Two Cases of Zolpidem-Associated Homicide

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ABSTRACT

Zolpidem is the most commonly prescribed medication for the short-term treatment of insomnia. Adverse reactions include nightmares, confusion, and memory deficits. Reported rare adverse neuropsychiatric reactions include sensory distortions such as hallucinations. Previous research has identified 4 factors that may place a patient at increased risk of zolpidem-associated psychotic or delirious reactions: (1) concomitant use of a selective serotonin reuptake inhibitor (SSRI), (2) female gender, (3) advanced age, and (4) zolpidem doses of 10 mg or higher. In this article, 2 cases are presented in which individuals killed their spouses and claimed total or partial amnesia. Neither individual had a history of aggressive behavior. Both had concomitantly taken 10 mg or more of zolpidem in addition to an SSRI (paroxetine).

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Zolpidem is the most commonly prescribed medication for the short-term treatment of insomnia. It is a nonbenzodiazepine receptor agonist with high binding affinity for the inhibitory neurotransmitter γ-aminobutyric acid. Although it is generally far safer than such alternatives as benzodiazepines and barbiturates, reported central nervous system side effects include headache, dizziness, nightmares, confusion, depression, sleepiness, and memory deficits.[1,2] A 3-year postmarketing study of 1,972 patients found that 1% reported confusion and/or delirium and 0.3% reported illusions and/or hallucinations.[3]

Reported adverse neuropsychiatric reactions to zolpidem include hallucinations, sensory distortions, delirium, amnesia, and complex behaviors such as nocturnal eating, sleep driving, and somnambulism with object manipulation.[4–15] The duration of such phenomena is generally very brief. However, Katz[9] described a patient who hallucinated for approximately 4 hours after her first dose of zolpidem (10 mg). Elko et al[7] reported that 5 patients experienced 1- to 7-hour episodes of hallucinations shortly after taking zolpidem, and Inami et al[13] related that a 31-year-old woman experienced visual hallucinations that persisted for 6 days after taking zolpidem and paroxetine.

Hill et al[16] described a 67-year-old woman with no history of psychiatric illness who began taking zolpidem 10 mg. After 4 weeks, she began to exhibit increased agitation, rapid speech, and confusion. Four days before being taken to an emergency room, she began to exhibit paranoia. In the emergency room, she said that the US Federal Bureau of Investigation was watching her and that the evaluating psychiatrist could kill her and her daughter.

The above-referenced authors[5,7–13,15,16] identify 4 factors associated with increased risk of zolpidem-associated psychotic or delirious reactions: (1) the concomitant use of a selective serotonin reuptake inhibitor (SSRI), (2) female gender, (3) advanced age, and (4) zolpidem doses of 10 mg or higher. Toner et al[2] reviewed 17 cases of zolpidem-associated hallucinations and found that 58.8% of individuals were also taking an SSRI and 82.4% were female.

We present 2 cases of individuals in whom concomitant zolpidem and paroxetine use was associated with uncharacteristic, complex acts of violence for which they claimed total or partial amnesia. Neither individual had a history of aggression before killing his or her spouse; both most likely took more than 5 mg of zolpidem on the nights of their offenses.

CASE 1

Mr A was a 45-year-old, employed, hospital worker. The first and second authors (C.M.P. and L.A.S.) were retained by defense counsel to assess his mental state at the time of the offense. Mr A had 2 prior major depressive episodes. The first occurred at age 18 years, after graduating from high school, and the second, a few years later, after separating from his first wife. Antidepressant medications were ineffective, and Mr A required psychiatric hospitalization and treatment with electroconvulsive therapy (ECT). Each depressive episode fully resolved.

Mr A had no history of substance abuse disorder, arrests, known commission of domestic violence, or known serious marital problems. He had no history of acting violently, although he was described by some as self-centered, argumentative, and easily angered.

Clinical Points

- Zolpidem has been associated with adverse neuropsychiatric reactions, including hallucinations, sensory distortions, delirium, and amnesia.
- Gender, age, concomitant use of selective serotonin reuptake inhibitors, and zolpidem dose are factors that may increase the risk of adverse reactions.
- Patients taking zolpidem should be monitored for adverse reactions, and zolpidem should be considered as a potential contributing factor in instances of uncharacteristic, seemingly motiveless violence when accompanied by combinations of psychosis, amnesia, and confusion.

At the time of the offense, Mr A was living with his wife and their 13-month-old daughter in the upstairs apartment of his parents' house. After the baby's birth, he began working the night shift to earn extra money. Mr A developed an agitated depression with insomnia approximately 6 months following the birth of his child. The onset may have been precipitated by the stress of parenting and/or the change in his sleep-wake cycle. Mr A took medical leave from his job a week before he killed his wife.

