

# “I Did What?” Zolpidem and the Courts

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Zolpidem is a widely prescribed nonbenzodiazepine hypnotic medication available in the United States since 1992. Attention has been drawn recently to its potential to cause sleep-related, complex behaviors such as sleepwalking and sleep driving. These automatic behaviors have led to a deluge of legal claims. To the authors' knowledge, this is the first review in the forensic literature of the legal ramifications of zolpidem. In this article, the medical literature will be reviewed to explore the current understanding of zolpidem's specific psychopharmacology. Case law will be explored to determine how the courts have handled the claims surrounding sleep-related, complex behaviors alleged to be caused by zolpidem. Finally, a summary of recommendations will be provided for forensic psychiatrists who are asked to be experts in these cases.

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A young adult with no prior history of psychiatric illness used zolpidem once a week to fall asleep. One night, she took a shower after her dose of zolpidem and went to sleep later than her usual time. She woke up with a garden axe on her nightstand with no memory of how it got there. Later she scrolled through her text messages from the night before and discovered a conversation that she had had with her partner after her shower. She had no memory of writing the text messages. In them, she described to her partner hearing voices from her kitchen and seeing moving images out of the corner of her eye. Concerned for her safety, she had gotten the axe from the tool shed and placed it on her nightstand. (This is a composite description.)

## Background

Zolpidem is an imidazopyridine hypnotic agent that is approved by the U.S. Food and Drug Administration (FDA) for the short-term treatment of insomnia in the United States.<sup>1</sup> It has been on the U.S. market since 1992, sold under the trade name Am-

bien by the French company Sanofi-Aventis. Ambien has been widely prescribed, ranking as the ninth most prescribed medication in the United States in 2006, with more than 20 million prescriptions,<sup>2</sup> grossing nearly 2 billion dollars in sales<sup>3</sup> that year alone. In 2007, Ambien's patent protection expired, and zolpidem became available as a generic medication manufactured by 13 different companies.<sup>4</sup> Zolpidem remains a top prescribed medication, with more than 28 million prescriptions written in 2008, ranking as the 16th most prescribed generic medication that year,<sup>5</sup> with gross sales of over \$700 million.<sup>6</sup> These figures do not include the ongoing sales for Ambien CR (controlled release), which had more than 7 million prescriptions in 2008.<sup>7</sup>

Zolpidem is one of 13 hypnotosedative medications approved by the FDA for treatment of insomnia,<sup>8</sup> although by far it has been the most prescribed hypnotosedative over the past decade. Its popularity is the likely result of aggressive marketing<sup>9</sup> and early reports of low rates of daytime sedation and low abuse potential.<sup>10</sup>

However, postmarketing studies and case reports began to show that zolpidem was associated with sleep-related, complex behaviors. These included sleep driving, sleep cooking, sleep eating, sleep conversations, and, rarely, sleep sex, generally accompanied by anterograde amnesia for the event.<sup>8</sup> As these behaviors became recognized, the FDA requested that specific warnings be put on all hypnotosedative

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medications. This regulation took effect in March 2007<sup>11</sup> and was widely publicized.

The sleep-related, complex behaviors associated with zolpidem have been the basis of two legal strategies of interest in the forensic psychiatry arena: the concept of “the pill made me do it” and the sleep-walking defense. Discussions with colleagues confirm that many cases have arisen where a history of zolpidem treatment is used as a means to influence criminal or civil liability. Psychiatrists are frequently consulted by attorneys to assess the credibility of these allegations.

To the authors' knowledge, this is the first published review in the forensic psychiatry literature of the legal ramifications of zolpidem use. In this article, we review the medical literature that describes the pharmacologic properties specific to zolpidem that are associated with its potential to cause sleep-related, complex behaviors. We examine appellate level cases involving zolpidem, to illustrate how the courts have applied the current scientific knowledge in contemporary cases. We use these examples to formulate recommendations to assist experts who are consulted on such cases.

## Methods

A PubMed search was conducted using the keyword zolpidem, along with complex behaviors, sleep-walking, driving, eating, parasomnias, memory, forensic, legal, amnesia, violence, and aggression. The search returned dozens of articles. Representative articles were selected for review. The search included articles through January 2010.

