Benzodiazepines and other sedative-hypnotic drugs are prescribed to many older adults despite the nearly 5-fold increased risk of adverse cognitive events associated with their use (95% confidence interval [CI] 1.47 to 15.47), the 2.6-fold increased risk of adverse psychomotor events (95% CI 1.12 to 6.09), the association with falls and hip fractures and the 5-fold increased risk of hospital admission after a motor vehicle collision. The number needed to treat with a sedative-hypnotic drug for improved quality of sleep is 13, whereas the number needed to harm is 6. Harm can include drowsiness, fatigue, headache, nightmares and gastrointestinal disturbances.

In the 2012 updated Beers criteria for potentially inappropriate medication use in older adults, a strong recommendation based on high-quality evidence has been made to avoid all benzodiazepines in older adults. Yet, 16%–33% of older people living in the community use benzodiazepines, and 54% use them daily. The most widely reported indication is insomnia (64%). People who take benzodiazepines tend to be older women, to have lower education levels, to consume less alcohol but more tobacco, to have higher depression and anxiety scores and to use other psychotropic drugs.

The appropriate assessment and management of chronic insomnia is crucial. Insomnia affects quality of life and has been shown to be an independent risk factor for falls (adjusted odds ratio [OR] 1.52, 95% CI 1.38 to 1.66). A current evidence-based consensus guideline can assist clinicians in managing chronic insomnia.

In this review, we address questions regarding sedative-hypnotic drugs, their discontinuation and effective alternative options among older adults. This review is based on a systematic literature search (Box 1). Most of the relevant evidence identified consisted of small, short-term, randomized trials.

How can long-term use of sedative-hypnotic drugs be prevented?

Prescribing sedative-hypnotic drugs in hospital has a substantial impact on long-term use. A case–control study of new benzodiazepine prescriptions found that cases were 3 times more likely than controls to have been admitted to hospital within 30 days after the index date. In another study, at 1 month after discharge, patients were more likely to stop previous benzodiazepine use if they did not receive them during the hospital stay (OR 3.58, 95% CI 1.56 to 8.21) and were more likely to start taking benzodiazepines if they were prescribed them during the hospital stay (OR 3.57, 95% CI 1.66 to 8.08). No literature was identified around the role of counselling or other strategies to prevent long-term use.

Are non-benzodiazepine sedative-hypnotic drugs a safer alternative?

Medications commonly used to treat insomnia include the “Z drugs” (non-benzodiazepine sedative-hypnotic drugs, of which zopiclone and zolpidem have been approved for use in long-term use). They are sometimes considered safer for long-term use than benzodiazepines. However, non-benzodiazepine sedative-hypnotic drugs have been associated with adverse events, including withdrawal symptoms, rebound insomnia and cognitive dysfunction. In a recent meta-analysis, non-benzodiazepine sedative-hypnotics were associated with a higher risk of adverse events compared with placebo.

This review highlights the need for continued research to identify effective and safe interventions for the management of insomnia in older adults.
Canada), melatonin, ramelton, diphenhydramine, antidepressants and atypical antipsychotics. A systematic analysis of the pharmacologic treatment of insomnia in patients over 60 years old found that, although sleep was better with sedatives than with placebo, adverse cognitive events were more common (OR 4.78, 95% CI 1.47 to 15.47), as were adverse psychomotor events (OR 2.25, 95% CI 0.93 to 5.41), although the latter did not reach significance.

Z drugs
We found 2 randomized trials that compared zopiclone with triazolam in older adults (Table 1). Overall, the studies were small (n = 10–41) and of short duration (15–17 days). Therefore, although the results showed improvement in some sleep-quality indices, there was insufficient evidence to support the efficacy and safety of long-term use.

Two randomized trials were found that compared zolpidem with triazolam in older adults (Table 1). Although the number of participants was greater than in the studies of zopiclone (n = 205–335), the duration was short (21–28 days). As a result, the efficacy and safety of zolpidem for long-term use remains unclear. In a case–control study of Medicare and Medicaid data from one US state, the risk of hip fracture was increased with zolpidem use compared with no use (adjusted OR 1.95, 95% CI 1.09 to 3.51) and similar compared with benzodiazepines (adjusted OR 1.47; 95% CI 0.74 to 2.93). Furthermore, Health Canada has issued an advisory for zolpidem following reports of complex sleep-related behaviours.

