Zopiclone

Is it a pharmacologic agent for abuse?

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ABSTRACT

OBJECTIVE To determine whether the hypnosedative drug zopiclone could be an agent for abuse.

SOURCES OF INFORMATION Using MEDLINE and PubMed, English-language medical literature was systematically reviewed for reports of direct drug abuse and addiction. A review was also conducted for clinical trials or patient series that discussed issues of addiction or rebound effects.

MAIN MESSAGE Evidence of drug abuse and dependency was found in case reports and small patient series. Dependency symptoms of severe rebound, severe anxiety, tremor, palpitations, tachycardia, and seizures were observed in some patients after withdrawal. Abuse occurred more commonly among patients with previous drug abuse or psychiatric illnesses. Many clinical trials have found evidence of rebound insomnia after recommended dosages were stopped, albeit for a minority of patients. Comparative studies of zopiclone and benzodiazepines or other "Z" drugs are conflicting.

CONCLUSION Zopiclone has the potential for being an agent of abuse and addiction. While many have suggested that the addictive potential for this and other "Z" drugs is less than for most benzodiazepines, caution should be taken when prescribing this agent for insomnia. Ideally, prescriptions should be given for a short period of time and within the recommended dosage guidelines.

RÉSUMÉ

OBJECTIF Déterminer si l'agent hypnosédatif zopiclone présente un risque d'accoutumance.

SOURCE DE L'INFORMATION À l'aide de MEDLINE et de PubMed, on a effectué une revue systématique de la littérature anglaise sur des cas de toxicomanie et d'accoutumance de ce type. On a également relevé les essais cliniques et les séries de patients relatifs à l'accoutumance et à l'effet rebond.

PRINCIPAL MESSAGE On a trouvé des rapports de cas et des petites séries de patients décrivant des cas de toxicomanie et d'accoutumance. Chez certains patients en sevrage, on a observé de graves symptômes de rebond et d'anxiété, de tremblement, de palpitations, de tachycardie et de convulsions. Les patients avec antécédents de toxicomanie ou de maladie psychiatrique étaient plus susceptibles de toxicomanie. Plusieurs essais cliniques ont observé chez un petit nombre de patients de l'insomnie rebond à l'arrêt d'un traitement aux doses recommandées. Les études comparant la zopiclone aux benzodiazépines et aux autres médicaments de type «Z» sont contradictoires.

CONCLUSION La zopiclone a le potentiel d'entraîner de l'accoutumance et de la toxicomanie. Même si plusieurs auteurs donnent à penser que le risque de toxicomanie avec cet agent et les autres médicaments de type «Z» est moins élevé qu'avec la plupart des benzodiazépines, il y a lieu d'être prudent lorsqu'on le prescrit pour l'insomnie. Idéalement, ces prescriptions devraient être de courte durée et respecter les doses recommandées.

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Case

A 49-year-old man presented to an outpatient clinic with complaints of chronic insomnia. He was known to have an obsessive-compulsive disorder and was seen frequently in conjunction with a psychiatrist. He had been taking zopiclone for approximately 5 years. Initially, he was given 7.5 mg nightly, but this dose increased to 15 mg and then 22.5 mg.

The patient claimed that he was using only the prescribed amount, but he had been prescribed 60 tablets only 11 days earlier. Review of pharmacy records revealed that the patient had been prescribed approximately 500 tablets (7.5 mg) during the previous 100 days. When confronted with this information, the patient admitted to taking 4 to 7 tablets every night and afterward admitted he was addicted to zopiclone. Trials of trazodone and amitriptyline were then prescribed as he attempted to reduce the zopiclone doses. Regular follow-up visits were also recommended to help him manage his addiction.

Zopiclone is a commonly used hypnosedative that has been mainly promoted as a sleep aid.[1] It is available in several generic formulations in Canada but has been marketed under the trade names Imovane and Rhovane.

Zopiclone is one of the "Z" drug sedative-hypnotics and became clinically available in the mid 1980s. (Others include zaleplon [Starnoc in Canada and Sonata in the United States], zolpidem [Ambien in the United States], and eszopiclone [S-isomer of zopiclone; Lunesta in the United States].) It is not one of the benzodiazepine drugs but has many similarities to them when used for sleep. These include decreased latency to sleep initiation, increased duration of sleep, and reduced episodes of awakening. There was hope that "Z" drugs would be less addictive or less associated with post-use rebound than benzodiazepines.[2]

Chemically, zopiclone is a cyclopyrrolone.[3] It is a type A γ-aminobutyric acid (GABA) receptor agonist and therefore enhances GABA-related neuronal inhibition. Benzodiazepines also bind to and affect the function of GABA receptors. Few interactions with other drugs are documented.[4] Zopiclone is typically prescribed in the range of 5 mg to 7.5 mg daily and at 3.75 mg daily for the elderly.