Mr A's depression was severe and included intermittent psychotic (particularly paranoid) symptoms. At times, he believed people could read his mind and that his ex-wife could influence him through mind control. He sought psychiatric treatment 1 month before the offense. The psychiatric consultation note related that he was "ruminating" about his ex-wife and indicated the diagnosis of major depressive disorder. Initially, Mr A was prescribed paroxetine extended release (ER) 12.5 mg daily and lorazepam 1 mg twice daily as needed. The next week, his paroxetine ER dose was raised to 25 mg daily. In the third week, zolpidem 10 mg and quetiapine 25 mg daily were added. Mr A's symptoms, however, did not remit. The following week, his quetiapine dose was increased to 100 mg, and his paroxetine ER dose was increased to 37.5 mg daily. Mr A was also referred to another psychiatrist for assessment for treatment with ECT. His wife preferred that the treatment be performed on an outpatient basis.

Mr A received 1 ECT treatment 3 days before the homicide. During the next few days, family members reported that he was pacing all night and unable to sleep. They described him as agitated and distraught, but not delirious.

Mr A reported having only fragmentary memory of the hours before the killing. He recalled that his wife gave him his usual nighttime medications, including zolpidem 10 mg. He was unable to fall asleep, and she gave him an extra pill, presumably zolpidem, around 1:30 AM. "The next thing I remember," he said, "was awaking in a wheelchair. I didn't know where I was. I asked the doctor why I was handcuffed." He had stabbed his wife more than 20 times. In conjunction with his lack of known history of violence, the ferocity of the attack underscored the highly uncharacteristic nature of his behavior.

There are several indications that Mr A was confused for many hours after the killing. He remained in his apartment with his wife's body for approximately 12 hours. When he came downstairs the next day, family members recalled he was mumbling incoherently and appeared "catatonic" with "glassy" eyes.

Mr A was questioned while being videotaped hours after being taken into custody. He was unshaven and barely responded to questions. He stared blankly ahead, mumbling, "I need help. I need help." The assistant district attorney could obtain no information and terminated the interview.

No testing for zolpidem or quetiapine blood levels was performed in the emergency room where Mr A was taken approximately 2 days following his arrest. Emergency department records indicate that he was "acting irrationally" and appeared to be "responding to internal stimuli." Approximately 2 years after the offense, after suffering a seizure in court, the patient underwent a lumbar puncture, magnetic resonance imaging scan, and computed tomography scan. No pathology was detected.

This article's first and second authors (C.M.P. and L.A.S.) diagnosed Mr A with major depressive disorder with psychotic features (*DSM-IV* criteria) and concluded that his violent behavior and amnesia were linked to his use of zolpidem. The prosecution-retained psychiatrist also diagnosed Mr A with major depressive disorder but concluded that the defendant was malingering amnesia.

The first and second authors testified at the trial that Mr A's mental state satisfied New York State's criteria for lack of criminal responsibility due to mental disease or defect. The prosecution-retained psychiatrist testified otherwise, opining that Mr A killed his wife because of "acute stresses" and underlying personality features.

After a few hours of deliberation, the jury found Mr A guilty of murder in the second degree. The presiding judge sentenced him to 25 years to life in prison.

CASE 2

Ms B was 62 years old when she killed her husband by hitting him several times on the head with a metal pipe and then placing a plastic bag over his head. The third author (S.B.K.) was retained by defense counsel to assess her mental state at the time of the offense. Ms B's psychiatric history consisted of a relatively brief period of minor depression that resolved after separating from her first husband, whom she described as verbally abusive, and brief counseling.

Ms B subsequently remarried. Collateral interviews revealed a consistent portrait of Ms B as affectionate and conscientious. Her marriage was described as loving, and she and her husband were viewed as "the ideal couple." No evidence of domestic violence was uncovered.

A few months before he was killed, Ms B's husband suffered a stroke that left him with significant cognitive and physical deficits. His deficits did not resolve, and Ms B became anxious and mildly depressed, with moderately severe insomnia.

Ten days before the offense, Ms B's internist diagnosed her with anxiety unspecified and prescribed paroxetine 10 mg daily, which she began taking 5 days later. When her insomnia did not resolve, the physician added zolpidem 10 mg nightly, which Ms B reported beginning 3 days before the offense. The night before she killed her husband, Ms B took 2 or 3 10-mg pills of zolpidem because, she explained, the prescribed amount had not relieved her insomnia the prior 2 nights. Ms B took 1 or more additional zolpidem pills later that night or in the early morning because, she stated, she still "couldn't sleep."

