

# Straight Tox

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## **Zolpidem (Ambien®): Asleep at the Wheel** *(and in the kitchen, and on the phone, and at the supermarket, etc.)*

by Dwain C. Fuller, D-FTCB, TC-NRCC

If you were writing this column, which story would you open with? Perhaps the one about the man who took 10 mg of zolpidem went to bed, then arose during the night, cooked a meal, consumed it, and returned to bed. Even after several nights of this epicurean pursuit, he would not believe the testimony of the witnesses of this activity until confronted with videotaped evidence. Or how about the one where the man took 10 mg of zolpidem at bedtime then was witnessed by his son to leave his house, start his truck and back into a tree, return to the driveway and go back inside his house. Upon having trouble opening the bedroom door, the man kicked the door down, returned to bed and went back to sleep. The next morning had no recollection of the events. Or, for the more tabloid-minded, perhaps the one about U.S. Representative Patrick Kennedy who reportedly took zolpidem and promethazine before driving his car into a security barricade near the U.S. Capitol, claiming he was “late for a vote”. He was correct in his assertion, however -- the last vote was some 6 hours earlier. It is only fair to mention that bizarre parasomnias are not the exclusive realm of zolpidem, but are also reported with several sedative-hypnotic medications. The “Z-drugs”, however, zolpidem, zopiclone and zaleplon, going by the trade names Ambien®, Lunesta® and Sonata®, respectively, even if just anecdotally, seem to be more highly correlated to these phenomena. The Z-drugs share similar pharmacodynamic and pharmacokinetic profiles. Ambien®, however, perhaps due to its market share, estimated by some to be 52% of all new sleep-aid prescriptions and as much as 84% among the Z-drugs alone, seems to have the dubious distinction of being the leader in parasomnia reports.



## **Zolpidem and Driving**

Several authors have reported on the increase in zolpidem-impaired driving in recent years, and a rather well-defined toxidrome of the zolpidem-impaired driver has emerged. Some of the hallmarks of zolpidem-impaired driving are as follows:

- Hitting stationary objects, including stationary vehicles.
- Speed well above or below posted limits.
- Lane deviation.
- Leaving the roadway.
- Driving wrong direction.
- Eyes appear to “look right through” the officer.
- Slow speech.
- Unsteady gait with side to side and backward sway; often needing assistance to stand.
- Horizontal gaze nystagmus.
- Amnesia for events surrounding driving/accident/reason for stop.
- Unable to comprehend or remember officer’s instructions.

## **Sleep-driving**

Beyond the, sometimes entertaining, sleep-eating, sleep-shopping, and sleep-sex stories lies the more serious and dangerous realm familiar to the forensic toxicologist -- the sleep-driver. Defining a sleep-driver is rather elusive. Arguably, any driver exhibiting the signs and symptoms listed above, especially with amnesia for the event, could be classified as a sleep-driver. Some may wish to define a true sleep-driver as one who has not violated any of the prescribing guidelines. That is, one who has taken the drug in the proper dosage, without alcohol or other CNS depressants, and immediately prior to retiring to bed for an intended 8 hours of sleep. Obviously, the latter condition is the most difficult to determine with any certainty. One must also ask the somewhat metaphysical question: What role does intent and the lack of memory of the intent play in the equation; is it intent if you don’t remember having the intent? This notwithstanding, the evidence seems to be clear that some people do retire to bed after taking zolpidem, only to arise and perform complex tasks including driving without remembering having done so. The exact definition, I will leave to you.

Zolpidem alone has been implicated in sleep-driving behavior, but as I have previously alluded to, there is a correlative, if not necessarily a causal, relationship with the coadministration of zolpidem and SSRI’s, benzodiazepines, or other CNS depressant medications with this phenomenon. It is certainly logical to assume that co-ingestion of other medications with CNS depressant effects in addition to zolpidem would contribute to the observed impairment. However, as Reidy, Gennaro, Steele, and Walls aptly point out, “The combination of antidepressants and zolpidem is expected because of the large

number of cases of depressed patients finding it difficult to sleep and requiring the coadministration of these drugs.”