Overall, trials of the Z drugs have shown improvement in some sleep domains. However, it is premature to presume that these drugs are either safe or effective when used long-term in older adults. Until their long-term use has been studied, these medications should be prescribed with caution to frail older adults.

Melatonin
The data for the effectiveness of melatonin as a sleep aid are mixed. In a study of melatonin versus placebo, there was lack of significant effect on sleep time, sleep latency, number of awakenings and sleep efficiency. However, pooled data from randomized double-blind trials of prolonged-release melatonin showed statistically significant improvement in quality of sleep (~9.2 mm vs. ~3.7 mm with placebo, as measured by the Leeds Sleep Evaluation Questionnaire visual analog scale) and decrease in subjective sleep latency (26 min vs. 8 min with placebo; p = 0.02).

Ramelton, a prescription melatonin agonist, was recently approved in the United States and Japan but is not currently available in Canada. A systematic review of ramelton found improvements in total sleep time (9 min, 95% CI 4.94 to 12.49) and in latency to persistent sleep (~4 min, 95% CI −5.66 to −2.77). However, in subgroup analysis, there were no significant improvements among those over 65 years.

Diphenhydramine
In a 14-day crossover trial of diphenhydramine 50 mg versus temazepam 15 mg versus placebo, total sleep time, sleep quality and sleep latency were not significantly improved in the diphenhydramine arm. In a trial involving 14 healthy older volunteers (mean age 71.6 yr), psychomotor impairment was present after 75 mg of diphenhydramine versus placebo; however, no psychomotor impairment was detected with 50-mg dose. The updated Beers criteria strongly advise against the use of diphenhydramine in older adults because of its anticholinergic effects.

Doxepin
Doxepin, a histamine H1-receptor antagonist, was shown to significantly increase subjective total sleep time by 18 minutes, from 317 to 335 minutes (p < 0.01) after 1 week of treatment in older adults. In this trial, there were no reports of anticholinergic effects or memory impairment in the doxepin group.

Other agents
We found no data on the use of atypical antipsychotics, trazodone or other antidepressants for sleep in older adults, despite the use of these medications for their sedating properties. In the general population, data supporting the use of

Box 1: Methods
We searched MEDLINE (1946–September 2012), Embase (1980–September 2012) and the Cochrane Database of Systematic Reviews (2005–September 2012) using the following key search terms: MeSH and Embase terms for benzodiazepines, sleep initiation and maintenance disorders, and drug withdrawal and abuse, as well as key words for sleep, addiction, dependence, insomnia, specific drug names, and terms for taper, withdrawal and alternative therapies. Further details about the literature search are available from the authors upon request. We retrieved 284 unique citations and reviewed 190 full articles. Each citation and full article was independently reviewed for inclusion by 2 of us, so that each of us reviewed two-thirds of all citations.

We included articles if the majority of patients studied were over the age of 65 years; the study was a systematic review, randomized controlled trial, cohort study or case–control study; and the focus of the study was use of benzodiazepines or comparative interventions as a sleep aid, or about their discontinuation. We excluded articles if they were not written in English; benzodiazepine use was primarily for a reason other than sleep aid; the article was a case report, case series or editorial; or only the abstract was available.
trazodone for sleep in the absence of a coexisting mood disorder are lacking.26

When should problematic use of sedative-hypnotics be suspected?

In a randomized controlled discontinuation trial, patients who used more than 10 mg of diazepam equivalent, who had high scores on a noncompliance measure or who drank more than 2 units of alcohol per day failed to achieve long-term abstinence (defined as receiving no benzodiazepine prescriptions during 15 months of follow-up).27 In a longitudinal study involving older people, long-term benzodiazepine use was associated with treatment for nervous conditions, restless sleep, being female, being divorced and having increased contact with medical services.7 Similarly, associations between benzodiazepine use and depressive or anxious symptoms, increased use of nonpsychotropic drugs and female sex were found in a study involving older benzodiazepine users in France.8

As part of the work-up for insomnia, it is necessary to investigate the reason for long-term sedative-hypnotic use and to rule out other axis I disorders such as mood and anxiety disorders. Other sleep-related disorders should also be considered, such as obstructive sleep apnea, restless leg syndrome, sleep walking and narcolepsy.

