

# Acute Delirium Caused by Single Small Dose of Zolpidem

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**Abstract** Zolpidem, a non benzodiazepine hypnotic, exhibits minimal anxiolytic, muscle relaxant, and anticonvulsant properties due to its minimal effect on BZ2 receptors. Due to low drug abuse and better safety profile, Zolpidem has been increasingly used in practice. More number of patients with rare side effects is being reported due to increasing use of this drug. Zolpidem is considered safe and frequently used in hospitals when patients complain of insomnia during their stay in the hospital. In recent years, there have been reported cases of acute delirium and psychosis after zolpidem use. Majority of these rare neuropsychiatric side effects were seen in patients with the history of psychiatric illness and those taking more than 10mg of zolpidem. We present a case of acute agitation, confusion and hallucinations after administration of a small one time dose (5mg) of zolpidem in a male with no prior history of any psychiatric or substance abuse.

**Keywords:** *zolpidem, delirium, psychosis, hypnotics*

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## 1. Introduction

Zolpidem (Ambien) is a sedative, hypnotic agent of imidazopyridine family which is used for the short-term treatment of insomnia [1]. It acts by selectively blocking GABA1 receptors, which Account for its relative lack of muscle relaxing and anticonvulsant effect when compared to benzodiazepines. It has gained popularity for short-term insomnia treatment due to its milder and less problematic side effects than benzodiazepines. Due to better safety profile and less dependency, increasing number of patients is being treated with zolpidem for insomnia. Its increased use has led to rising incidence of rare side effects. In recent years there have been reported cases of acute delirium and psychosis after zolpidem use [2,3]. However, in majority of these cases, the dose of zolpidem used was more than the recommended dose (>10mg) and most of the patients had a history of psychiatric disease or substance abuse [4].

## 2. Case Presentation

An 81 year old male with the past medical history of hypertension and hyperlipidemia presented to Emergency department after passing out while he was standing and walking around. He had been complaining of non postural dizziness for about the past 3 or 4 days prior to admission. He then had a dizziness followed by a syncopal episode, which lasted approximately 5 minutes. The patient denied any palpitations, headache, confusion or trauma before

losing consciousness. There was no head trauma, seizure, bowel or bladder incontinence during syncopal episode. In the emergency department, he was noted to have significant bradycardia as well as elevated cardiac enzymes. EKG did not show any ST or T wave changes. A temporary transvenous pacemaker was inserted and cardiac catheterization was done. The patient was found to have a stenotic lesion in the left anterior descending, which was stented successfully. Subsequently, patient received permanent pacemaker for symptomatic bradycardia.

During his stay as an inpatient, he complained of difficulty sleeping at night, and was given 1 dose of Zolpidem, as it was reported to the nurse by the patient that this was his home medication and he has tried ambien before for insomnia without any side effects. He was ordered 5mg of ambien but 1 hour later the patient started having confusion, restlessness and visual hallucinations. His vitals were stable, but he was combative and was not oriented to person, place and time. Pupils were equal and reactive to light and he was moving all 4 extremities wildly. He was given 2 mg of Haloperidol IV twice and soft restraints were applied. His past medical history and home medications were reviewed to find the cause of delirium. He did not have any alcohol abuse or other psychiatric history. He was not on any psychiatric medications both at home and in the hospital.

All baseline labs including cbc, chem 7, Urine analysis, ABGs, EKG, MI units and urine drug screen were ordered which came back normal. CT scan of head was also ordered which was normal too [Figure 1]. All nursing notes and physician orders were reviewed and it was noted that patient's symptoms started 1 hour after Zolpidem use.

Patient's family was called to find whether Zolpidem is one of his home medications or not. It was noted that patient was never prescribed ambien. The patient did subsequently return to normal mental function in 8 hours after medication wore off. He got only 2 dosages of haldol

in the mean time for his agitation and hallucinations. Zolpidem was added to his allergy list due to acute onset delirium after its use. Patient was followed up closely on outpatient basis. He denied any more episodes of confusion, agitation and hallucinations.



