabolized predominantly by CYP 3A4 (Hwang et al., 2010).

Alcohol and other central nervous system depressants including antihistamines may also potentiate CSB (Dolder and Nelson, 2008). For example, CSB may be precipitated by the concomitant use of NBRAs with other medications including: paroxetine, trifluoperazine, aripiprazole with venlafaxine, clonazepam, alprazolam with bupropion, amitriptyline with gabapentin, doxepin, pramipexole, diphenhydramine, temazepam, and sibutramine (Paulke et al., 2014; Katz 1995; Hoyler et al., 1996; Sharma and Dewan 2005; Toner et al., 2000; Mckay and Dundee, 1980). A case report by Poceta described a 33-year-old male who had sleep driving CSB when prescribed zolpidem 31.25 mg in addition to diphenhydramine (dosage not mentioned) (Poceta, 2011). While considering possible drug interactions, the protein binding capacity of zolpidem should also be considered as medications and their metabolites such as paroxetine and sibutramine can interact by competitive binding and increase the free zolpidem concentration consequently increasing the risk of CSB (Toner et al., 2000).

***Risk factors for CSB***

The number of pharmacological and non-pharmacologic risk factors for zolpidem-associated CBS are notable: younger age; female gender; co-morbid mood disorders; co-morbid medical disorders (e.g., OSA, sleep periodic limb movements); drug interactions; concomitant use of sedatives and/or alcohol; family history and/or veteran history of parasomnias; sleep deprivation; medication noncompliance (e.g., age or disease related); higher doses of zolpidem; and zolpidem use other than at bedtime (Hwang et al., 2010; Poceta, 2011). Moreover, parenteral administration increases the incidence of memory impairment for BZDs and NBRAs (Mckay and Dundee 1980). Persons with CSB often have a positive family history of this parasomnia. Lecendreux et al. (2003) reported the association of CSB with HLA-DQB1*0501 and sleep walking, suggests that there is familial genetic risk involved in motor control during sleep. Female gender is also associated with CSB when monoaminergic drugs are prescribed. In a review of 47 case reports, Cubala and Gabrielsson (2014) found a higher risk of CSB and memory deficits in females suffering from mood disorders with concomitant use of monoaminergic medications. The gender difference is thought to be related to the lower testosterone level in women, which lowers CYP 3A4 activity (Cubala & Gabrielsson 2014). Consequently, compared with men taking the same zolpidem dose, women may have 50 percent higher blood levels of zolpidem which significantly increases the occurrence of CBS (Cubala et al., 2010).

In the above case report, the veteran arrived at the MHC clinic taking sertraline 100 mg a day, hydroxyzine 25 mg every 6 hours as needed for anxiety, zolpidem 10 mg at night for insomnia, metformin 500 mg twice a day for DM II and cholecalciferol 1000 mg a day for calcium replacement. He had been taking all these medications for greater than one year. The veteran also had several other risk factors for CSB including OSA, RLS, and DM II although he never developed sleep walking, sleep eating or other CSB symptoms after sertraline was increased to 200 mg. Drug interactions between zolpidem and sertraline are not known to increase the level of zolpidem as several CYP 450 enzymes catalyze sertraline, with CYP 2B6 contributing the greatest, with lesser contributions from CYP 2C19, CYP 2C9, CYP 3A4, and CYP 2D6 (Obach et al., 2005). On the other hand, diphenhydramine is primarily metabolized by

CYP 2D6 and CYP 1A2, while CYP 2C19, CYP 2C9 have very minimum roles. These metabolic differences minimize the possibility of a diphenhydramine and zolpidem drug interaction.

The veteran's diabetes was well controlled and he had not been using his CPAP for an extended period of time with no reported prior CSB episodes. Therefore, nocturnal hypoglycemia can be ruled out as he experienced a single sleep eating, sleep walking episode the one night he used zolpidem 10 mg and diphenhydramine 25 mg together. Notably, he had not used the hydroxyzine for anxiety for greater than one week before this sleep eating/walking related episode. Thus, the combination of zolpidem 10 mg and diphenhydramine 25 mg appears to have been the cause of the CSB related episode based on the veteran's history: no past history of similar episodes in spite of taking zolpidem 10 mg for 1 year; no prior CSB family history; no alcohol or drug use; no associated interaction with sertraline increase to 200 mg; and no additional CSB episodes when diphenhydramine 25 mg was stopped. Diphenhydramine is well known to affect all of the sleep stages, with depressed REM sleep and increased sleep spindles, which also adds support to the risk of the medication combination of zolpidem 10 mg and diphenhydramine 25 mg increasing the risk of sleep eating related episodes and CSB in general.

***Management strategies***

Literature supports the discontinuation of the CSB precipitating agent as the best strategy to manage CSB episodes (Tsai et al., 2007). As CSB appears to be dose-dependent, using lower doses, implementing sleep hygiene education and cognitive behavior therapy for insomnia (CBT-I) may also be beneficial (Sivertsen et al., 2006). Other strategies include utilizing high dosage of caffeine. Four cups of caffeine beverages may partially reverse the effect of adverse effects of zolpidem (Cysneiros et al., 2007). In one case series cannabidiol (CB) 75-300 mg/day improved CSB associated with REM sleep behavior disorder in Parkinson's disease possibly as CB1 receptors are widely present in brain areas controlling our sleep (Chagas et al., 2014).

When prescribing NBRAs, clinicians need to be vigilant of any adverse medication interactions and other non-pharmacological risk factors of sleep-related CSB. Among the NBRAs, zolpidem has been identified as the most frequent CSB precipitant, with zopiclone, eszopiclone, and zaleplon less frequent causal agents (Ferentinos and Paparrigopoulos, 2008; Liskow and Pikalov, 2004). Zolpidem's higher affinity for $\alpha_1$ $GABA_A$ and its widespread use may also be associated with its prominent role in CSB.

**Conclusion**

CSB associated with the prescription of BZDs and NBRAs has many pitfalls including medico-legal consequences. Due to medication induced memory deficits, patients may not report CSB unless specifically asked about this important adverse effect of zolpidem and other hypno-sedatives. When prescribing zolpidem, concomitant medications need to be reviewed thoroughly to minimize drug-drug interactions, especially with CNS depressants. Zolpidem should be avoided or used in low dosages for high-risk CSB groups. Along with patient education, involving the patient's family members and educating them about zolpidem and other hypno-sedative adverse effects may be beneficial.

**Conflict of interest**: None

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