What strategies are effective for stopping sedative-hypnotic drug use?

Effective strategies, used alone or in combination, include simple recommendations to stop, tapering protocols, cognitive behavioural therapy and melatonin. In particular, there is evidence for combining tapering protocols with cognitive behavioural therapy.

Cognitive behavioural therapy is administered by registered psychologists and psychiatrists who have received special training. Sessions are usually 90 minutes long and often occur weekly over a

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-benzodiazepine</th>
<th>Benzodiazepine or placebo</th>
<th>Study duration, d</th>
<th>No. of patients</th>
<th>Mean age, yr</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Venter et al.14 | Zopiclone 7.5–15 mg | Triazolam 0.25–0.5 mg | 17                | 41             | 76.8        | • The zopiclone group woke up once on average and the triazolam group woke up nearly twice on average (mean 1.7; \( p = 0.06 \))  
  • Adverse events reported in 35% of zopiclone and 38% of triazolam patients; difference not significant |
| Mouret et al.15 | Zopiclone 7.5 mg   | Triazolam 0.25 mg         | 15                | 10             | 65          | • Subjective aspects of sleep did not differ between groups  
  • Sleep recordings did not differ between groups |
| Leppik et al.16 | Zolpidem 5 mg      | Triazolam 0.125 mg, or temazepam 15 mg, or placebo | 28               | 335            | 69          | • Subjective sleep latency with zolpidem decreased significantly from baseline by 32.7 to 39.7 min per night for weeks 1 through 4; difference was significant compared with placebo for a given week (\( p < 0.05 \))  
  • Subjective sleep latency with temazepam decreased significantly from baseline by 30–39.4 min per night for weeks 1 through 4; difference was not significant compared with placebo at any time  
  • Subjective sleep latency did not differ significantly between zolpidem and temazepam groups  
  • Duration of subjective sleep did not change in any of the treatment groups compared with placebo |
| Roger et al.17 | Zolpidem 5 or 10 mg | Triazolam 0.25 mg         | 21                | 205            | 81          | • Questionnaire results, subjective sleep quality, and number of awakenings at night and in early morning improved in both groups (\( p < 0.01 \))  
  • Proportion of patients who fell asleep in less than 30 min increased from 20% to 65% in both groups based on questionnaire responses (\( p < 0.001 \))  
  • The increase in mean total sleep time was 1.5 h in the 5-mg zolpidem group v. about 2 h in the 10-mg zolpidem group and the triazolam group (\( p < 0.001 \)) |
defined period. Treatments consist of behavioural, cognitive and educational interventions that target different aspects of insomnia.\textsuperscript{26} Interventions include sleep restriction (limiting time in bed to actual sleep time), stimulus control (re-associating the bedroom with sleep) and cognitive therapy designed to change faulty beliefs about sleep.\textsuperscript{26}

In a cohort study involving 31 patients taking benzodiazepines or a Z drug who received a recommendation to alter their sedative drug use, 68% were adherent at follow-up.\textsuperscript{29} In a trial involving 591 patients, those in the intervention group were given instructions to withdraw, reduce or change psychotropic medications, in addition to a 1-hour lecture about the drugs and their adverse effects. The number of patients who were regular users of benzodiazepines decreased by 35% in the intervention group and increased by 4% in the controls.\textsuperscript{30}

Among patients with insomnia who had been using hypnotic-sedative drugs for at least 1 month, cognitive behavioural therapy resulted in significant reductions in Pittsburgh Sleep Quality Index scores from 13 at baseline to 3 at 3-month follow-up to 2 at 6-month follow-up (lower scores indicate reduced severity of sleep disturbance); reductions in sleep latency from 60 minutes at baseline to 28 minutes at 3-month follow-up to 30 minutes at 6-month follow-up; and improvement in sleep efficiency score (representing the percentage of time in bed spent as sleep) improved from 2.2 at baseline to 0.7 at both the 3- and 6-month follow-up assessments (Table 2).\textsuperscript{31} Patients who received

