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.
Zopiclone is typically prescribed in the short-term treatment of insomnia, 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. From 5% to 30% of any particular population might be affected. In response, a considerable amount of hypnotic use is prescribed yearly. Studies show the use of benzodiazepines and “Z” drugs to be as high as 5% to 30% among the elderly.

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. In Alberta it is now the most frequently dispensed hypnotic agent (47.4% of such agents compared with 0.1% to 28.7% for individual benzodiazepines). Investigators have found substantial increases in the use of zopiclone in Canada in the years 1996–1997, 1998–1999, and 2000–2001. It appears that the increases might have come at the expense of declining use of some benzodiazepines. In a 2003 lays review 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 500000 prescriptions) of 100 brand-name drug products sold in Canada; only Ativan ranked higher (14th; approximately 2.5 million prescriptions) as a brand-name hypnotic.

Initial reports have proposed that zopiclone did not cause rebound or withdrawal phenomena or dependence. Postmarketing surveillance reports have been favourable. Some have indicated that “Z” drugs were less likely to be habit forming than benzodiazepines. However, animal data support the potential for addiction. 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.

Table 1 provides examples of zopiclone abuse and addiction. 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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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. In one report, use of zopiclone appeared to instigate a relapse into narcotic use. The drug has become well known in addict circles, and in the United Kingdom, the tablets have been labeled as zim-zims. 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. 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. 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. Some even believe zopiclone is not addictive at all. In a recent, although small, survey 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. 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>mg/d</th>
<th>Study Group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamelak et al, 1982</td>
<td>6</td>
<td>7.5</td>
<td>Insomniac patients</td>
<td>Zopiclone, treated for 3 wk, no carry over effect and no rebound insomnia</td>
</tr>
<tr>
<td>Dorian et al, 1983</td>
<td>9</td>
<td>7.5</td>
<td>Normal volunteers</td>
<td>Double-blind placebo controlled, treated for 3 wk, increased anxiety and lighter sleep on withdrawal for days shortly after discontinuation</td>
</tr>
<tr>
<td>Lader and Denney, 1983</td>
<td>10</td>
<td>2.5 to 10</td>
<td>Normal volunteers</td>
<td>Double-blind placebo controlled, dose response curve for residual overnight effects as determined with electroencephalogram and psychological tests</td>
</tr>
<tr>
<td>Bechelli et al, 1983</td>
<td>40</td>
<td>3.75</td>
<td>Weaned alcoholics</td>
<td>Zopiclone vs triazolam, double-blind randomized crossover, zopiclone use likened to alcohol use, more likely to choose zopiclone over triazolam</td>
</tr>
<tr>
<td>Boissel et al, 1983</td>
<td>40</td>
<td>3.5</td>
<td>Weaned alcoholics</td>
<td>Zopiclone vs triazolam, double-blind randomized crossover, no difference in replacement potential for alcohol</td>
</tr>
<tr>
<td>Lader and Frcka, 1987</td>
<td>10</td>
<td>3.75 to 7.5</td>
<td>Normal volunteers</td>
<td>Zopiclone and placebo and temazepam, double-blind comparisons, zopiclone rebound effects minimal, withdrawal of total dose no different than tapering</td>
</tr>
<tr>
<td>Fleming et al, 1990</td>
<td>48</td>
<td>7.5</td>
<td>Chronic insomniacs</td>
<td>Zopiclone vs triazolam, double-blind, worse psychomotor deterioration after triazolam than zopiclone, 3 of 24 zopiclone patients felt agitated early after withdrawal</td>
</tr>
<tr>
<td>Ponciano et al, 1990</td>
<td>24</td>
<td>7.5</td>
<td>Chronic insomniacs</td>
<td>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</td>
</tr>
<tr>
<td>Ngen and Hassan, 1990</td>
<td>15</td>
<td>7.5</td>
<td>Insomniac patients</td>
<td>Zopiclone and placebo and temazepam, randomized study, treated for 2 wk, no psychomotor performance deterioration</td>
</tr>
<tr>
<td>Pecknold et al, 1990</td>
<td>11</td>
<td>7.5</td>
<td>Chronic insomniacs</td>
<td>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</td>
</tr>
<tr>
<td>Begg et al, 1992</td>
<td>88</td>
<td>7.5</td>
<td>General sleep disorder</td>
<td>Zopiclone vs midazolam, treated for 1 wk, more rebound insomnia with zopiclone</td>
</tr>
<tr>
<td>Lemoine et al, 1995</td>
<td>102</td>
<td>7.5</td>
<td>Chronic insomniacs</td>
<td>Treated for 3 mo, withdrawal effects despite tapering dose</td>
</tr>
<tr>
<td>Mann et al, 1996</td>
<td>11</td>
<td>7.5</td>
<td>Normal volunteers</td>
<td>Treated for 12 d, rebound insomnia after discontinuation, increased REM sleep after discontinuation, no effect on nocturnal melatonin secretion</td>
</tr>
<tr>
<td>Sikdar and Ruben, 1996</td>
<td>100</td>
<td>90 to 380</td>
<td>Multidrug abusers</td>
<td>Strong cravings, feeling edgy, rebound insomnia, tolerance to sedative properties</td>
</tr>
<tr>
<td>Stip et al, 1999</td>
<td>20</td>
<td>7.5</td>
<td>Insomniac patients</td>
<td>Zopiclone and placebo and temazepam, double-blind, treated for 3 wk, no rebound insomnia or anxiety with either</td>
</tr>
<tr>
<td>Voderholzer et al, 2001</td>
<td>11</td>
<td>7.5</td>
<td>Normal volunteers</td>
<td>Zopiclone and zolpidem and triazolam and placebo, double-blind, treated for 4 wk, minimal rebound effects</td>
</tr>
<tr>
<td>Tsutsui et al, 2001</td>
<td>248</td>
<td>7.5</td>
<td>Insomniac patients</td>
<td>Zopiclone vs zolpidem, treated for 2 wk, zopiclone group had 15.4% with rebound insomnia</td>
</tr>
<tr>
<td>Johansson et al, 2003</td>
<td>23</td>
<td>Not reported</td>
<td>Alcoholics Controls</td>
<td>Alcoholics more often dependent on zopiclone than controls</td>
</tr>
<tr>
<td>Jaffe et al, 2004</td>
<td>297</td>
<td>Not reported</td>
<td>Addiction treatment centres</td>
<td>5.1% claimed to be addicted to zopiclone</td>
</tr>
</tbody>
</table>

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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 source53 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). 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? |

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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