While zopiclone is a highly effective sleep aid, there is controversy about the extent of its addiction potential. In practice, zopiclone is often used for treating insomnia, but it is not uncommon for patients with drug-seeking behaviour to request it. Although recommended for short-term treatment of insomnia,[5] it is also not uncommon for patients, including the elderly, to take the drug nightly or continuously for many months. When discussing potential addiction to zopiclone use with their physicians, some prospective patients say they have been told it is not addictive.

The costs and consequences of insomnia in the Canadian population have been estimated.[6] From 5% to 30% of any particular population might be affected. In response, a considerable amount of hypnosedatives is prescribed yearly. Studies show the use of benzodiazepines and "Z" drugs to be as high as 5% to 30% among the elderly.[7,8]

Sources of information

Using MEDLINE and PubMed, English-language medical literature was systematically reviewed for reports of direct drug abuse and addiction. A review was also conducted for clinical trials or patient series that discussed issues of addiction or rebound effects.

Main message

Zopiclone has quickly gained acceptance by practitioners and patients.[9] In Alberta it is now the most frequently dispensed hypnosedative agent (47.4% of such agents compared with 0.1% to 28.7% for individual benzodiazepines).[10] Investigators have found substantial increases in the use of zopiclone in Canada in the years 1996-1997, 1998-1999, and 2000-2001.[11] It appears that the increases might have come at the expense of declining use of some benzodiazepines. In a 2003 lay review[12] of Canadian pharmaceuticals, zopiclone ranked 30th among the top 100 generic drug products sold (nearly 1.5 million prescriptions of generic zopiclone), and the brand name Imovane ranked 74th (more than 500 000 prescriptions) of 100 brand-name drug products sold in Canada; only Ativan ranked higher (14th; approximately 2.5 million prescriptions) as a brand-name hypnosedative.[12]

Initial reports have proposed that zopiclone did not cause rebound or withdrawal phenomena or dependence.[13-15] Postmarketing surveillance reports have been favourable.[16,17] Some have indicated that "Z" drugs were less likely to be habit forming than benzodiazepines.[18-20] However, animal data support the potential for addiction.[21] Although not much has been published on this topic, a somewhat different picture has emerged with the few anecdotes, case series, and controlled studies. Parallels with other addictive substances have been heralded and reviewed.[22,23]

Table 1 provides examples of zopiclone abuse and addiction.[24-31] In some circumstances, the drug was initiated at a standard dose of 7.5 mg daily but then increased. Most patients taking the drug suffered from pre-existing addiction or chemical abuse, or from underlying psychiatric disorders. Withdrawal symptoms were reported in several of these anecdotes, including

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Table 1. Patient reports of zopiclone abuse or addiction

REPORT	PATIENT SEX	PATIENT AGE	MG/D	UNDERLYING PROBLEMS	ADDICTION OR ABUSE HISTORY	COMMENTS
Sutherland,[24] 1991	Male	29	7.5	None reported	Narcotic	Relapsed with a narcotic addiction
Aranko et al,[25] 1991	Male	36	30 to 90	Depression, obsessive-compulsive disorder	Alcohol, benzodiazepines	Had withdrawal seizures
Thakore and Dinan,[26] 1992	Male	36	37.5 to 45	Affective disorder	Alcohol, benzodiazepines	
Sullivan et al,[27] 1995	Male	17	15 to 30	None reported	Multidrug	Better than temazepam when used with alcohol
Sullivan et al,[27] 1995	Male	16	7.5 to 37.5	Behavioural problems	Alcohol	
Sullivan et al,[27] 1995	Male	18	Intravenous use	None reported	Multidrug	
Jones and Sullivan,[28] 1998	Male	29	22.5	None reported	None reported	Multiple withdrawal symptoms
Jones and Sullivan,[28] 1998	Male	26	30	None reported	None reported	Multiple withdrawal symptoms
Jones and Sullivan,[28] 1998	Female	49	22.5	None reported	None reported	Rebound anxiety and insomnia
Jones and Sullivan,[28] 1998	Female	36	30	Bipolar disorder	Benzodiazepines	Multiple withdrawal symptoms
Sikdar,[29] 1998	Male and female (6 patients)	Various	45 to 390	None reported	None reported	Multiple withdrawal symptoms, tolerance; 2 patients forged prescriptions
Ayonrinde and Sampson,[30] 1998	Female	60	22.5	Schizophrenia	Alcohol, benzodiazepines	Multiple withdrawal symptoms
Ayonrinde and Sampson,[30] 1998	Male	40	30	Depression	None reported	Multiple withdrawal symptoms
Ayonrinde and Sampson,[30] 1998	Female	71	15	Depression	None reported	Multiple withdrawal symptoms
Flynn and Cox,[31] 2006	Female	76	67.5	Depression	None reported	Had withdrawal seizures

