Case Report of Zolpidem Dependence with Daytime and Nighttime Use

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Abstract
Insomnia disorder is the most prevalent sleep disorder, diagnosed when there is difficulty getting to sleep and/or staying asleep, with distress regarding sleep issue and/or daytime impairment. Zolpidem (Trade name Ambien) is the most commonly prescribed sleep medication which has been shown to be effective for treating insomnia on a short-term basis with fewer side effects than traditional benzodiazepines. There is indication that for some people zolpidem can have an anxiolytic effect at higher doses. It has also been demonstrated in case reports that increasing the dose of zolpidem for sleep can lead to withdrawal side effects during the daytime. We present a case of a patient with escalation of zolpidem dose for the treatment of insomnia with daytime use for symptoms of anxiety and subsequent withdrawal seizure upon abrupt discontinuation.

ABBREVIATIONS
CBTI: Cognitive Behavioral Therapy for Insomnia

INTRODUCTION
Insomnia disorder is the most prevalent sleep disorder, diagnosed when there is difficulty getting to sleep and/or staying asleep, with distress regarding sleep issue and/or daytime impairment [1]. Zolpidem (Trade name Ambien) is the most commonly prescribed sleep medication, with 39 million prescriptions written in the United States in 2011 [2]. It has been shown to be effective for treating insomnia on a short-term basis with fewer side effects than traditional benzodiazepines [3]. However, increased attention has been directed to the potential adverse effects of zolpidem [4,5]. Cases have been reported of zolpidem abuse and subsequent seizure withdrawal [6,7]. There is some indication that zolpidem can have an anxiolytic effect at higher doses and that with increasing dose of zolpidem for sleep can lead to withdrawal side effects during the daytime [8, 9]. We present a case of a patient with escalation of zolpidem dose for the treatment of insomnia with daytime use for symptoms of anxiety and subsequent withdrawal seizure upon abrupt discontinuation.

CASE PRESENTATION
The case is a 37 year-old Caucasian man who presented to the sleep clinic with a complaint of sleep difficulties for over 10 years. Psychiatric history was positive for generalized anxiety disorder (GAD) and insomnia disorder. He was not in treatment for GAD and had no history of suicidal ideation. Polysomnography had ruled out co-morbid sleep disorders. He denied use of alcohol, tobacco or illicit substances. He initially reported taking zolpidem nightly for many years, and over time, increased his dose to a reported 20mg. He had tried other medications, such as mirtazapine (next-day “hang-over”), eszopiclone (limited efficacy, metallic taste) and trazodone (limited efficacy). He was interested in cognitive behavioral therapy for insomnia (CBTI), to learn alternative ways to manage his insomnia symptoms. CBTI is a multicomponent treatment that includes cognitive therapy, behavioral treatment modifications, and relaxation techniques [10].

The patient started CBTI and he complained of dependence on zolpidem, with difficulty initiating and maintaining sleep without it. He reported significant sleep-related anxiety. He was instructed on how to taper the sleep medication and replace with cognitive and behavioral strategies. Over the course of 5 CBTI sessions, he demonstrated continued non-adherence to the CBTI cognitive recommendations (i.e. cognitive restructuring, re-framing, worry-time) and behavioral recommendations (i.e. stimulus control guidelines, sleep restriction), and unbeknownst to the treating provider had increased his zolpidem to taking 60-80mg nightly. In order to take such high doses, he had found an on-line supplier that would provide him unlimited supplies without a prescription.

He discontinued CBTI treatment after 5 sessions and 3 months later presented at a local emergency room after a “zolpidem-withdrawal” seizure due to acute withdrawal from being unable...
to obtain medication from his online supplier. The patient admitted to increasing his nightly usage, and additional usage of zolpidem (initially a one-time dose in the morning which he described made him feel somewhat euphoric, and was now up to 15-20 mg 2-3x a day) during the day. He denied suicidal intention with the dose escalation. He had noted that using zolpidem for sleep initiation helped to diminish his sleep-specific anxiety, and generalized usage to his non-specific anxiety in the morning. He described an increase in his perceived daytime anxiety as feeling jittery, tremulous and nervousness. He reported zolpidem helped him feel relaxed, better able to engage in daily activities because of decreased anxiety.