A Lexis-Nexis search was conducted using the keyword zolpidem or Ambien, along with involuntary intoxication, voluntary intoxication, criminal responsibility, negligence, and malpractice. The search included cases through January 2010. An additional Lexis-Nexis search was performed to explore benzodiazepines for comparison cases using the keywords benzodiazepine, clonazepam, Klonopin, diazepam, Valium, alprazolam, Xanax, triazolam, or Ambien, along with criminal responsibility, voluntary intoxication, involuntary intoxication, negligence, and malpractice. The Lexis-Nexis database contains federal district court, appellate, and Supreme Court cases. The database also covers state and appellate level and Supreme Court cases. State level district court cases are not included in the database and were not reviewed for this article.

## Medical Literature

### Pharmacology

Zolpidem is a member of a newer class of hypnosedative drugs known as nonbenzodiazepine receptor agonists (NBRAs). NBRAs available in the United States include zolpidem, eszopiclone, and zaleplon. These medications bind to the same GABA<sub>A</sub> receptor complexes as the benzodiazepines, but are more selective to the  $\alpha$ -1 receptor subtype.<sup>8,12</sup> Six different  $\alpha$ -receptor subtypes are currently known. Agonism of the  $\alpha$ -1 receptor type is believed to result in sedation and amnesia. The other receptor types have anxiolytic, anticonvulsant, and muscle relaxant properties.<sup>8</sup> The selectivity of zolpidem for the  $\alpha$ -1 subtype was believed to confer more specific sedative properties along with less memory impairment and less residual daytime sedation, when compared with benzodiazepines.<sup>13</sup> Clinical studies of zolpidem have shown significant impairments in memory and psychomotor performances at one and four hours after ingestion.<sup>14</sup>

Zolpidem is rapidly absorbed in the gastrointestinal tract, with onset of action of approximately 30 minutes and average peak concentration at 90 minutes. When compared with most hypnosedatives, it has a short half-life, two to three hours. It is metabolized by hepatic metabolism by CYP 3A4 enzymes. Drug-drug interactions are possible with medications that affect 3A4 enzymes such as ketoconazole.<sup>1</sup> When compared with other hypnosedatives, zolpidem has a high binding affinity for the GABA<sub>A</sub> receptor. This property is similar to that of triazolam,<sup>8</sup> a benzodiazepine that gained notoriety in the early 1990s because of its association with aberrant behaviors, culminating with its removal from European markets and a successful product liability suit in the United States (*Freeman v. Upjohn Co.*, No. 89-09648-A (Tex. Dist. Ct. 1992)).<sup>15</sup>

### Adverse Drug Reactions

The FDA's prescribing information for zolpidem lists a variety of abnormal thinking and behavioral changes that can be associated with it and other hypnosedatives. These include disinhibition (extroversion or aggressiveness that seem out of character), depersonalization, hallucinations, and alterations in mood. Anterograde amnesia is also frequently reported with zolpidem. Complex, parasomnia-like behaviors have also been reported, such as driving,

talking, eating, and engaging in sex.<sup>1</sup> Postmarketing studies of zolpidem found the incidence of complex behaviors to be low, occurring in less than one percent of cases, although a recent case series found it higher, at five percent.<sup>16</sup> The incidence of hallucinations with zolpidem is reported to occur in less than one percent of patients.<sup>1</sup> Because these behaviors are accompanied by amnesia, it is likely that they are underreported.

#### *Sleep-Related Eating*

Sleep-related eating behavior has been associated with zolpidem. A case series from the Mayo Clinic described five patients who exhibited new-onset or worsening of sleep-related eating after initiation of zolpidem.<sup>17</sup> In these cases, the patients all had comorbid sleep disorders. In most but not all cases, patients were amnesic for the nocturnal eating. Weight gain of 50 pounds over a one-year period was described in a separate case of zolpidem-related sleep eating.<sup>18</sup> Amnesia and the appearance on the next day of a messy kitchen were reported in another case.<sup>19</sup> A theory presented in these cases is that zolpidem may aggravate underlying sleep pathology leading to nocturnal eating.

