

# A veteran who is suicidal while sleeping

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Mr. R, age 28, is a veteran with major depressive disorder and PTSD. One night while asleep, he puts an unloaded gun in his mouth and pulls the trigger. What could be causing this behavior?



## How would you handle this case?

Answer the **challenge questions** throughout this article

### **CASE** Suicidal while asleep

Mr. R, age 28, an Iraq and Afghanistan veteran with major depressive disorder and posttraumatic stress disorder (PTSD), is awoken by his wife to check on their daughter approximately 30 minutes after he takes his nightly regimen of zolpidem, 10 mg, melatonin, 6 mg, and hydroxyzine, 20 mg. When Mr. R returns to the bedroom, he appears to be confused. Mr. R grabs an unloaded gun from under the mattress, puts it in his mouth, and pulls the trigger. Then Mr. R holds the gun to his head and pulls the trigger while saying that his wife and children will be better off without him. His wife takes the gun away, but he grabs another gun from his gun box and loads it. His wife convinces him to remove the ammunition; however, Mr. R gets the other unloaded gun and pulls the trigger on himself again. After his wife takes this gun away, he tries cutting himself with a pocket-knife, causing superficial cuts. Eventually, Mr. R goes back to bed. He does not remember these events in the morning.

#### What could have caused Mr. R's nighttime suicidal behavior?

- severe depression with suicidal ideations
- personality disorder
- non-rapid eye movement (NREM) sleep arousal disorder/NREM parasomnia
- substance/medication-induced sleep disorder, parasomnia type

### The authors' observations

Parasomnias are sleep-wake transition disorders classified by the sleep stage from which they arise, either NREM or rapid eye movement (REM). NREM parasomnias could result from incomplete awakening from NREM sleep, typically in Stage N3 (slow-wave) sleep.<sup>1</sup> DSM-5 describes NREM parasomnias as arousal disorders in which the disturbance is not attributable to the physiological effects of substance; substance/medication-induced sleep disorder, parasomnia type, is when the disturbance can be attributed to a substance.<sup>2</sup> The latter also can occur during REM sleep.

NREM parasomnias are characterized by abnormal behaviors during sleep with significant harm potential.<sup>3</sup> Somnambulism or sleepwalking and sleep terrors are the 2 types of NREM parasomnias in DSM-5. Sleepwalking could involve complex behaviors, including:

- eating
- talking

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#### Disclosures

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

### Clinical Point

**Zolpidem is preferred for insomnia because of its low risk for abuse and daytime sedation; however, it is associated with NREM parasomnias**

- cooking
- shopping
- driving
- sexual activity.

Zolpidem, a benzodiazepine receptor agonist, is a preferred hypnotic agent for insomnia because of its low risk for abuse and daytime sedation.<sup>4</sup> However, the drug has been associated with NREM parasomnias, namely somnambulism or sleepwalking, and its variants including sleep-driving, sleep-related eating disorder, and rarely sexomnia (sleep-sex), with anterograde amnesia for the event.<sup>5</sup> Suicidal behavior that occurs while the patient is asleep with next-day amnesia is another variant of somnambulism. There are several reports of suicidal behavior during sleep,<sup>6,7</sup> but to our knowledge, there are only 2 previous cases implicating zolpidem as the cause:

- Gibson et al<sup>8</sup> described a 49-year-old man who sustained a self-inflicted gunshot wound to his head while asleep. He just had started taking zolpidem, and in the weeks before the incident he had several episodes of sleepwalking and sleep-eating. He had consumed alcohol the night of the self-inflicted gunshot wound, but had no other psychiatric history.

- Chopra et al<sup>4</sup> described a 37-year-old man, with no prior episodes of sleepwalking or associated complex behaviors, who was taking zolpidem, 10 mg/d, for chronic insomnia. He shot a gun in the basement of his home, and then held the loaded gun to his neck while asleep. The authors attributed the event to zolpidem in combination with other predisposing factors, including dehydration after intense exercise and alcohol use. The authors categorized this type of event as “para-suicidal amnesic behavior,” although “sleep-related pseudo-suicidal behavior” might be a better term for this type of parasomnia because of its occurrence during sleep and non-deliberate nature.

In another case report, a 27-year-old man took additional zolpidem after he did not experience desired sedative effects from an

initial 20 mg.<sup>9</sup> Because the patient remembered the suicidal thoughts, the authors believed that the patient attempted suicide while under the influence of zolpidem. The authors did not believe the incident to be sleep-related suicidal behavior, because it was uncertain if he attempted suicide while asleep.

