Chapter 13
Zolpidem: The Arrested Woman with No Recollection of Events

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Clinical History/Case

Ms. Miller was a 35-year-old married, working mother of two boys. She worked as a paralegal for a large law firm and struggled with dual responsibility-related stress. Her husband, an engineer, fell at a construction site and was at home on medical leave, which put even more pressure onto Ms. Miller to earn a good salary to support her family.

Ms. Miller, who has no prior personal or family history of psychiatric or sleep disorders, saw her primary care physician (PCP) with complaints of stress and initial insomnia. Her PCP prescribed zolpidem 5 mg, one to two pills at bedtime as needed, when she could not fall asleep. The next evening, Ms. Miller took two zolpidem pills (5 mg each) for the first time in her life at around 11:00 p.m. At about 11:20 p.m., she was in her bed and asleep, as per her husband. The next morning at about 8:00 a.m., Ms. Miller awoke and found herself in police custody at the local police station with no recollection of how she got there.

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She was informed that she was driving while intoxicated at around 1:00 a.m. and hit and seriously injured a pedestrian. When police arrived, Ms. Miller was able to follow simple directions and complete the sobriety test; however, she was unsteady and fell down twice. Ms. Miller had no recollection at all the following morning of driving, injuring another person with her car, or having been arrested.

Physical Examination/Mental Status Examination

The police took Ms. Miller to a nearby emergency center (EC) for an evaluation as she convincingly insisted that she had no recollection of last night's events and mentioned that she had taken a new sleeping pill prescribed by her PCP for the first time. In the EC, Ms. Miller was cooperative and forthcoming with the examination and also requested that her husband be called. She was wearing a night gown, was disheveled, and was genuinely confused about last night's events. She exhibited no abnormal movements, and her gait was normal. She described her mood as "stressed out" and her affect was anxious. Her speech and thought processes were normal, and she stated no perceptual abnormalities and no suicidal or homicidal ideations. She was oriented to person, date, time, place, and situation, and her cognition was intact. She was able to name recent events in the popular media and was able to do serial 7 s correctly, and her abstract thinking was normal as well. She was 64 inches (162 cm) tall and weighed 115 lbs. (52.2 kg). Her BMI was 19.89 kg/m^2, and her vital signs were normal.

Results

Ms. Miller's forensic blood toxicology screen was positive for zolpidem with a level of 140 ng/mL and negative for alcohol. Her urine drug screen (UDS) showed presence of zolpidem

Table 13.1 Polysomnography of Ms. Miller

Lights out	23:30
Total recording time	530 minutes
Total sleep time	480 minutes
Sleep efficiency	90.5%
Sleep latency	10 minutes
Wake	50 minutes
Stage N1	95 minutes (19.8% of total sleep time)
Stage N2	270 minutes (56.3% of total sleep time)
Stage N3	15 minutes (3.1% of total sleep time)
REM	100 minutes (20.8% of total sleep time)

but no other drugs. Findings of brain CT scan, EKG, blood counts, and chemistries were within normal limits. Ms. Miller underwent a diagnostic polysomnography (PSG), and the results are shown in Table 13.1.

During the sleep study, Ms. Miller slept in all positions. Mild snoring but no obstructive events were noted. Oxygen saturation was maintained above 96% throughout the night, and normal REM sleep with atonia was maintained. There were no periodic limb movements seen, and EEG montage did not detect any epileptiform activity. The study documented normal sleep stage architecture, and no complex behaviors or non-REM parasomnias were noted.