#### *Sleep Driving*

Incidents of sleep driving have been described in association with zolpidem.<sup>20</sup> A case series reviewed the clinical appearance of drivers convicted of driving while under the influence (DUI), with zolpidem found on toxicology analysis. In those drivers using only zolpidem, symptoms included slowed or slurred speech, disorientation, poor coordination, and blacking out.<sup>21</sup>

#### *Other Behaviors*

Other complex behaviors reported in the medical literature include manipulating objects (e.g., putting gas in a lawnmower), cleaning the house, and engaging in conversations and sex.<sup>8</sup> One case report described a patient who wrote an e-mail two hours after ingestion of zolpidem. She had no recollection of the e-mail the next day. She was able to input her username and password to log on. The e-mail, however, contained odd grammar, format, and punctuation.<sup>22</sup> Although sleepwalking has been associated with violence and murder,<sup>23</sup> the present review of the medical literature identified no reports of any such incidents associated specifically with zolpidem.

#### *Etiology*

It is helpful to conceptualize distinct mechanisms to explain these abnormal behaviors. A patient may inadvertently (or intentionally) remain awake after taking zolpidem and begin to experience disinhibition or hallucinations with associated anterograde amnesia. These patients typically retain the ability to speak in short, coherent phrases.<sup>14</sup> Le Bon and Neu<sup>24</sup> reported a case of a woman who had a conversation with her boyfriend about their relationship 45 minutes after ingesting 10 mg of zolpidem. She had no recollection of the conversation the next day. The boyfriend reported that she had a linear conversation with him, although she appeared disinhibited. This case is similar to the one described at the beginning of this article, in which the patient sent text messages reporting hallucinatory experiences after taking zolpidem and not going to sleep.

A second, similar mechanism occurs when the patient falls asleep, but then has an arousal from sleep while still under the influence of zolpidem. The patient may then engage in behaviors and not remember them because of the anterograde amnesic effects. The patient may be able to speak coherently, but act out of character.<sup>14</sup>

Finally, zolpidem may induce or aggravate parasomnias, such as sleepwalking, a distinct phenomenon wherein complex behaviors take place during electroencephalographically verifiable slow-wave sleep (non-REM Stages 3–4). These behaviors appear purposeless to outside observers.<sup>25</sup> Speech is typically incoherent. FDA data indicate that zolpidem does not significantly change sleep architecture,<sup>1</sup> but it has been reported that it decreases REM sleep with a corresponding increase in non-REM sleep time.<sup>26</sup> This increase in total non-REM sleep time may increase the risk of somnambulistic behaviors.<sup>25</sup> In a recent study of outpatients with sleep disorders, use of zolpidem was positively correlated with sleepwalking and sleep-related eating.<sup>27</sup>

A recent case report described a patient with no previous history of parasomnia who began sleepwalking after she started taking zolpidem. Her husband reported that she spoke incoherently during these episodes.<sup>14</sup> Another case report described a patient, who, after starting zolpidem, awoke in the middle of the night, walked into his parents' room with a blank stare, and spoke incoherently.<sup>28</sup> Yang *et al.*<sup>19</sup> reported on an inpatient who began getting out of bed in the middle of the night after initiation of zolpidem

10 mg. The man urinated on the floor and appeared confused. In all of these cases, the behaviors ceased when zolpidem was discontinued.

#### Risk Factors

The term parasomnia is used to refer to any of several sleep arousal disorders including sleepwalking, night terrors, and restless leg syndrome. Several risk factors have been previously identified for parasomnias including personal or family history of parasomnia, use of alcohol or drugs, sleep deprivation, fever, and personal stress.<sup>29</sup> In the cases reviewed here, the risk for sleep-related, complex behaviors associated with zolpidem tended to be dose-dependent, with higher doses increasing the risk. Concomitant use of other psychotropic medications may also have an additive risk for sleep-related, complex behaviors. Such complex behaviors are more likely to occur early in treatment but can happen at any time, in some reports after an individual has used the medication for as long as two years.<sup>17</sup> A recent review showed that zolpidem accounted for 15 of 17 case reports of sleep-related, complex behaviors within the NBRA class of medications. In this review, triazolam was the most frequent of the benzodiazepines to be reported to cause complex behavior.<sup>8</sup>

#### Case Law

The Lexis-Nexis search returned 28 relevant legal cases. The criminal cases by committing offense included: 7 violent crimes, 10 driving-related incidents, 1 sex offense, and 2 false reports. In these cases, the defendants argued that the use of zolpidem near the time of the offense reduced their criminal liability. Two additional criminal cases were identified, in which defendants appealed for a change of plea, arguing that use of zolpidem near the time of the plea had rendered them incompetent to enter a plea. Three employment-related cases were found in which the use of zolpidem was argued to mitigate civil responsibility. Two negligence tort cases were found in which plaintiffs sued Sanofi-Aventis for driving-related damages. The following will summarize key factors that have arisen when courts have evaluated these claims involving zolpidem.