**Figure 1.** CT head without contrast done at the time of confusion showed normal age related changes

### 3. Discussion

Zolpidem, a non benzodiazepine hypnotic, is a selective benzodiazepine-1 (BZ1) receptor agonist leading to sedative and hypnotic effects. As compared to benzodiazepine, zolpidem exhibits minimal anxiolytic, muscle relaxant, and anticonvulsant properties due to its minimal effect on BZ2 receptors [1]. Zolpidem has been increasingly used in practice due to better safety profile and low drug abuse potential. Hajak and Babelow studied 16,944 cases of zolpidem use and reported adverse events in 1.1% of cases [5]. The most common neuropsychiatric side effects associated with zolpidem are headache, drowsiness, depression, memory deficits and abnormal dreams [5]. However, a variety of rare side effects are increasingly being reported due to widespread use of zolpidem in clinical practice. Hallucinations, amnesia, suicidal ideation and sleep walking has been rarely reported with zolpidem dose [6,7]. Similarly, there are case reports of zolpidem induced delirium [8,9]. Majority of these rare neuropsychiatric side effects were seen in patients with a history of psychiatric illness and those taking more than 10 mg of zolpidem [4]. In addition, female sex gender, multiple psychiatric medications and underlying liver disease were considered risk factors for increased risk of zolpidem side effects. Acute delirium caused by single low dose zolpidem is a rare phenomenon which was seen in our case.

A variety of factors can lead to increased risk of neuropsychiatric side effects in patients taking zolpidem. Females tend to have 40 % higher serum concentration of zolpidem than men thus leading to increased risk of side effects [10]. Zolpidem neuropsychiatric effects are dose dependent with majority of rare effects reported in patients taking 10 mg or more of zolpidem [8]. Most (90%) of the dose of zolpidem is protein bound and it undergoes extensive hepatic metabolism by CYP enzymes, hence, low albumin and liver problems can lead to increased toxicity of zolpidem even at therapeutic doses. Similarly,

concomitant medications especially psychiatric medications can affect the metabolism of zolpidem because of cytochrome inhibition [1]. All rare side effects reported in the last few years had at least one or more of these risk factors.

Our patient presented with acute onset confusion, agitation and visual hallucinations after taking ambien. Patient was given single small dose (5mg) of zolpidem. Our differentials for acute delirium included polypharmacy, infections, stroke and metabolic encephalopathy. CT scan of head and all baseline investigations were normal. He did not have any psychiatric and drug or alcohol abuse history. He did not have any fever and no neck rigidity or stiffness was noted on examination. All hospital medications were reviewed, he was not on any psychiatric medications or opioids. The only pertinent finding in the history was his onset of symptoms after taking zolpidem. He was absolutely awake and well oriented before taking ambien, and was complaining of difficulty sleeping only. After ruling out other common causes of delirium, the diagnosis of zolpidem-induced delirium was made and he was given haldol. Patient returned to normal mentation after 8 hours and did well later on.

### 4. Conclusion

1: Non Benzodiazepine drugs are increasingly used for the short term treatment of insomnia due to better safety profile. However, rare side effects like delirium and psychosis are increasingly being reported. Such side effects may also occur in patients with a single small dose of zolpidem who have no previous psychiatric history or other risk factors.

2: These adverse effects may be reduced by avoiding 'per needed' use and prescribing lowest possible dose of zolpidem for the minimum duration of time.

3: Zolpidem-induced delirium should always be included in the differential diagnosis of acute onset delirium of unknown cause in hospitalized patients. All other common causes of delirium should be ruled out first before diagnosing zolpidem-induced delirium.

4: Patient's knowledge of home medications may be unreliable. Patient's home medications especially psychiatric medications should be confirmed from their pharmacy, primary care physician office or at least family before starting these medications in the hospital.

5: All sedative hypnotic drugs including non benzodiazepines should be used with extreme caution in very old patients (>75) as they are more prone to develop side effects.

Sleep hygiene and stimulus control techniques should be used first before starting hypnotics.

## Consent

Consent from patient was taken.

## Conflicts of Interest

Authors declare no conflicts of interest.

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