Differential Diagnosis

Sleep walking and sleep-related, complex behaviors, including sleep driving or sleep eating, have been documented with zolpidem ingestion and other hypnotic sedative medications

for insomnia. Whether Ms. Miller's sleep driving and aberrant behavior is induced by zolpidem is the primary question of interest. To answer this question, we need to consider the following:

1. Personal history: Ms. Miller had no prior history of non-REM parasomnias (such as sleep walking or sleep terrors during childhood) nor did she have a history of alcohol abuse, illicit drug abuse, fever, or sleep deprivation. She did, however, have personal stress, which is one of the risk factors for zolpidem-induced sleep-related, complex behaviors (see Table 13.2). Her negative history for sleep-related behaviors and for substance use supports that Ms. Miller's sleep driving was zolpidem-related, so-called Z-drug-induced sleep-related, complex behavior.
2. Family history: Ms. Miller had no family history of any sleep disorders. Typically, in individuals with somnambulism, someone in the extended family has a positive history of non-REM parasomnias. Since Ms. Miller has no such family history, it is more likely that her sleep driving was zolpidem-induced.
3. Timing of episodes: Z-drug-induced-parasomnia starts typically within 3 hours of drug ingestion. Ms. Miller's events started at 1:00 a.m. (2 hours after her medication ingestion which was at 11:00 p.m.). This time of onset further supports Z-drug-induced-parasomnia.
4. Toxicology data: Urine and blood samples help to establish the presence of zolpidem in sleep driving cases. While urine samples can confirm the presence of the common metabolite "ZCA" (zolpidem carboxylic acid) for up to 72 hours after zolpidem ingestion, blood levels allow for timing and dose calculations, i.e., likely dose amount taken and likely time of ingestion [1, 2]. Ms. Miller's urine sample was positive, and her blood revealed a zolpidem level of 140 ng/mL, which confirms the presence of zolpidem and supports zolpidem-induced sleep-related, complex behaviors. Studies reveal that higher doses of zolpidem are more conducive of sleep-related, complex behaviors. Ms. Miller's higher zolpidem blood level also supports

that she suffered from sleep-related, complex behaviors when she was driving.

5. Sleep studies and other relevant data: Ms. Miller's PSG documented normal sleep stage architecture. PSG and other diagnostic studies, such as CT scans and brain MRIs, are not used as confirmatory tools for somnambulism unless there is a suspicion of other sleep disorders (sleep apnea) or neurological disorders. While the Food and Drug Administration (FDA) data indicates that zolpidem typically does not significantly change sleep architecture, it may decrease REM sleep, which then can cause a corresponding increase in non-REM stage [3, 4], thus placing patients at higher risk for non-REM parasomnias, including Z-drug-induced sleep-related, complex behaviors.
6. Cognitive function: As per clinic reviews of Pressman (2011), sleep driving is categorized into two conditions [5]. The first category, sleep driving, occurs as a variant of sleep walking disorder in individuals with a genetic predisposition or positive personal history of somnambulism. These individuals with such genetic predisposition are more susceptible to sleep driving when there is co-occurrence of priming factors, such as stress or sleep deprivation. During a sleep driving episode, when these typical sleepwalkers (with positive personal or family history) are confronted, they may become agitated or violent. For example, when police officers confront them, they are usually not able to interact appropriately, nor do they understand any requests or instructions, and are usually unable to perform sobriety tests [5]. The second category consists of individuals with sleep driving induced by so-called Z-drugs. These individuals usually do not have any positive family history or personal history of parasomnias. They are prone to these events when they take higher medication doses, mix medications with other CNS depressants (such as alcohol), or have other concomitant sleep disorders (such as sleep apnea). The occurrence of sleep-related, complex behaviors, such as driving, stops immediately after discontinuation of the Z-drug. Z-drug-induced sleep-related, complex behaviors differ from typical

sleep walking. Based on roadside reports during arrests, Z-drug-induced drivers typically have some degree of preserved cognitive function despite their anterograde amnesia. They are better able to interact and understand police officers' requests and can often perform sobriety tests. Unlike typical sleepwalkers, Z-drug-induced drivers were found to have flaccid muscle tone, poor motor control, dysarthria, lack of balance, and unsteady gait. These impairments are believed to be due to Z-drugs' actions on the $GABA_A$ receptor complex. Also, the degree of impairment usually correlates well to the Z-drug blood plasma level [5, 6]. In our case, Ms. Miller was able to interact and follow police officers' directions during her arrest and was able to pass the sobriety test. However, she did have some unsteadiness, fell, and also experienced anterograde amnesia. These findings are compatible with Z-drug-induced sleep-related, complex behaviors.