During hospital admission, the patient was provided a cross-taper from zolpidem to diazepam. The emergency room physicians contacted treating providers to inform them of the situation. Following discharge from the hospital he followed up for a CBTI appointment, where he reported the above history. He was referred to a specialist in addiction psychiatry and support services.

The patient currently remains in an intensive outpatient treatment program. As of this writing, he has successfully tapered and been without medication for about nine months. He is surprised to find that his sleep without medication is the same as it was when he was taking zolpidem. He reports attempting to implement healthy sleep habits as learned in CBTI, but admittedly is focusing more on his substance use disorder and generalized anxiety.

**DISCUSSION**

Zolpidem is of a newer class of medications, called the “z-drugs” (including zolpidem, eszopiclone and zaleplon) which have gained quick popularity, due to the presumed improved safety profile observed with these medications. The older classes of sedative hypnotic medications, benzodiazepines and barbiturates, work by increasing the major inhibitory neurotransmitter g-aminobutyric acid (GABA) within the brain [11]. Benzodiazepines and the z-drugs are active at GABA_a receptors, which are made up of a, b, g subunits. Research completed in mice has demonstrated that different a subunits have different actions; for example, the a1 subunit is responsible for sedation, a2 is anxiety while a5 is responsible for the development of benzodiazepine tolerance [11,12]. Zolpidem is thought to be selective to a1 receptors, but also has some action at a2, 3, and 5 receptors, which may increase at higher doses [12]. Though the potency of zolpidem for a1 is much greater than for other receptors, it may be that at higher doses, zolpidem overwhelms the a2 receptors, creating the anxiolytic effect which may explain initial daytime use of zolpidem for the above case [8]. Indeed, zolpidem has been found to have intoxicating effects similar to pentobarbital or alcohol, such as feeling “high,” “good effects,” or “loose,” particularly at a supratherapeutic dose [13]. We theorize the patient initially experienced this effect when he was taking a one time morning dose of zolpidem. We posit that what occurred later for this patient is that at the higher nightly doses, he developed dependence, tolerance and withdrawal, and what he perceived to be increased daytime symptoms of anxiety actually represented withdrawal symptoms. Withdrawal symptoms from zolpidem can include insomnia, anxiety, delirium, tremor, palpitations, and seizures [5]. The a1 subunit has also been associated with dopaminergic reward pathways, suggesting that even the more-selective z-drugs can have an addictive component [11].

A collection of other case reports have described similar stories of dose escalation and withdrawal [7-9,14-16] and others have reported similar daytime use for the curbing of morning anxiety [8]. In this case, we hypothesize that the patient was using zolpidem to initially treat his insomnia and sleep related-anxiety which he found useful and generalized to morning use to treat his daytime anxiety given he experienced an intoxicating like effect. Over time, he increased his nighttime dose thus developing dependence and daytime withdrawal symptoms, which he perceived as increased anxiety, and which increased his self-medicating with zolpidem during the daytime. His zolpidem use led to a cycle of dependence.

After the hospitalization and taper off of the zolpidem he ultimately relied on the cognitive and behavioral techniques that he had learned and has found that he sleeps as well as he did previously. Prior research utilizing CBTI to support tapering sleep medications has shown higher remission of insomnia when medication discontinuation is integrated with cognitive and behavioral interventions; this benefit is thought to be due to the patient attributing benefit to new psychological tools rather than the medication itself [17]. It is our hope that this patient continues to implement strategies he learned from CBTI treatment and refrains from future zolpidem use.

**REFERENCES**