cravings, severe rebound insomnia, anxiety or panic attacks, weakness, tremor, palpitations, and tachycardia. Withdrawal seizures were also recorded.

Addicts report that ingesting zopiclone and alcohol together heightens euphoria.[27] In one report,[24] use of zopiclone appeared to instigate a relapse into narcotic use. The drug has become well known in addict circles,[32] and in the United Kingdom, the tablets have been labeled as *zim-zims*.[27] Drug abusers have also used zopiclone as a replacement for benzodiazepines. With many generic versions becoming available, the cost of zopiclone on the street has decreased. Oral use of zopiclone predominates, but intravenous use has also been reported. In clinical practice, other patients are possibly at risk for dependence, especially after prolonged use.

Table 2 also provides some insight from various studies.[32-50] Some of the data pose contradictions; however, rebound insomnia and withdrawal symptoms soon after cessation are not uncommon whether patients took the usual dose or excessive doses. Symptoms might also occur despite a tapering of the dose. As with benzodiazepines, zopiclone was recognized as a potential replacement for alcohol. These phenomena occurred with what would have been considered standard daily doses. One addiction centre reported that 5.1% of addicts presenting to addiction centres admitted to zopiclone addiction.[50]

Zopiclone will continue to be prescribed for insomnia given that most believe, generally and scientifically, that it is associated with fewer clinical problems than benzodiazepines.[18] Some even believe zopiclone is not addictive at all. In a recent, although small, survey[51] of 40 British psychiatrists, zopiclone was found to be commonly prescribed; however, many respondents were unaware of its dependence potential. The *Compendium of Pharmaceuticals and Specialties* warns of potential addiction.[5] It also recommends limiting the agent's

use (to approximately 7 to 10 days). Although the initial manufacturer's recommendations include limits for length of therapy, long-term use in geriatric or general populations is not uncommon.

Table 2. Studies addressing withdrawal or addiction associated with zopiclone

STUDY	NO. OF PATIENTS	MG/D	STUDY GROUP	FINDINGS
Mamelak et al,[33] 1982	6	7.5	Insomniac patients	Zopiclone, treated for 3 wk, no carry over effect and no rebound insomnia
Dorian et al,[34] 1983	9	7.5	Normal volunteers	Double-blind placebo controlled, treated for 3 wk, increased anxiety and lighter sleep on withdrawal for days shortly after discontinuation
Lader and Denney,[35] 1983	10	2.5 to 10	Normal volunteers	Double-blind placebo controlled, dose response curve for residual overnight effects as determined with electroencephalogram and psychological tests
Bechelli et al,[36] 1983	40	3.75	Weaned alcoholics	Zopiclone vs triazolam, double-blind randomized crossover, zopiclone use likened to alcohol use, more likely to choose zopiclone over triazolam
Boissl et al,[37] 1983	40	3.5	Weaned alcoholics	Zopiclone vs triazolam, double-blind randomized crossover, no difference in replacement potential for alcohol
Lader and Frcka,[38] 1987	10	3.75 to 7.5	Normal volunteers	Zopiclone and placebo and temazepam, double-blind comparisons, zopiclone rebound effects minimal, withdrawal of total dose no different than tapering
Fleming et al,[39] 1990	48	7.5	Chronic insomniacs	Zopiclone vs triazolam, double-blind, worse psychomotor deterioration after triazolam than zopiclone, 3 of 24 zopiclone patients felt agitated early after withdrawal
Ponciano et al,[40] 1990	24	7.5	Chronic insomniacs	Zopiclone and placebo and flurazepam, double-blind randomized, treated for 3 wk, zopiclone has no effect on early morning performance and free of residual sedative activity
Ngen and Hassan,[41] 1990	15	7.5	Insomniac patients	Zopiclone and placebo and temazepam, randomized study, treated for 2 wk, no psychomotor performance deterioration
Pecknold et al,[42] 1990	11	7.5	Chronic insomniacs	Treated for 7 to 8 wk, return of sleep variables to pretreatment baseline after withdrawal, 1 of 11 patients had marked rebound insomnia and daytime anxiety for the first wk off
Begg et al,[43] 1992	88	7.5	General sleep disorder	Zopiclone vs midazolam, treated for 1 wk, more rebound insomnia with zopiclone
Lemoine et al,[44] 1995	102	7.5	Chronic insomniacs	Treated for 3 mo, withdrawal effects despite tapering dose
Mann et al,[45] 1996	11	7.5	Normal volunteers	Treated for 12 d, rebound insomnia after discontinuation, increased REM sleep after discontinuation, no effect on nocturnal melatonin secretion
Sikdar and Ruben,[32] 1996	100	90 to 380	Multidrug abusers	Strong cravings, feeling edgy, rebound insomnia, tolerance to sedative properties
Stip et al,[46] 1999	20	7.5	Insomniac patients	Zopiclone and placebo and temazepam, double-blind, treated for 3 wk, no rebound insomnia or anxiety with either
Voderholzer et al,[47] 2001	11	7.5	Normal volunteers	Zopiclone and zolpidem and triazolam and placebo, double-blind, treated for 4 wk, minimal rebound effects
Tsutsui et al,[48] 2001	248	7.5	Insomniac patients	Zopiclone vs zolpidem, treated for 2 wk, zopiclone group had 15.4% with rebound insomnia
Johansson et al,[49] 2003	23 120	Not reported	Alcoholics Controls	Alcoholics more often dependent on zopiclone than controls
Jaffe et al,[50] 2004	297	Not reported	Addiction treatment centres	5.1% claimed to be addicted to zopiclone