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of treatment</th>
<th>Participants</th>
<th>Study group</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Morgan et al.\textsuperscript{31}</td>
<td>6 wk of active treatment; follow-up at 3 and 6 mo</td>
<td>209 people using benzodiazepines for &gt; 1 mo; mean duration of use 13.4 yr</td>
<td>68 Six 50-min sessions of cognitive behavioural therapy</td>
<td>Usual care with crossover to cognitive behavioural therapy At 3 mo, intervention group had significant improvement in Pittsburgh scores (mean difference –3.8, 95% CI –4.8 to –2.8), decrease in sleep latency (mean difference –24.1, 95% CI –37.2 to –11.1), improvement in sleep efficiency (mean difference –0.9, 95% CI 1.2 to –0.6) and increase in total sleep time (mean difference 0.5 min, 95% CI 0.1 to 0.8); 47.4% v. 17.3% reported low-frequency use (p &lt; 0.001); 30% v. 11% reported zero hypnotic drug use over 7-d follow-up assessment period (p = 0.005) At 6 mo, intervention group had significant decrease in sleep latency (mean difference –27.9 min (95% CI –43.4 to –12.6) and improvement in sleep efficiency score (mean difference –1 (95% CI –1.3 to –0.6); 54% v. 18% reported low-frequency use (p &lt; 0.001); 33% v. 8% reported zero hypnotic drug use (p &lt; 0.001))</td>
</tr>
<tr>
<td>Morin et al.\textsuperscript{32}</td>
<td>10 wk</td>
<td>76 chronic benzodiazepine users (&gt; 50% of nights for &gt; 3 mo); mean 6.7 nights per wk; mean duration of use 19.3 yr</td>
<td>62.5 Combined benzodiazepine tapering and cognitive behavioural therapy</td>
<td>Benzodiazepine tapering alone or cognitive behavioural therapy alone Overall, 90% reduction in quantity of benzodiazepine consumption and 80% reduction in frequency of medicated nights across the 3 groups; 63% of patients were benzodiazepine free within 7 wk on average; 85% in combined treatment arm were benzodiazepine free after initial intervention v. 48% in tapering arm and 54% in cognitive behavioural therapy arm</td>
</tr>
<tr>
<td>Baillargeon et al.\textsuperscript{33}</td>
<td>8 wk</td>
<td>65 daily benzodiazepine users for &gt; 3 mo; mean duration of use 152 mo (12.7 yr)</td>
<td>67.4 Combined benzodiazepine tapering and cognitive behavioural therapy (90-min group session weekly for 8 wk)</td>
<td>Benzodiazepine tapering alone 77% in combined treatment arm v. 38% in tapering arm were benzodiazepine free immediately after treatment (OR 5.3, 95% CI 1.8 to 16.2); this outcome persisted at 12 mo, with 70% benzodiazepine free in combined treatment arm v. 24% in tapering only arm (OR 7.2, 95% CI 2.4 to 23.7)</td>
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<tr>
<td>Voshaar et al.\textsuperscript{34}</td>
<td>3 mo</td>
<td>180 regular benzodiazepine users for &gt; 3 mo; mean duration of use 165 mo (13.8 yr)</td>
<td>63.4 Benzodiazepine tapering alone or combined with cognitive behavioural therapy (2-h session weekly for 5 wk)</td>
<td>Usual care 62% in tapering arm and 58% in combined treatment arm were successful with discontinuation v. 21% in usual care arm</td>
</tr>
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Note: CI = confidence interval, OR = odds ratio.
cognitive behavioural therapy reported reductions in hypnotic drug use (54% reported low-frequency use v. 18% of controls; 33% in the intervention group v. 8% of controls reported zero hypnotic drug use). Cognitive behavioural therapy in combination with a drug tapering program may result in greater success. In a randomized trial, the frequency of medicated nights was lower and the proportion of benzodiazepine-free patients higher in the combined treatment group than in the groups that received cognitive behavioural therapy only or tapering alone (Table 2). There was a 90% overall reduction in the quantity of benzodiazepines used and an 80% overall reduction in the frequency of medicated nights across all 3 treatment groups, which was maintained at 3 and 12 months’ follow-up. In a similar trial, a greater proportion of participants in the combined treatment group than in the tapering only group reported completed discontinuation of hypnotic drugs (Table 2). At the 12-month follow-up, 70% in the combined treatment group, as compared with 24% in the tapering only group, were benzodiazepine free. Patients took an average of 7 weeks to stop benzodiazepine use.