Mr. R does not remember the events his wife witnessed while he was asleep. To our knowledge, Mr. R’s case is the first sleep-related pseudo-suicidal behavior case resulting from zolpidem, 10 mg/d, without concurrent alcohol use in an adult male veteran with PTSD and no suicidal ideation while awake.

### HISTORY Further details revealed

Mr. R says that in the days leading to the incident he was not sleep-deprived and was getting at least 6 hours of restful sleep every night. He had been taking zolpidem every night. He has no childhood or family history of NREM parasomnias. He says he did not engage in intense exercise that evening or have a fever the night of the incident and has abstained from alcohol for 2 years.

His wife says that after he took zolpidem, when he was woken up, “He was not there; his eyes were glazed and glossy, and it’s like he was in another world,” and his speech and behavior were bizarre. She also reports that his eyes were open when he engaged in this behavior that appeared suicidal.

Three months before the incident, Mr. R had reported nightmares with dream enactment behaviors, hypervigilance on awakening and during the daytime, irritability, and anxious and depressed mood with neurovegetative symptoms, and was referred to our clinic for medication management. He also reported no prior or current manic or psychotic symptoms, denied suicidal thoughts, and had no history of suicide attempts. Mr. R’s medication regimen included tramadol, 400 mg/d, for chronic knee pain; fluoxetine, 60 mg/d, for depression and PTSD; and propranolol ER, 60 mg/d, and propranolol,



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10 mg/d as needed, for anxiety. He was started on prazosin, 2 mg/d, titrated to 4 mg/d, for medication management of nightmares.

Mr. R also was referred to the sleep laboratory for a polysomnogram (PSG) because of reported loud snoring and witnessed apneas, especially because sleep apnea can cause nightmares and dream enactment behaviors. The PSG was negative for sleep apnea or excessive periodic limb movements of sleep, but showed increased electromyographic (EMG) activity during REM sleep, which was consistent with his report of dream enactment behaviors. Two months later, he reported improvement in nightmares and depression, but not in dream enactment behaviors. Because of prominent anxiety and irritability, he was started on gabapentin, 300 mg, 3 times a day.

#### What increased the likelihood of parasomnia in Mr. R?

- high zolpidem dosage
- concomitant use of other sedating agents
- sleep deprivation
- dehydration

#### The authors' observations

Factors that increase the likelihood of parasomnias include:

- zolpidem >10 mg at bedtime
- concomitant use of other CNS depressants, including sedative hypnotic agents and alcohol
- female sex
- not falling asleep immediately after taking zolpidem
- personal or family history of parasomnias
- living alone
- poor pill management
- presence of sleep disruptors such as sleep apnea and periodic limb movements of sleep.<sup>1,4,5,10</sup>

Higher dosages of zolpidem (>10 mg/d) have been identified as the predictive risk factor.<sup>5</sup> In the Chopra et al<sup>4</sup> case report on

sleep-related suicidal behavior related to zolpidem, 10 mg at bedtime, concomitant dehydration and alcohol use were implicated as facilitating factors. Dehydration could increase serum levels of zolpidem resulting in greater CNS effects. Alcohol use was implicated in the Gibson et al<sup>8</sup> case report as well, and the patient had multiple episodes of sleepwalking and sleep-related eating. However, Mr. R was not dehydrated or using alcohol.

An interesting feature of Mr. R's case is that he was taking fluoxetine. Cytochrome P450 (CYP) 3A4 is involved in metabolizing zolpidem, and norfluoxetine, a metabolite of fluoxetine, inhibits CYP3A4. Although studies have not found pharmacokinetic interactions between fluoxetine and zolpidem, these studies did not investigate fluoxetine dosages >20 mg/d.<sup>11</sup> The inhibition of CYP enzymes by fluoxetine likely is dose-dependent,<sup>12</sup> and therefore concomitant administration of high-dosage fluoxetine (>20 mg/d) with zolpidem might result in higher serum levels of zolpidem.