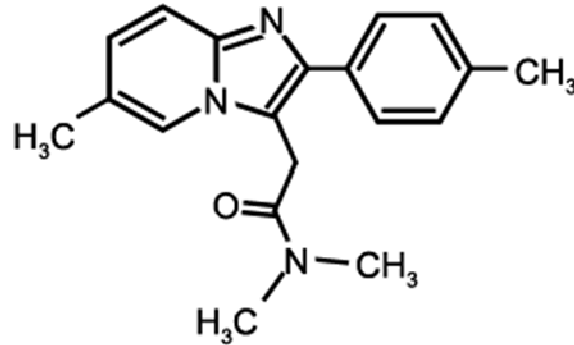
In these days of the internet, rumor and anecdotal accounts often feed public hysteria and take on a life of their own. Indeed, as claimed by the manufacturer, the percentage of zolpidem-related parasomnias may be quite low as a percentage; however, with nearly 30 million prescriptions for zolpidem in the U.S. alone, even statistical outliers can become prominent numbers. As one might expect, it is difficult to obtain good numbers as to the incidence of complex parasomnias such as sleep-driving and their relation to zolpidem. However, amnesia and somnambulism are both behaviors related to the events we are discussing. Gleaning from Ambien’s prescribing information, there was a 1% incidence of amnesia in three placebo-controlled long-term efficacy trials involving Ambien®. Also, while being reported, somnambulism had an incidence of less than 0.1% in a clinical trial involving 3,660 subjects. To play with the math a little, if one takes the amnesia number at face value and gives the benefit of the doubt to the somnambulism number and assumes that the “less than 0.1%” is actually only 0.01%, at 30,000,000 prescriptions, one would expect 300,000 incidents of amnesia and 3000 incidents of somnambulism. This is obviously speculative and perhaps even an abuse of statistics, however, for whatever reasons, the Food and Drug Administration has taken notice.

In December of 2006 the FDA issued a request to manufacturers of multiple sleep disorder products, including the makers of Ambien® to revise the product labeling to include warnings about potential adverse events including, *“Complex sleep-related behaviors which may include sleep-driving, making phone calls, and preparing food (while asleep).”* Accordingly the package insert for Ambien® now contains this warning:

*“Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naïve as well as sedative-hypnotic-experienced persons. Although behaviors such as “sleep driving” may occur with Ambien alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien appears to increase the risk of such behaviors, as does the use of Ambien at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep driving”, patients usually do not remember these events.”*

## Pharmacology and Metabolism

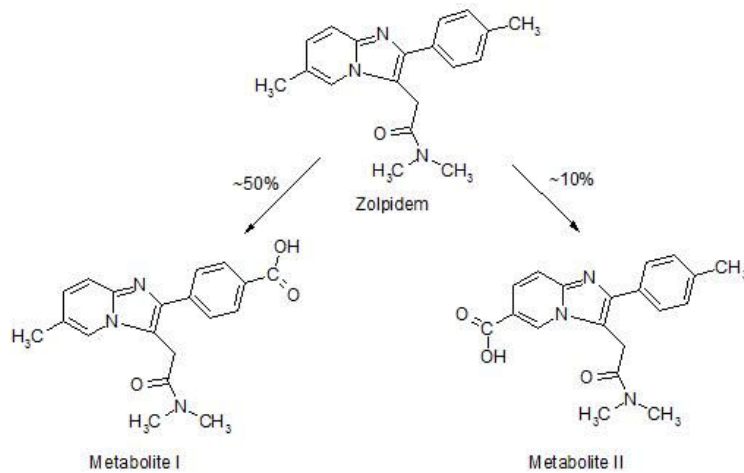
Zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines, or other drugs with known hypnotic properties. Zolpidem acts primarily at the GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. However, in contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem in-vitro binds the BZ<sub>1</sub> receptor preferentially with a high affinity ratio of the  $\alpha_1/\alpha_5$  subunits. This selective binding of zolpidem on the BZ<sub>1</sub> receptor, while not absolute, may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.



