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PSYCHOSIS TRIGGERED BY ZOLPIDEM: CLINICAL OBSERVATIONS FROM TWO ADULT CASES.

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Abstract
Zolpidem, a non-benzodiazepine hypnotic commonly prescribed for insomnia, is generally considered safe for short-term use. However, adverse neuropsychiatric reactions, including psychosis, though rare, have been increasingly reported.

Introduction
Zolpidem is commonly used short-term to help treat insomnia. It can be used to help people fall asleep faster or help them wake up fewer times during the night.[1] Zolpidem, a non-benzodiazepine hypnotic agent that acts selectively on α1-containing GABA-A receptors, is widely prescribed for short-term management of insomnia.[2] While generally considered safe at therapeutic doses, emerging case reports have documented psychiatric adverse effects including hallucinations, delusional thinking, and frank psychotic episodes.[3] Despite widespread prescription, zolpidem-induced psychosis remains under-recognized, with fewer well-documented cases worldwide over the past two decades, most lacking rechallenge confirmation or structured causality assessment. Here we presenting two cases of zolpidem-induced psychotic symptoms in Indian population, with reproducible temporal association and remission upon discontinuation, contributing to the limited literature on this phenomenon particularly in Indian population.

Case 1
A 50-year-old female, not formally educated, housewife, belonging to Hindu joint family of middle socio economy status of Delhi presented with symptoms of low and sad mood, anxiety, loss of interest and easily fatigability, sleep disturbance and with multiple somatic symptoms presented to the psychiatry outpatient clinic. On the basis of history and Mental status examination according to ICD 10 diagnosis of Moderate Depression with somatic symptoms (F32.11) was made and patient started on Tab Sertraline 50 mg which was later titrated up to 200mg along with that Tab clonazepam 0.5mg was also initiated. There was no history of neurological illness, substance use, or family history of psychiatric disorders. Within two months patient reported significant improvement but sleep problem still persists. Because of that 5mg of Zolpidem was added which was increased to 10mg in next two

weeks. On the first night of administration of 10 mg of Zolpidem, the patient experienced an episode characterized by unresponsive staring, hallucinatory speech and behaviour, and brief unresponsiveness lasting approximately 30 minutes. Over the subsequent two weeks, she experienced five similar nocturnal episodes, each occurring exclusively on nights she ingested zolpidem. Informant also reported that whenever she skipped the dose there was no such symptom reported. On clinical evaluation, there were no features suggestive of seizure activity (absence of tongue bite, incontinence, or postictal confusion), no fluctuating sensorium to indicate delirium, and no evidence of dissociative episodes. Neurological and metabolic workup, including neuroimaging, were unremarkable. There was no past history of Psychotic episode in past and no use of other medications that could explain the symptoms. Considering the temporal relationship, Zolpidem induced psychotic symptom was suspected. So, Zolpidem was discontinued, following which the episodes resolved entirely, with no recurrence over a four-week drug-free observation period.

Case 2

A 34-year-old married male, graduate, working as manager in a private company, belonging to Hindu joint family of middle socio-economic status of urban background of Varanasi with no significant past medical, surgical, or psychiatric history, presented to the psychiatry outpatient department with complaints of low mood, irritability, disturbed sleep, and anxiety for the past three weeks. Symptoms started after his recent transfer from his hometown Varanasi to Delhi for occupational reasons. There was no history of substance use, head injury, seizures, or psychiatric illness in the patient or family. Patient was prescribed Tab Escitalopram 5mg which was later increased to 15mg along with that Tab Clonazepam 0.5mg was also added. Within a few days of initiating treatment all his target symptoms were improved but there was no improvement in sleep so the dose of Clonazepam was increased to 1mg but still no improvement was reported. Therefore, Tab Zolpidem 5mg was started within a week patient reported some improvement in sleep, so the zolpidem was titrated up to 10mg. Within 2 days there was significant improvement in sleep but family also noted that he developed suspiciousness, irritability, muttering to self, and disturbed behaviour. He reported visual hallucinations, fleeting persecutory ideas, and heightened anxiety. Because of all these symptoms family member stopped all the medication by themselves and symptoms subsided by itself within 2 days. After that they came for follow up, where medicine was again started but after taking single dose of zolpidem dose at night patient again started to experience same symptoms, so patient again visited OPD after 1 day. On detail assessment and general physical examination There was no evidence of disorientation, confusion, or memory impairment. On mental status examination, the patient was irritable, with restricted affect, increased psychomotor activity, and reported perceptual abnormalities. Thought content revealed persecutory ideas, and insight was impaired. Physical examination and baseline investigations (complete blood count, liver and renal function tests, thyroid profile, CT head) were within normal limits. A provisional diagnosis of Zolpidem-induced psychosis (substance/medication-induced psychotic disorder as per ICD-10/DSM-5) was made. Zolpidem was discontinued immediately. The patient was managed with Tab Escitalopram 15mg and for sleep disturbance Tab. Quetiapine 12.5mg was added.

Discussion

Zolpidem is a selective agonist of the α1 subunit of the GABA-A receptor complex, primarily inducing sedation.[1] However, paradoxical neuropsychiatric effects such as hallucinations, agitation, and psychosis have been documented.[4] The exact mechanism is unclear but may involve dysregulation of dopaminergic transmission in mesolimbic pathways or altered receptor sensitivity.[5] Our first case highlights zolpidem-induced psychotic symptoms in a middle-aged female with stable depressive disorder in remission. The temporal correlation, reproducibility on rechallenges, remission on discontinuation, and exclusion of alternative etiologies strengthen the causal association.[6] Previous studies have identified similar neuropsychiatric adverse reactions to zolpidem, particularly among females and elderly individuals, attributable to slower metabolism via CYP3A4/5 and consequently higher plasma levels at equivalent doses.[2] Concomitant use of SSRIs and benzodiazepines, as in this

case, may further potentiate zolpidem's central effects.[7] Our second case highlights that even in the absence of risk factors—such as psychiatric comorbidity, family history, or substance use—zolpidem can precipitate acute psychosis. Early recognition and prompt discontinuation are crucial for symptom resolution. Clinically, these presentations are often misattributed to primary psychotic disorders, resulting in unnecessary antipsychotic initiation or escalation of existing treatment. Our case underscores the need for clinicians to recognize this rare adverse drug reaction and to maintain a high index of suspicion when new-onset psychotic symptoms emerge temporally with hypnotic initiation.[8]

Conclusion

This case series adds to the growing literature documenting zolpidem-induced psychosis, particularly in the context of psychosocial stress. Healthcare providers should maintain high clinical suspicion for medication-induced psychiatric symptoms, especially in patients with recent medication changes and no prior psychiatric history. The case underscores the importance of using zolpidem at the lowest effective dose and providing adequate patient education about potential adverse effects. Additionally, individuals experiencing significant life transitions may require closer monitoring when prescribed psychoactive medications. The rapid resolution of symptoms following drug discontinuation supports the causal relationship and emphasizes the potential for complete recovery when appropriate interventions are implemented promptly. This case serves as a reminder that even commonly prescribed medications can produce serious psychiatric adverse effects, particularly in vulnerable populations.

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