Final Diagnosis

Ms. Miller's history, signs, and symptoms are compatible with Z-drug-induced sleep-related, complex behaviors and not typical non-REM parasomnia sleep walking.

Discussion

Zolpidem (Ambien®) is an FDA-approved imidazopyridine hypnotic sleep medication which has been on the US market since 1992 [1]. While it is one of the most commonly prescribed medications in the USA, it has received growing attention for sleep-related, complex behaviors, including sleep walking, sleep eating, having sex while asleep, and sleep driving. In 2007, the FDA placed a specific warning on all hypnosedative sleep medication regarding sleep-related behaviors and abnormal thinking and behaviors, such as parasomnia-like behaviors, disinhibition, aggressiveness,

mood alterations, and anterograde amnesia. The incidence of such complex behaviors is approximately 5% [1, 7].

Zolpidem has become popular since it is thought to not greatly alter sleep architecture, is believed to have low rates of daytime sleepiness and a low abuse potential, and facilitates sleep onset within approximately 30 minutes with an average peak concentration at 90 minutes. While zolpidem binds to the $GABA_A$ receptor much like benzodiazepines, zolpidem is more selective to the α-1 receptor subtype, which was believed to cause more sedation with less memory impairment and less daytime sleepiness [1].

However, patients taking zolpidem show significant memory impairments and psychomotor performance problems at 1 and 4 hours after ingestion. Zolpidem does decrease REM sleep with a corresponding increase in non-REM time, which increases the risk of non-REM parasomnias since patients spend more time in non-REM sleep. Risk factors for parasomnia (see Table 13.2) are personal or family history of parasomnia as well as sleep deprivation, stress, fever, and alcohol or drugs. Of note, the risk for zolpidem-induced sleep-related, complex behaviors is dose-related, i.e., higher zolpidem doses increase the risk [1].

It is believed that zolpidem can cause three different sleep-related scenarios [1]: (1) After taking zolpidem patients may stay awake and exhibit disinhibition and hallucinations and may speak in coherent sentences but have anterograde amnesia for events. (2) Patients may fall asleep after taking zolpidem but then arouse from sleep while still under its influence. These patients may speak coherently but usually act out of character and also exhibit anterograde amnesia. (3) Zolpidem may also induce or aggravate parasomnias, such as non-REM stages 3–4 sleep walking, with incoherent sleep and purposeless actions.

Surprisingly, zolpidem can cause persistent hallucinations and sleep-related, complex behaviors when prescribed concurrently with antidepressants [8]. While the exact cause remains unclear, the hypothesis is that both zolpidem and antidepressants suppress REM sleep, which causes a cor-

responding non-REM sleep increase. As we know, sleep walking disorder is associated with an increase in slow wave sleep (stage 3 non-REM). Thus, it is postulated that the combination of zolpidem and antidepressants can create an increased amount of slow wave sleep and can occasionally cause a rapid entry into slow wave sleep [8, 9].

There is also a proposed theory [10] postulating that zolpidem can cause desensitization of $GABA_A$ receptors. This desensitization then creates increased activity of serotonergic neurons causing some delay in compensatory decrease in serotonin release through the autoregulatory mechanism regulated by $5HT_{1A1B}$ receptors. According to this model, the delay between desensitization of the $GABA_A$ receptors and a compensatory decrease in serotonin release can create a window of time for parasomnia occurrence. If during this window a short-acting hypnotic like zolpidem is given, there is possibility of dreamlike mentation or parasomnia occurrence depending upon autoregulation of serotonin release and upon individual differences in receptor desensitization. Therefore, additional caution should be applied when zolpidem is prescribed in combination with antidepressants [10].

There are several known potential risk factors which can induce Z-drug-induced sleep-related, complex behaviors, and Z-drug-prescribing clinicians need to be familiar with such risk factors (see Table 13.2).