#### Involuntary Intoxication Defense

In several of the cases reviewed, defendants advanced an argument of reduced or negated criminal liability attributable to involuntary intoxication. In

this legal strategy, the defendant must show that at the time of the accused crime he was in an altered state of mind, such that he was unaware of his actions. The defendant must also show that an intoxicating substance caused the behavior and that he did not knowingly consume the substance. Alcohol and illegal drugs cannot be used as part of an involuntary intoxication defense. The courts presume that anyone who consumes alcohol or illegal drugs knows or should know the potential to induce unconscious states. Prescription medications, however, can be considered for an involuntary intoxication defense as long as the defendant can show that he was not aware of the potentially adverse effect at the time of ingestion. If the defendant is able to prove that he was intoxicated, but is unable to prove that the intoxication was involuntary, the defendant may still try to argue a case of voluntary intoxication. This defense does not absolve him of criminal responsibility, but may succeed in negating a specific-intent element of a crime (for example premeditated murder) and reduce the severity of the charges.<sup>15</sup>

In *Bingham v. State*,<sup>30</sup> Mr. Bingham shot his wife and his stepson during a domestic dispute. His wife died of the injuries while his stepson survived. Mr. Bingham was charged with first-degree murder and attempted murder. At his trial, he raised the defense of involuntary intoxication, arguing that his use of prescription drugs, including zolpidem, created a “distorted thought process.” The jury found him guilty of the lesser charges of voluntary manslaughter and attempted murder. The court of appeals upheld the conviction, finding that Mr. Bingham did not provide sufficient evidence to prove that his intoxication by prescription medications was involuntary. Records were introduced that showed that Mr. Bingham’s physician had counseled him on all known effects of his medication.

#### Foreseeability

The trier of fact seeks to determine to what degree the defendant (or plaintiff) could have foreseen the consequences of taking zolpidem. Direct warnings include warnings by physicians and labels on prescription bottles. In some cases, the courts will consider what a reasonable person would have done in similar circumstances. An often-cited case involving a benzodiazepine is *People v. Chaffey*.<sup>31</sup> Ms. Chaffey took an overdose of 120 alprazolam tablets in a suicide attempt and then drove recklessly while in a

delirious state. Although the court ruled that she did not intend to drive her car, they found that it was foreseeable that such an ingestion could lead to unpredictable behavior. She was convicted of driving while intoxicated.

Foreseeability was at issue in the case of *Kelly v. Salt Lake City Civil Service Commission*.<sup>32</sup> Ms. Kelly was a police officer until her termination after improper conduct. After work one evening she took several tablets of zolpidem and deliberately remained awake to play video games. While intoxicated, she made several crank phone calls to police dispatch that included sexual innuendos and a false report of a fire behind her home. She appealed the decision to terminate her employment on the grounds that her behavior was an involuntary result of taking prescribed medication. The court ruled that even if her physician had not warned her of the potential side effects of zolpidem, she had voluntarily taken more than the prescribed dose and stayed awake. The court stated that “the very point of a sleep aid is to fall asleep.” The court also considered that Ms. Kelly had a history of abusing zolpidem and had in fact attempted suicide in the past by overdose of the drug.

The question of warnings by physicians introduces a potential conflict for those who may also be sued by defendants. In *People v. Johns*, a California case,<sup>33</sup> Ms. Johns was charged with vehicular manslaughter after she hit a pedestrian while under the influence of zolpidem and alprazolam. Her prescribing physician testified that he had warned Ms. Johns of the dangers of driving while taking these medications. The defense argued that the physician had motive to lie because Ms. Johns had a civil lawsuit pending against him in the same matter.

### **Proof of Ingestion of Zolpidem**

Ultimately, it is a matter of fact to determine whether a defendant has taken zolpidem (or any other substance). Toxicology data can establish the likely presence or absence of zolpidem at the time of the offense. Toxicologists have used blood<sup>34</sup> and urine<sup>35</sup> samples to introduce evidence of the presence of zolpidem. Blood samples have been used to approximate the timing and dosage of the drug, whereas urine samples have been used to corroborate its presence. Absent toxicology data, the expert must rely on the statement of the defendant as to whether zolpidem was ingested before the offense.