Mr. R also was taking several sedating agents (gabapentin, hydroxyzine, melatonin, and tramadol). The concomitant use of these sedative-hypnotic agents could have increased his risk of parasomnia. A review of the literature did not reveal any reports of gabapentin, hydroxyzine, melatonin, or tramadol causing parasomnias. This observation, as well as the well-known role of zolpidem<sup>5</sup> in etiopathogenesis of parasomnias, indicates that the pseudo-suicidal behavior Mr. R displayed while asleep likely was a direct result of zolpidem use in presence of other facilitating factors. Gabapentin, which is known to increase the depth of sleep, was added to his regimen 1 month before his parasomnia episode. Therefore, gabapentin could have triggered parasomnia with zolpidem therapy.<sup>1,13</sup>

Conditions that provoke repeated cortical arousals (eg, periodic limb movement dis-

#### Clinical Point

**Gabapentin, which is known to increase the depth of sleep, was added to Mr. R's regimen a month before the event**

### Clinical Point

REM sleep behavior disorder could be explained by use of a selective serotonin reuptake inhibitor and comorbidity with PTSD

order [PLMD] and sleep apnea) or increase depth or pressure of sleep (intense exercise in the evening, fever, sleep deprivation) are thought to be associated with NREM parasomnias.<sup>1,4</sup> However, Mr. R underwent in-laboratory PSG and tested negative for major cortical arousal-inducing conditions, such as PLMD and sleep apnea.

Some other sleep disruptors likely were involved in Mr. R's case. Auditory and tactile stimuli are known to cause cortical arousals, with additive effect seen when these 2 stimuli are combined.<sup>3,14</sup> Additionally, these exogenous stimuli are known to trigger sleep-related violent parasomnias.<sup>15</sup> Mr. R displayed this behavior after his wife woke him up. The auditory stimulus of his wife's voice and/or tactile stimulus involved in the act of waking Mr. R likely played a role in the suicidal and violent nature of his NREM parasomnia.

#### What factor increases the risk of NREM parasomnias with zolpidem compared with benzodiazepines?

- greater preservation of Stage N3 sleep
- lesser degree of muscle relaxation
- both a and b
- none of the above

#### The authors' observations

In general, the mechanisms by which zolpidem causes NREM parasomnias are not completely understood. The sedation-related amnesic properties of zolpidem might explain some of these behaviors. Patients could perform these behaviors after waking and have subsequent amnesia.<sup>4</sup> There is greater preservation of Stage N3 sleep with zolpidem compared with benzodiazepines. Benzodiazepines also cause muscle relaxation while the motor system remains relatively more active during sleep with zolpidem because of its selectivity for  $\alpha$ -1 subunit of gamma-aminobutyric acid A receptor. These factors might increase the likelihood of

NREM parasomnias with zolpidem compared with benzodiazepines.<sup>4</sup>

### Types of parasomnias

According to DSM-5, there are 2 categories of parasomnias based on the sleep stage from which a parasomnia emerges.<sup>2</sup> REM sleep behavior disorder (RBD) refers to complex motor and/or vocalizations during REM sleep, accompanied by increased EMG activity during REM sleep (*Table*).<sup>2,3</sup>

The pseudo-suicidal behavior Mr. R displayed likely was NREM parasomnia because it occurred in the first third of the night with his eyes open and impaired recall after the event. Interestingly, Mr. R had RBD in addition to the NREM parasomnia likely caused by zolpidem. This is evident from Mr. R's frequent dream enactment behaviors, such as kicking, thrashing, and punching during sleep, along with increased EMG activity during REM sleep as recorded on the PSG.<sup>10</sup> The presence of RBD could be explained by selective serotonin reuptake inhibitor (fluoxetine) use, and comorbidity with PTSD.<sup>2,16</sup>

### Management of parasomnias

Initial management of parasomnias involves decreasing the risk of parasomnia-related injury. Suggested safety measures include:

- sleeping away from windows
- sleeping in a sleeping bag
- sleeping on a lower floor
- locking windows and doors
- removing potentially dangerous objects from the bedroom
- putting gates across stairwells
- installing bells or alarms on door knobs.<sup>15</sup>

Removing access to firearms or other weapons such as knives is of utmost importance especially with patients who have easy access during wakefulness. If removing weapons is not feasible, consider disarming, securing, or locking them.<sup>15</sup> These considerations are relevant to veterans with PTSD because of the high prevalence of symptoms,

Table

## Distinguishing features between NREM sleep arousal disorder and REM sleep behavior disorder

Characteristics	NREM sleep arousal disorder/ NREM parasomnia	REM sleep behavior disorder
Time of the night	First third of the night	Last half of the night
Sleep stage	N3 or slow-wave sleep	REM sleep
Behaviors	Simple/complex behaviors	Typically gross motor movements (kicking, punching, etc.) related to content of the dream; loud and emotion-laden vocalizations
Eye position during the episode	Open	Closed
Sensorium if awakened during the episode	Confused, disoriented	Fully awake, alert, and oriented
Recall after the episode	Complete or partial amnesia	Often able to recall the dream mentation
Arousal threshold	High	Low
Triggers	Sleep deprivation, noise, touch, sleep apnea, PLMD, hypnotic medications, alcohol use	Alcohol withdrawal, antidepressants
PSG findings	Frequent arousals (micro-arousals or frank awakenings) and hypersynchronous delta EEG waves during Stage N3 sleep	Increase EMG activity during REM sleep