Some have argued that the frequency of "Z" drug misuse must be low given the many prescriptions written and the few case reports published worldwide.[52] However, an Internet source[53] has enumerated 24 people who have sought advice regarding zopiclone dependency, and this number rivals the total available case reports cited worldwide in the medical literature. Because some drug abusers do not seek treatment, the true frequency of abuse or dependence is certainly higher than reported.

Conclusion

Physicians prescribing zopiclone should have the same concerns as they would for prescribing benzodiazepines (**Table 3**[54]). Ideally, use should be short-term; long-term use must be monitored carefully. Physicians are also advised to be cautious about giving prescriptions to patients who misuse alcohol or drugs. A direct and especially new request for zopiclone should raise concern for potential abuse. Such abuse might include personal use or sale of the drug on the street. Physicians could try low-dose antidepressants, such as amitriptyline or trazodone, if a pharmacologic agent is absolutely required for insomnia.

Table 3. Points to consider when prescribing hypnosedative drugs

1. Have nonpharmacologic approaches or therapies been considered?
2. Is a pharmacologic agent required?
3. Is the target short-term therapy? Is the target long-term therapy?
4. Are there medical or drug interaction contraindications?
5. Is the most cost-effective and safe treatment being considered (ie, dose, type of medication, compliance, and age considerations)?
6. Is insomnia part of an underlying illness that will require some other treatment (eg, depression)?
7. Is the patient at risk for withdrawal symptoms? If so, what strategy is there to avoid them?
8. Does the patient have an addictive personality, or is the patient seeking drugs?
9. Is there a mechanism to assure appropriate use or to have appropriate follow-up?

Adapted from Hajak and Rodenbeck.[54]

Cognitive behavioural therapy is another alternative to or replacement for medication.[55] In studies of the elderly, for example, meta-analysis has proposed that short-term treatment with hypnosedatives is more likely to cause adverse effects than to improve sleep.[8] Other nonpharmacologic interventions are also likely to be successful.[56] Managing insomnia should not consist solely of using prescription medication.

EDITOR'S KEY POINTS

- Zopiclone is a hypnosedative drug commonly used to treat insomnia. Investigators have found substantial increases in its use in Canada.
- While zopiclone is a highly effective sleep aid, there is controversy about the extent of its addiction potential.
- When prescribing zopiclone, physicians should have the same concerns as they would for prescribing benzodiazepines.

POINTS DE REPÈRE DU RÉDACTEUR

- L'hypnosédatif zopiclone est fréquemment utilisé contre l'insomnie. Certaines recherches indiquent que cet agent est de plus en plus utilisé au Canada.
- La zopiclone est très efficace pour favoriser le sommeil, mais son potentiel d'accoutumance fait l'objet de controverse.
- La prescription de zopiclone requiert les mêmes précautions que la prescription de benzodiazépines.

Competing interests

None declared

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