### **Proof of Altered State of Mind**

Defendants using a defense related to zolpidem typically call experts to testify to the propensity of zolpidem to cause abnormal behaviors and amnesia. The expert then can testify to what extent the defendant showed evidence of impairment at the time of the offense. The courts look at the record as a whole in determining as a matter of fact whether the person was intoxicated as a result of zolpidem.

In *People v. Walden*,<sup>36</sup> Mr. Walden entered the home of his ex-girlfriend and assaulted her and her boyfriend. He was charged with burglary, assault, criminal trespass, and harassment. Mr. Walden claimed that he had taken zolpidem before the assault and had no memory of the incident. The defense expert psychiatrist testified that a combination of zolpidem, alcohol, and cessation of an antidepressant rendered the defendant unconscious during the attack. The prosecution instructed the jury to consider statements made by the defendant during the attack, such as his apology, as evidence that he acted intentionally and knowingly. The jury convicted Mr. Walden of criminal trespass and harassment and dismissed the assault charges.

Methods of the experts came under fire in *Gibson v. Sanofi-Aventis U.S.*<sup>37</sup> Ms. Gibson sued Sanofi-Aventis for product liability when she had a car accident after taking zolpidem. The plaintiff's experts testified that it was medically probable that Gibson's accident was the result of sleep-driving caused by zolpidem. Ms. Gibson took zolpidem approximately 30 minutes to one hour before her accident. She had curlers in her hair and a mud mask on her face and was not wearing her glasses. The experts argued that this suggested behavior out of character for her. They also pointed to case reports in the literature of sleep-driving associated with zolpidem. The judge ruled that the methods of the experts were speculative and did not have a scientific basis. He found they had not applied any concrete knowledge of sleep medicine in establishing that Ms. Gibson was in fact in a somnambulistic state. He excluded the expert testimony and entered summary judgment in favor of the defendant.

In *People v. Hudson*,<sup>34</sup> another California case, testimony of witnesses at the time of the offense played an important role in adjudication of the zolpidem defense. Around 11 p.m. one evening, Mr. Hudson was observed driving recklessly. A high-speed police chase ensued. After being cornered in a cul de sac, he

resisted arrest and punched an officer in the face. He was taken to the hospital where his blood alcohol level was measured at 0.13 (0.13 mg alcohol present in 100 mL blood). He stated the last thing he remembered was taking 10 mg of zolpidem at 9:30 p.m. He had no recollection of drinking alcohol, the car chase, or treatment in the hospital. An expert in sleep medicine testified to the propensity of zolpidem to induce bizarre behaviors with associated amnesia. He acknowledged that these behaviors were rare, but that he “believe[d] Mr. Hudon” and had “confidence that this is an Ambien defense” (Ref. 34, p 4).

The prosecution presented the testimony of the nurse who treated Mr. Hudon shortly after his arrest. He had answered all of her medical history questions. His Glasgow Coma Scale score was normal. She testified that he did not exhibit any signs of toxic effects from zolpidem. The prosecution also called one of the responding officers. He testified that Mr. Hudon’s behavior was consistent with someone under the influence of alcohol, not prescription drugs. The jury convicted Mr. Hudon on all counts.

#### **Presence of Alcohol and Other Potentially Intoxicating Substances**

Alcohol is known to potentiate the effects of zolpidem.<sup>1</sup> In many of the cases reviewed, alcohol was consumed in combination with zolpidem. The courts tend to look at alcohol as evidence of voluntary intoxication, and it tends to be an aggravating factor. Courts believe that alcohol itself has amnesic effects on those who abuse it.<sup>37</sup>

#### **Credibility**

Witnesses who claim that they were acting in an unconscious state of mind assert an affirmative claim to mitigate their personal responsibility. In doing so, their credibility becomes an issue for the trier of fact. The question becomes complicated when people are under the influence of zolpidem, because they can be disinhibited and can confabulate. In *Bradley v. Commonwealth of Virginia*,<sup>38</sup> the appellate court questioned Mr. Bradley’s credibility because the statements he made at the time of the instant offense while under the influence of zolpidem conflicted with his testimony at trial.