Ms B reported possessing only dream-like fragments of memory for the events surrounding the killing. She stated that she specifically remembered standing in the garage of her house while holding a metal bar and hitting her husband in their bedroom with the bar. She did not, however, recall entering the bedroom or placing a plastic bag around his head. She further remembered that, at some point, she touched her husband's cold hand and realized he was dead. She did not clearly recall when she touched him or how many hours had passed.

Ms B remained in her home for approximately 24 hours after the homicide. Friends who spoke with her via telephone that day described her as disturbed and confused. One individual recalled that she sounded "bizarre . . . like [she was] not there," and spoke in a slow "broken" manner. One friend wondered whether Ms B had suffered a stroke or heart attack. Another friend was so concerned that she and her mother visited Ms B's house. They called 911 after discovering Ms B in the bathtub holding a knife to her throat.

Ms B reported taking "a lot of pills" and cutting her wrists after she realized that her husband was dead. Paramedics discovered empty prescription bottles for paroxetine and zolpidem. Each originally contained 30 pills. In the emergency room, probably more than 24 hours after the offense, Ms B declared that she had killed her husband with a crowbar and wished to die. She did not conceal her responsibility for the killing.

Ms B exhibited multiple signs of delirium. She was described as disoriented in the emergency room. Police officers who were summoned to her home described her as displaying a fluctuating level of consciousness and cognition.

Ms B told police at her home that she had killed her husband only a few hours earlier. Particularly strikingly, she confused her husband's name, at least once calling him by her first husband's name. Supporting the presence of confusion or psychotic-like phenomena, Ms B delusionally told police, "He wanted me to shoot him. But I didn't have a gun, so he told me to get the crowbar for him. He tried to hit himself but couldn't, so he asked me to." Investigation revealed there was no basis to believe that her husband wanted to die.

The third author (S.B.K.) further noted the presence of dissociative features at the time of the offense. Ms B described feeling emotionless, like in "a dream," and perceived the events unfolding as "something that wasn't real." She recounted her actions as automaton-like, both during and after assaulting her husband. Additionally, Ms B described experiencing memory disturbances, specifically anterograde deficits and fragmentary recall, which commonly characterize genuine delirium. Her memory disturbance caused her to possess a discontinuous, episodic sense of events. Her inaccurate recollections were best understood as representing, at least in part, unwitting efforts to impose some type of logical order upon permanent gaps in her recall of time and space, ie, as confabulations.

Malingering of amnesia was considered and excluded. The following factors support this conclusion: (1) the form of her lack of recall was consistent with how genuine amnesia manifests, (2) the content of such was consistently reported, (3) she reported recalling information that was not legally self-serving, and (4) she did not display evidence of psychopathy.

The third author (S.B.K.) diagnosed Ms B with major depression and delirium not otherwise specified (*DSM-IV* criteria) acutely induced by excessive zolpidem use. He believed that Ms B's agitation, "islands of lucidity," and (emotional) dissociation emanated from her delirium. He concluded that she had lacked substantial capacity to appreciate the wrongfulness of killing her husband.

The prosecution-retained psychiatrist reached a different conclusion. He opined that Ms B had acted under extreme emotional disturbance and was responsible for killing her husband. In New York State, an affirmative defense of extreme emotional disturbance lowers the charge from murder to manslaughter. Ultimately, Ms B was offered and accepted a plea to the charge of manslaughter in exchange for a sentence of 6 years. She was paroled after serving 4 1/2 years.

DISCUSSION

Although zolpidem is generally both safe and effective, studies and case reports suggest that zolpidem in rare instances produces adverse neuropsychiatric phenomena, including manifestations of memory disturbance, delirium, and psychosis. In the 2 cases presented here, the evaluees violently killed a spouse and reported being totally or partially amnestic for such. Both, notably, had concomitantly taken 10 mg or more of zolpidem and an SSRI, ie, paroxetine. Both possessed previously suggested risk factors for developing zolpidem-associated adverse reactions.

In the first case, 4 weeks before the offense, paroxetine ER was prescribed for severe depression with psychotic features, and 2 weeks later, zolpidem and low-dose quetiapine were added. No rational motive for the homicide could be

discerned; Mr A had no history of violence, and there was no evidence of domestic violence or serious marital problems. He claimed total amnesia for the killing.

We considered whether the 1 ECT treatment contributed to Mr A's violent behavior or amnesia. ECT is associated with both retrograde and anterograde memory deficits,[17] as well as with confusion and agitation. These effects are generally short-lived, and ECT has not been linked with the type of complete amnesia and organized, uncharacteristic behavior exhibited by Mr A.[17–20] Such treatment, however, might have rendered him particularly vulnerable to adverse effects from zolpidem. Hoyler et al[21] reported on a 61-year-old woman who, 48 hours after her last of 7 ECT treatments and 1 hour after taking 10 mg of zolpidem, experienced agitation, disorientation, tangential thinking, and loose associations.