According to zolpidem's drug prescription information, after the ingestion of a 5-mg dose of zolpidem, a mean peak concentration of 59 ng/mL (range 29–113 ng/mL) was found, and after taking a 10-mg dose of zolpidem, a mean peak concentration of 121 ng/mL (range 58–272 ng/mL) was found. For both doses, time to maximum concentration was 1.6 hours, and the drug half-life was approximately 2.6 hours. The SSRI fluoxetine prescribed concurrently with zolpidem increases zolpidem's half-life by 17%, while sertraline increases zolpidem's half-life by 43% [11, 12].

In 2013, the Food and Drug Administration (FDA) required zolpidem manufacturers to lower the approved dose of zolpidem based on data showing that higher morning blood levels in some people caused impaired driving and alertness. Thus, the FDA recommended that manufacturers

Table 13.2 Potential risk factors for Z-drug sleep driving

Risk factors
1. Concomitant ingestion of CNS depressants (alcohol, sedating medications) or antidepressants (SSRI, SNRI)
2. Concomitant sleep disorder (sleep disorder breathing or periodic limb movement disorder)
3. Personal history of parasomnia
4. Family history of parasomnia
5. Hypnotic sedative ingestion during stressful events, sleep deprivation, or agitated state
6. Hypnotic sedative ingestion at times other than habitual bedtime
7. Living alone
8. Individuals with cognitive impairment (dementia, delirium, intellectual disability) or with a history of poor management of pills

Modified and adapted from Poceta [12]

decrease the recommended dose of zolpidem in women, elderly, and debilitated patients to 5 mg due to slower zolpidem elimination rates in those populations [13].

Zolpidem also has received considerable forensic psychiatry and courtroom attention with a growing number of patients blaming their behavior either on "the pill made me do it" or on sleep walking [1]. Criminal defendants who used alcohol and/or illegal drugs at the time of their crimes are held responsible for their actions. Courts hold that people realize that such substances can negatively impact behavior, and the legal system does not intend for people to use voluntary intoxication as an excuse to escape the consequences of criminal behavior. However, prescription medication use may be considered for an involuntary intoxication defense and may render the defendant not culpable as long as the defendant can show that he/she had no prior knowledge of adverse reactions and behaviors at the time of ingestion [1]. It is important that a defendant prove that he/she indeed took the medication and was under the influence at the time of their crime(s) by obtaining blood and urine toxicology samples at the time of arrest. While urine samples can simply prove the presence of medication(s), blood levels can reveal plasma concentration, which then allows for

calculations of likely ingested medication amounts and medication concentrations at the time of the crime(s).

If the defendant is unable to prove that he/she involuntarily ingested the medication(s), he/she may argue a case of voluntary intoxication. While this still usually renders the defendant culpable, it may lower the severity of the charges, i.e., it may negate specific intent in a murder resulting in a lesser charge of manslaughter. Since Ms. Miller suffered from zolpidem-induced sleep-related, complex behaviors and had no prior knowledge that she would react idiosyncratically to zolpidem, she may qualify for an involuntary intoxication defense, therefore, potentially rendering her not culpable for driving under the influence and hitting a pedestrian with her car.

Pearls/Take-Home Points

- Z-drugs and other hypnotic drugs can induce sleep-related, complex behaviors, such as sleep driving and sleep walking.
- Z-drug drivers may present with some preservation of cognitive and social function, may interact appropriately, follow directions, and pass sobriety tests despite of their anterograde amnesia and unsteady gait.
- Urine and blood toxicology is necessary in establishing the diagnosis. Drug levels help determining 1) the likely time of ingestion and 2) the likely Z-drug amount ingested.
- While sleep studies are not used to confirm Z-drug-induced sleep-related, complex behaviors, they can help to rule out triggers, such as sleep apnea.
- Caution when prescribing zolpidem with an antidepressant as this combination can cause persistent hallucinations and sleep-related, complex behaviors.
- Although voluntary alcohol and illicit drug intoxication still render a person responsible for their actions, persons with Z-drug-induced sleep-related, complex behaviors may argue a case for involuntary or voluntary medication intoxication.

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