ONLINE EXCLUSIVE

THE PATIENT

49-year-old man

SIGNS & SYMPTOMS

- Chronic insomnia
- Nightly zolpidem use
- Concern for tapering withdrawals

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THE CASE

A 49-year-old man with chronic insomnia was referred to the pharmacist authors (LF and DP) to initiate and manage the tapering of nightly zolpidem use. Per chart review, the patient had complaints of insomnia for more than 30 years. His care had been transferred to a Nebraska clinic 5 years earlier, with a medication list that included zolpidem controlled release (CR) 12.5 mg nightly. Since then, multiple interventions to achieve cessation had been tried, including counseling on sleep hygiene, adjunct antidepressant use, and abrupt discontinuation. Each of these methods was unsuccessful. So, his family physician (SS) reached out to the pharmacist authors (LF and DP).

THE APPROACH

Due to the patient's long history of zolpidem use, a lack of literature on the topic, and worry for withdrawal symptoms, a taper schedule was designed utilizing various benzodiazepine taper resources for guidance. The proposed taper utilized 5-mg immediate release (IR) tablets to ensure ease of tapering. The taper ranged from 20% to 43% weekly reductions based on the ability to split the zolpidem tablet in half.

DISCUSSION

Zolpidem is a sedative-hypnotic medication indicated for the treatment of insomnia when used at therapeutic dosing (ie, 5 to 10 mg nightly). Anecdotal efficacy, accompanied by weak chronic insomnia guideline recommendations, has led prescribers to use zolpidem as a chronic medication to treat insomnia.[1,2] There is evidence of dependence and possible seizures from supratherapeutic zolpidem doses in the hundreds of milligrams, raising safety concerns regarding abuse, dependence, and withdrawal seizures in chronic use.[2,3]

Additionally, there is limited evidence regarding the appropriate process of discontinuing zolpidem after chronic use.[2] Often a taper schedule—similar to those used with benzodiazepine medications—is used as a reference for discontinuation.[1] The hypothetical goal of a taper is to prevent withdrawal effects such as rebound insomnia, anxiety, palpitations, and seizures.[3] However, an extended taper may not actually be necessary with chronic zolpidem patients.

Tapering with minimal adverse effects

Pharmacokinetic and pharmacodynamic studies have suggested minimal, if not complete, absence of rebound or withdrawal effects with short-term zolpidem use.[4] The same appears to be true of patients with long-term use. In a study, Roehrs and colleagues[5] explored whether long-term treatment (defined as 8 months) caused rebound insomnia upon abrupt

withdrawal. The investigators concluded that people with primary insomnia do not experience rebound insomnia or withdrawal symptoms with chronic, therapeutic dosing.

Another study involving 92 elderly patients on long-term treatment of zolpidem (defined as > 1 month, with average around 9.9 ± 6.2 years) experienced only 1 or 2 nights of rebound insomnia during a month-long taper.[1,6] Following that, they experienced improvements in initiation and staying asleep.

A possible explanation for the lack of dependence or withdrawal symptoms in patients chronically treated with zolpidem is the pharmacokinetic profile. While the selectivity of the binding sites differentiates this medication from benzodiazepines, the additional fact of a short half-life, and no repeated dosing throughout the day, likely limit the risk of experiencing withdrawal symptoms.[1] The daily periods of minimal zolpidem exposure in the body may limit the amount of physical dependence.

This case documents a successfully accelerated taper for a patient with a chronic history (> 5 years) of zolpidem use.

Discontinuation of zolpidem

The 49-year-old man had a history of failed abrupt discontinuation of zolpidem in the past (without noted withdrawal symptoms). Thus, various benzodiazepine taper resources were consulted to develop a taper schedule.

We switched our patient from the zolpidem CR 12.5 mg nightly to 10 mg of the IR formulation, and the pharmacists proposed 20% to 43% weekly decreases in dosing based on dosage strengths. At the initial 3-day follow-up (having taken 10 mg nightly for 3 days), the patient reported a quicker onset of sleep but an inability to sleep through the night. The patient denied withdrawal symptoms or any significant impact to his daily routines. These results encouraged a progression to the next step of the taper. For the next 9 days, the patient took 5 mg nightly, rather than the pharmacist-advised dosing of alternating 5 mg and 10 mg nightly, and reported similar outcomes at his next visit.

This success led to the discontinuation of scheduled zolpidem. The patient was also given a prescription of 2.5 mg, as needed, if insomnia rebounded. No adverse effects were noted despite the accelerated taper. Based on patient response and motivation, the taper had progressed more quickly than scheduled, resulting in 3 days of 10 mg, 9 days of 5 mg, and 1 final day of 2.5 mg that was used when the patient had trouble falling asleep. At the 6-month follow-up, the patient informed the physician that he had neither experienced insomnia nor used any further medication.

THE TAKEAWAY

This case documents a successfully accelerated taper for a patient with a chronic history (> 5 years) of zolpidem use. Although withdrawal is often patient specific, this case suggests the risk is low despite the chronic usage. This further adds to the literature suggesting against the need for an extended taper, and possibly a taper at all, when using recommended doses of chronic zolpidem. This is a significant difference compared to past practices that drew from literature-based benzodiazepine tapers.[6] This case serves as an observational point of reference for clinicians who are assisting patients with chronic zolpidem tapers. JFP

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REFERENCES

1. Lähteenmäki R, Neuvonen PJ, Puustinen J, et al. Withdrawal from long-term use of zopiclone, zolpidem and temazepam may improve perceived sleep and quality of life in older adults with primary insomnia. *Basic Clin Pharmacol Toxicol*. 2019;124:330-340. doi: 10.1111/bcpt.13144
2. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13:307-349. doi: 10.5664/jcsm.6470
3. Haji Seyed Javadi SA, Hajiali F, Nassiri-Asl M. Zolpidem dependency and withdrawal seizure: a case report study. *Iran Red Crescent Med J*. 2014;16:e19926. doi: 10.5812/ircmj.19926
4. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. *Clin Pharmacokinet*. 1995;29:142-153. doi: 10.2165/00003088-199529030-00002
5. Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. *J Psychopharmacol*. 2012;26:1088-1095. doi: 10.1177/0269881111424455
6. Lader M. Benzodiazepine harm: how can it be reduced? *Br J Clin Pharmacol* 2014;77:295-301. doi: 10.1111/j.1365-2125.2012.04418.x