In the second case, Ms B also had no apparent rational motive for killing her husband. She had been taking paroxetine for 10 days and zolpidem for 3 days before the offense because she was experiencing mild depression, anxiety, and insomnia. Her behavior was grossly discordant with her character and the reported/observed nature of her marital relationship. The prosecutor described the case to the press as one with no apparent motive.

Previous reports have linked zolpidem-associated adverse neuropsychiatric reactions with female gender, elderly age, concomitant use of SSRIs, and dosages of 10 mg or more.[2,4,9,14,22] Delirium and hallucinations have never been reported in patients taking 5 mg or less of zolpidem.[2,4,9] Both individuals described here were prescribed a 10-mg dose but reported being unable to sleep and taking extra doses the nights of their offenses. Mr A recalled that his wife gave him his nightly zolpidem dose and then later extra medication, but he could not remember whether the extra pill was zolpidem. The authors could not definitively determine which medication he received, but circumstances strongly suggest that it was zolpidem. If so, Mr A ingested 20 mg of zolpidem the night of his offense. Ms B clearly recalled taking 2 10-mg tablets of zolpidem. She may have taken more.

Ms B was 62 years old when she killed her husband. Women, particularly elderly women, may be more susceptible to having zolpidem-associated adverse reactions.[2,11] At equivalent dosages, women have been found to have higher serum zolpidem concentrations than men.[2,23] Salvà and Costa[23] reported that after administration of equivalent zolpidem doses, women had higher serum zolpidem concentrations than men of a similar age. Serum concentration was 45% higher in young women and 63% higher in elderly women.[23]

The role of blood levels in the assessment of zolpidem-associated adverse reactions is currently unknown. Daley et al[24] recommend that, in criminal cases in which zolpidem-associated adverse neuropsychiatric effects are suspected, forensic experts should obtain toxicologic analyses. These analyses may determine the time and amount of the last zolpidem dose and whether other medications were prescribed.

There are several limitations to consider. Our conclusions are based on a study of 2 cases, not controlled clinical trials. We were retained by defense counsel, which could be a source of bias. There are alternate explanations for the behaviors of Mr A and Ms B. It is possible that they intentionally misrepresented their mental states at the time of the offense. It is also possible that the zolpidem was unrelated to the acts of violence but did cause their impaired memory. Their aggression may have been related to psychiatric illness or stress. Mr A's behavior could have resulted from a worsening psychotic depression that was not recognized or adequately treated rather than the addition of zolpidem. It is also possible that these 2 individuals had some unrecognized, underlying medical vulnerability to adverse effects. Many individuals who are prescribed zolpidem suffer from a depressive and/or anxiety disorder. The authors are unaware of any studies or controlled clinical trials investigating zolpidem-associated adverse neuropsychiatric effects among those with major depression with psychotic features or those receiving ECT.

Both of the individuals were also taking paroxetine. Previous cases of SSRI-induced aggressive behavior have been reported, and the pharmaceutical companies include warning labels with antidepressants about the risk of suicide and violence.[25] Another factor to consider is pharmacodynamic drug-drug interactions. Conjoint use of paroxetine and zolpidem, because both are highly protein bound, may elevate free zolpidem blood levels. SSRIs may displace zolpidem from the transport protein, thus increasing the risk of related adverse effects.[2,22]

In a LexisNexis search for legal cases associated with zolpidem use, Daley et al[24] found 7 violent crimes, including at least 1 shooting homicide. They found 10 driving-related incidents, including at least 1 case of vehicular manslaughter.[24] We are not aware of any other reports of zolpidem-associated homicides. Because of the prevalence of zolpidem use, it is reasonable to consider whether the drug may have contributed to other acts of violence.

Treating and evaluating professionals should be aware that zolpidem has been associated with adverse neuropsychiatric reactions. Gender, age, concomitant use of SSRIs, and zolpidem dose are factors that may increase the risk of adverse reactions. Notably, both of the individuals discussed here experienced adverse reactions early in the course of their use of zolpidem, Mr A after a week and Ms B after 3 days. Elko et al[7] reported that, in most of the 5 cases they examined, patients began taking zolpidem less than a week before developing visual hallucinations. Surveillance for development of zolpidem-associated neuropsychiatric difficulties should probably be especially heightened following its initiation or when prescribed in combination with an SSRI. Because zolpidem may produce anterograde amnesia, evaluation should include questioning of family members about unusual nighttime behaviors. Zolpidem use should be examined as a potential contributing factor to an individual's actions in instances of uncharacteristic, violent outbursts accompanied by manifestations of psychosis or delirium.

Drug names: lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), zolpidem (Ambien, Edluar, and others).

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