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Detoxification of high-dose zolpidem using phenobarbital and gabapentin: two case reports

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Summary

Zolpidem is a hypnotic drug from the imidazopyridine family that is chemically distinct from benzodiazepines (BDZ). Contrary to classic BDZ, zolpidem acts selectively on α 1 subunit-containing GABA-A benzodiazepine (BZ1) receptors. There are a considerable number of zolpidem dependence case reports in the recent literature. Regarding the similarities of zolpidem and BDZ in pharmacodynamic and addictive characteristics, it has been suggested that recommended detoxification protocols for short half-life BDZ may also be useful in high-dose zolpidem withdrawal management. Safety and effectiveness of phenobarbital for inpatient BDZ detoxification has been established and it may be useful for zolpidem detoxification, as shown in two case reports presented here.

drug dependence, detoxification, zolpidem, phenobarbital

INTRODUCTION

Zolpidem is a hypnotic drug from the imidazopyridine family that is chemically distinct from benzodiazepines (BDZ)[1,2]. It is an agonist of the gamma-aminobutyric acid A type (GABA-A) receptor. It has been suggested that contrary to classic BDZ, zolpidem acts selectively on α 1 subunit-containing GABA-A benzodiazepine (BZ1) receptors presenting low or no affinity for other subtypes. Therefore, it has been assumed that it is devoid of benzodiazepines-like side-effects, and has minimal abuse and dependence potential. The recent literature [3] contains a considerable number of case reports describing zolpidem dependence, but there is no clear consensus for zolpidem detoxification in either clinical guidelines or literature. In published case reports diazepam [4], clonazepam [5], flumazenil [1], gabapentin [6], pregabalin [7] and quetiapine [8] have been suggested as possible treatment options for zolpidem detoxification. Regarding the similarities of zolpidem and BDZ considering their pharmacodynamic and addictive features, it has been suggested that recommended detoxification protocols for short half-life BDZ may also be useful in high-dose zolpidem withdrawal management [4]. The safety and effectiveness of phenobarbital for inpatient BDZ detoxification has been established [9] and it may be useful for zolpidem detoxification. We describe two cases of zolpidem dependence where patients were detoxified with oral phenobarbital.

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CASE REPORT

Patient 1

A 40-year-old female patient with no history of substance use started using zolpidem 10mg 3 years ago, following her divorce. She continued to experience insomnia, anxiety and agitation, and gradually increased the zolpidem dose, mostly during the last 6 months. On admission, she had daily use of 2g zolpidem (200 of 10mg tablets) in divided doses. She went through significant withdrawal episodes during the last year. She was referred to a psychosomatic inpatient unit, where she disclosed her problem and concerns about the negative effects of zolpidem on her physical health to the emergency physician. She was motivated to quit but was worried about withdrawal symptoms. She was admitted to the psychosomatic unit of our university general hospital for zolpidem detoxification. Due to the heavy use of zolpidem, we decided to use phenobarbital for withdrawal management. After admission, zolpidem was discontinued and the patient underwent phenobarbital detoxification (Table 1). After the first day, phenobarbital was tapered and discontinued in 6 days. In the first 3 days, she received up to 30mg zolpidem daily as needed, to control her severe withdrawal symptoms (agitation, insomnia and tremor).

Table 1. Detoxification program of patient 1

Day	Phenobarbital dose
1	100mg/1h until emergence of toxicity signs (the patient needed 5 doses or 500mg in day 1)
2	60mg/4h (360mg in day 2)
3	60mg/6h (240mg in day 3)
4	60mg/8h (180mg in day 4)
5	60mg/12h (120mg in day 5)
6	60mg/24h (60 mg in day 6)
7	Phenobarbital discontinued

After discontinuation of zolpidem and phenobarbital, gabapentin was administered for residual withdrawal symptoms' control (agitation and insomnia) and its dose was gradually increased up to 900mg/day undivided doses. Gabapentin was tapered and discontinued in 10 days. After 3 weeks of hospitalization, all of the patient's symptoms were controlled and she was discharged from hospital.

Patient 2

A 31-year-old woman with complaints of depressed mood, anxiety and insomnia was using 400mg zolpidem daily when she was admitted to a psychosomatic ward with a diagnosis of major depressive disorder (MDD) and zolpidem use disorder according to DSM-5 criteria. She had the diagnosis of MDD since she was 23 years old, and she had history of four psychiatric admissions in the past 4 years for severe MDD and suicidal ideations. She was treated with electroconvulsive therapy (ECT) in one instance. She was treated with different antidepressants in the past years and fluoxetine had shown the best treatment response for her depressive symptoms. She was prescribed 10mg zolpidem nightly 7 years ago to control her insomnia. She started to develop tolerance and was using higher doses. In her prior admission, a year earlier, she was using 150mg/day zolpidem in divided doses. At the time, her zolpidem use was managed with clonazepam tapering, but 6 months after discharge she restarted zolpidem and escalated the dose gradually to 400mg/day in divided doses in the last 2 months. During the last admission, zolpidem was discontinued and phenobarbital detoxification protocol was started as shown in Table 2. After the first day of loading protocol, phenobarbital was tapered and discontinued in 5 days.

Table 2. Detoxification program of patient 2

Day	Phenobarbital dose
1	60mg/1h until emergence of toxicity signs (the patient needed 5 doses or 300mg in day 1)
2	60mg/6h (240mg in day 2)
3	60mg/8h (180mg in day 3)
4	60mg/12h (120mg in day 4)
5	60mg/24h (60mg in day 5)
6	Phenobarbital discontinued.

Gabapentin was then administered to control the residual withdrawal symptoms (anxiety and insomnia), starting at 300mg/day and gradually increased up to 1500mg/day in divided doses. Gabapentin was tapered and discontinued after 10 days. Fluoxetine (20mg/day) was administered for treatment of MDD and after 2 weeks of hospitalization the patient was discharged from hospital with significant improvement.

DISCUSSION

In supratherapeutic doses, zolpidem has been associated with unusual anxiolytic effects, memory loss, complex sleep behaviors, abuse, dependence, and withdrawal symptoms [3, 10, 11]. It seems that in high doses, zolpidem abandons its selectivity for BZ1 receptors and demonstrates all the actions of classic BDZ [3]. Withdrawal symptoms are another indicator for this theory. Same as BDZ, zolpidem withdrawal symptoms vary, from anxiety and autonomic nervous system dysfunction to severe, generalized tonic-clonic seizures [12–14]. To clarify how the two patients in the case report had access to medication, the first patient was a medical staff member and the second patient used her educational background to obtain medication.

To the best of our knowledge, this is the first report of zolpidem detoxification with phenobarbital. Phenobarbital is a medication that binds to the GABA-A receptor like BDZ. Its half-life is two times longer and, in some cases, up to six times longer than long-acting BDZ (gold standard agents for BDZ detoxification). Lethal doses of phenobarbital are many times higher than toxic doses and the signs of toxicity (for example, sustained nystagmus, slurred speech and ataxia) are easy to observe. It has been used to treat alcohol withdrawal safely [9, 15] and due to its antiepileptic and anxiolytic effect, it seems rational to use phenobarbital for zolpidem detoxification.

The patients were detoxified successfully in 5 and 6 days and withdrawal symptoms were mild to moderate. They used very high doses of zolpidem and detoxification with BDZ would have required longer admission and higher doses of BDZ. Phenobarbital may be particularly useful for zolpidem detoxification in patients with a history of using high doses of zolpidem.

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