EMG: electromyography; NREM: non-rapid eye movement; PLMD: periodic limb movement disorder; PSG: polysomnography; REM: rapid eye movement

Source: References 2,3

### Clinical Point

A review found that sedating medications, including antidepressants, can lead to NREM parasomnias

including depression, insomnia, and pain, which require sedating medications.<sup>17</sup> A review of parasomnias among a large sample of psychiatric outpatients revealed that a variety of sedating medications, including antidepressants, can lead to NREM parasomnias.<sup>18</sup> Therefore, exercise caution when prescribing sedating medications, especially in patients vulnerable to developing dangerous parasomnias, such as a veteran with PTSD and easy access to guns.<sup>19</sup>

### TREATMENT Zolpidem stopped

Mr. R immediately stops taking zolpidem because he is aware of its association with abnormal behaviors during sleep, and his wife removes his access to firearms and knives at night. Because of his history of clinical benefit and no history of parasomnias with mirtazapine, Mr. R is started on mirtazapine for insom-

nia that previously was treated with zolpidem, and residual depression. Six months after discontinuing zolpidem, he does not experience NREM parasomnias, and there are no changes in his dream enactment behaviors.

### Summing up

Zolpidem therapy could be associated with unusual variants of NREM parasomnia, sleepwalking type; sleep-related pseudo-suicidal behavior is one such variant. Several factors could play a role in increasing the likelihood of NREM parasomnia with zolpidem therapy. In Mr. R's case, the pharmacokinetic drug interactions between fluoxetine and zolpidem, as well as concomitant use of several sedating agents could have played a role in increasing the likelihood of NREM parasomnia, with audio-tactile stimuli contributing to the violent and suicidal nature of the parasomnia. Exercise

## Clinical Point

Advise patients to avoid exogenous and endogenous sleep disruptors and alcohol, and remove firearms and other potential weapons

## Related Resources

- American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
- Kryger M, Roth T, Dement WC. Principles and practice of sleep medicine. 2nd ed. Philadelphia, PA: Elsevier; 2017.

### Drug Brand Names

Fluoxetine • Prozac	Propranolol • Inderal
Gabapentin • Neurontin	Tramadol • Ultram
Hydroxyzine • Vistaril	Trazodone • Desyrel, Olepro
Mirtazapine • Remeron	Zolpidem • Ambien,
Paroxetine • Paxil	Edluar, Intermezzo
Prazosin • Minipress	

caution when using CYP enzyme inhibitors, such as fluoxetine and paroxetine, in combination with zolpidem. Knowledge of the potential interaction between zolpidem and fluoxetine is important because antidepressants and hypnotics are commonly co-prescribed because insomnia often is comorbid with other psychiatric disorders.

In veterans with PTSD who do not have suicidal ideations while awake, life-threatening non-intentional behavior is a risk because of easy access to guns or other weapons. Sedative-hypnotic medications commonly are prescribed to patients with PTSD. Exercise caution when using hypnotic agents such as zolpidem, and consider sleep aids with a lower risk of parasomnias (based on the author's experience, trazodone, mirtazapine, melatonin, and gabapentin) when possible. Non-pharmacologic treatments of insomnia, such as sleep

hygiene education and, more importantly, cognitive-behavioral therapy for insomnia, are preferred. If a patient is already taking zolpidem, nightly dosage should not be >10 mg. Polypharmacy with other sedating medications should be avoided when possible and both exogenous (noise, pets) and endogenous sleep disruptors (sleep apnea, PLMD) should be addressed. Advise the patient to avoid alcohol and remove firearms and other potential weapons. Discontinue zolpidem if the patient develops sleep-related abnormal behavior because of its potential to take on violent forms.

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## Bottom Line

Zolpidem has been associated with variants of non-rapid eye movement parasomnia prototype sleepwalking. Suicidal behavior during sleep is one such unusual and life-threatening variant. Exercise caution when prescribing zolpidem in vulnerable patients, such as veterans with posttraumatic stress disorder who have easy access to weapons. Avoid using multiple sedating agents when possible, and consider non-drug therapies such as sleep hygiene education and cognitive-behavioral therapy as first-line treatments for insomnia.

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## Commentary

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