Zolpidem

The pharmacokinetic profile of zolpidem is characterized by a rapid absorption from the gastrointestinal tract and a short elimination half-life. In a single-dose crossover study of 45 healthy subjects administered 5 and 10 mg of zolpidem tartrate tablets, the mean  $C_{max}$  were 50 (range: 29 – 113) and 121 (range: 58 – 272) ng/mL, respectively, with a mean  $T_{max}$  of 1.6 hours for both. The half-life of zolpidem is reported to be approximately 2.5 hours (range: 1.4 – 4.5 hrs). The major metabolic isoforms involved in zolpidem metabolism are CYP3A4 (~60%), CYP2C9 (~22%), and CYP1A2 (~14%). The fact that approximately 60% of zolpidem's metabolism is mediated by the CYP3A4 isoform, gives rise to the possibility that CYP3A4 inhibitors, including grapefruit juice, may prolong the elimination half-life of zolpidem.

The metabolism of zolpidem produces at least six inactive metabolites. The two major metabolites are formed by the methyl oxidation of the phenyl and imidazopyridine moieties of zolpidem.



When taken alone and as directed, that is, sleeping for a full 8 hours after use, zolpidem has been shown to exert no significant residual driving effects 10 – 11 hours after one night of bedtime treatment, which is in contrast to many benzodiazepine hypnotics.

### Analytical considerations

Immunoassays are commercially available for zolpidem, however, since zolpidem is extensively metabolized and not readily excreted unchanged in the urine, immunoassays should be carefully selected for target compounds consistent with the specimens to be analyzed.

Zolpidem is readily detectable by GC or GC/MS analysis following a common Foerster-Mason type extraction for alkaline drugs. However, because both of the major metabolites of zolpidem, I and II, are amphoteric molecules, a directed SPE extraction followed by derivatization would likely be more appropriate for these compounds.

### Zolpidem and the courts

As previously mentioned, zolpidem-impaired driving is becoming a major issue in the courts. Interestingly, with the advent of the FDA-requested warnings for zolpidem and related drugs, the “admission” of these possible parasomnias has become useful as a defense against DWI or DUID charges. This is known as the “Ambien Defense”.

In 2007, the DWI charges against a North Texas woman, Phyllis Graham, were dropped after successfully arguing that she did not intentionally drive nor have any recollection of driving her husband’s truck down the block and crashing it into a house before walking back home and returning to bed. Ms. Graham’s urine test showed only zolpidem and traces of phenobarbital, the latter presumably from a gastrointestinal medication, but no alcohol.

In Massachusetts, in 2006, Ki Yong O, a pharmaceutical attorney, drove off the road onto the shoulder and struck Anthony Raucci, knocking him into the middle of the highway and severing his leg. Mr. Raucci was pronounced dead at the scene. Subsequent toxicology tests showed that Mr. O's blood was positive for zolpidem. Mr. O was charged with operating under the influence and motor vehicle homicide. However, after a six day trial, Mr. O was acquitted. In his decision, Judge Kenneth Fishman wrote that "the court is unable to conclude beyond a reasonable doubt that the defendant was voluntarily intoxicated when he operated his motor vehicle."

While one would presumably be more able to take advantage of the "Ambien Defense" if the driver was taking zolpidem as directed, that is, without alcohol and without other CNS depressants, that is not always the case.

In New South Wales, Australia, Robert James Kingston was found not guilty of driving with a blood alcohol concentration of 0.105 %, after Judge Colin Phegan found on appeal that there was a "real possibility" that he was "sleep-driving" after taking a Stilnox® (zolpidem) tablet. Judge Phegan said he was satisfied that the scientific evidence was now strong enough to "at least raise a possibility, a real possibility, that the explanation for what happened on this occasion was a state of sleep-driving caused by the use of the drug". Judge Phegan further explained that Mr. Kingston's state of undress, his apparent hallucination, the fact that he was on the wrong side of the road at the time of the accident, and his inability to remember anything of the incident were consistent with a state of "automatism" - where a person has no control over their actions – caused by taking the drug.

## **Conclusion**

When taken as directed, zolpidem is apparently an effective and safe sleeping medication, as nearly 30 million prescriptions would indicate. However, as with most medications, that is not to say it is without side-effects or potential complications, especially considering the many possible interindividual differences in metabolism, etc. And while many of the driving under the influence cases involving zolpidem also involve a driver using zolpidem in a manner inconsistent with prescribing guidelines, the objective observer must concede that in some cases at least, the driver may simply be guilty of having the bad luck of being a statistical outlier in a vast population.

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