The presence of a motive can also be used by the prosecution to discredit the defendant. In *Davidson v. State*,<sup>39</sup> Mr. Davidson was charged with murder after shooting the boyfriend of his ex-wife. He

claimed that he was in a dissociative state as the result of taking zolpidem. Considered at trial was the fact that Mr. Davidson had maintained a sexual relationship with his former wife and had made statements to witnesses that he wished that her new boyfriend were dead. The jury convicted Mr. Davidson of murder.

Assertion of an involuntary intoxication defense may allow the prosecution to introduce evidence of prior acts of the defendant that may have been otherwise excluded as prejudicial. This was the case in *People v. Hudon*.<sup>34</sup> The prosecution was allowed to present testimony by the arresting officer that Mr. Hudon had said to him that he was running from the police because of a prior DUI charge. This evidence directly disputed the innocent state of mind claimed by the defense.

## **Conclusions**

### **Recommendations for Forensic Consultation**

Whether use of zolpidem led to aberrant behavior in a specific case is ultimately a decision for the trier of fact. Experts can enhance their testimony by grounding their observations in known scientific facts about zolpidem. The onset of aberrant behavior in relation to the timing of the dose of zolpidem is a key consideration. Blood samples can produce toxicology data that can verify the last dose and time of the medication. Consultation with a toxicologist can enhance the credibility of such an analysis. Consideration of other medications that the patient was taking is also helpful. Psychiatrists have special expertise in the effects of combinations of psychotropic medications on the mental state of patients.

Reviewing collateral reports of those who witnessed the patient under the influence of zolpidem is also important. Incoherence of speech and disorganization of behavior suggest behavior consistent with sleepwalking. It may be possible to replicate this behavior in a sleep laboratory. The medical literature suggests that zolpidem and other hypnotosedatives can aggravate parasomnias in those patients at risk. Consultation with a sleep medicine expert will help ground expert opinions on whether the behavior in question was likely a sleep-related, complex behavior. The medical literature also contains guidelines for parasomnia evaluation.<sup>40</sup>

Finally, psychiatric experts can be helpful to the court if they can comment on the foreseeability of the aberrant behavior. These include consideration of

history, apparent warnings, and discussion with their physicians of risks. Psychiatrists should also consider any potential evidence of deliberate abuse or misuse of zolpidem. Newer studies have suggested that zolpidem carries a higher abuse potential than was once thought.<sup>41</sup>

### Future Directions

As the risks of sleep-related, complex behaviors associated with zolpidem become more widely appreciated, its criminal and civil applications may decrease, as people increasingly will be expected to be aware of these side effects. In light of the widespread publicity and appearance in popular culture of zolpidem-induced sleep-related, complex behaviors, it may become harder to prove that a defendant's intoxication was not foreseeable. Civil tort cases have so far targeted the manufacturer of zolpidem. This may reflect the overall trend of shifting liability burden from physicians to manufacturers as a result of direct-to-consumer marketing strategies.

Ongoing clinical trials are under way to better characterize the wide range of effects of zolpidem. Anecdotal reports have suggested that it improves symptoms of several neurological disorders previously thought intractable, including persistent vegetative state, aphasia, central pontine myelinolysis, and progressive supranuclear palsy.<sup>13</sup> One preliminary placebo-controlled trial of zolpidem in 16 subjects with disorders of consciousness found one clinical response: A patient improved from a vegetative state to a minimally conscious state.<sup>42</sup> This potential application of zolpidem has implications for medical decision-making, where physicians are often called as expert witnesses to testify to the risks and benefits of medical interventions involved in end of life care. One such case recently occurred in the British court system, where the judge ordered a trial of zolpidem, over the objection of the family, for a patient in a persistent vegetative state.<sup>43</sup> The judge based his ruling on the expert opinion proffered by a professor who had reviewed the case report literature on zolpidem and the persistent vegetative state.

### Summary

Zolpidem is different from other medications that are commonly used to treat insomnia. Although aberrant sleep-related behaviors associated with zolpidem are uncommon, its widespread use in the population increases the likelihood that such cases will

occur. When claims of zolpidem-related behavior are raised in the legal system, the effectiveness of forensic psychiatric experts may be enhanced by their familiarity with the literature summarized in this review.

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