In a trial involving 180 long-term benzodiazepine users randomly assigned to tapering plus cognitive behavioural therapy, tapering alone or usual care, discontinuation of benzodiazepine use was significantly more successful in both intervention groups than in the usual care group, with no significant difference between the intervention groups (Table 2). Patients who were using a benzodiazepine other than diazepam were switched to an equivalent dose of diazepam for 2 weeks. If more than one benzodiazepine was being used, the dosages were added together. The daily equivalent dose of diazepam was reduced by 25% per week over 4 weekly visits. Overall, 88% of the physicians found the protocol to be feasible in practice, 83% said they would encourage others to use it, and 52% had already started using it for other patients.

In a randomized trial of a benzodiazepine withdrawal program involving 180 patients, the independent predictors of successful benzodiazepine discontinuation were offering a tapering program (hazard ratio [HR] 2.9, 95% CI 1.8 to 4.8), combining a tapering program with cognitive behavioural group therapy (HR 2.4, 95% CI 1.5 to 3.9), a lower daily benzodiazepine dose at the start (HR 1.5, 95% CI 1.2 to 1.9), a substantial dosage reduction by patients themselves before the tapering protocol (HR 2.1, 95% CI 1.4 to 3.3), less severe benzodiazepine dependence (HR 2.4, 95% CI 1.1 to 5.2), and no concomitant alcohol use (HR 1.7, 95% CI 1.2 to 2.5). In a placebo-controlled trial involving 38 long-term benzodiazepine users asked by their general practitioner to participate in a discontinuation program in combination with melatonin or placebo, there was no significant difference in outcomes between the groups. However, among older patients who were encouraged to decrease their benzodiazepine doses while taking melatonin or placebo, sleep quality scores, as measured by the Northside Hospital Sleep Medicine Institute Test, were improved in the melatonin group, and 9 of 14 habitual benzodiazepine users were able to discontinue benzodiazepine use.

Are nonpharmacologic therapies effective for insomnia?

Nonpharmacologic therapies have been successful to varying degrees in older adults with insomnia. Among the most successful strategies are cognitive behavioural therapy and brief behavioural therapy.

In a 6-week study involving 46 adults with chronic primary insomnia assigned to cognitive behavioural therapy, zopiclone 7.5 mg or placebo, the total wake time at 6 weeks was reduced by 52% in the cognitive behavioural therapy group (from 108 min to 51 min), as compared with 4% in the zopiclone group (from 103 min to 99 min) and 16% in the placebo group (from 154 min to 130 min). At the 6-month follow-up, total sleep time continued to increase in the cognitive behavioural therapy group (by 26 minutes [from 336 min at 6 wk to 362 min at 6 mo]), total wake time decreased further (from 52 min at 6 wk to 47 min at 6 mo), sleep efficiency improved (from 81% at 6 wk to 83% at 6 mo), and slow-wave sleep increased (from 80 min at 6 wk to 84 minutes at 6 mo).

Cognitive behavioural therapy can be time intensive and requires a specially trained psychologist or psychiatrist. Brief behavioural interventions have been explored as an alternative, which consist of individualized 45–60-minute sessions followed by a 30-minute follow-up session and two 25-minute telephone calls. The intervention involves reducing time spent in bed not sleeping; getting up at the same time every day; not going to bed unless tired; and not staying in bed unless asleep. Napping is discouraged. In a randomized trial involving 79 older adults with chronic insomnia, brief behavioural therapy resulted in significantly better outcomes for depression and anxiety ratings, sleep quality index, sleepiness scale and insomnia remission compared with only providing information.
the intervention group, 55% of the participants no longer met the criteria for insomnia at the end of treatment, as compared with 13% in the information-only group. At the 6-month follow-up, 64% no longer met the criteria for insomnia, and the mean total sleep time had significantly increased further, from 340 minutes to 386 minutes. A similar randomized trial of brief behavioral therapy resulted in remission rates of 53% at follow-up. Exercise may play a role in the treatment of insomnia. In randomized controlled trials, participants who took tai chi 2–3 times per week for 3–6 months had significant reductions in Pittsburgh Sleep Quality Index scores compared with controls from 9.4 before the intervention to 3.6 afterward (where a lower score indicates less severe sleep symptoms). Sleep education of caregivers may help improve sleep among patients with dementia. The intervention consists of 4 sessions in which caregivers are taught nonpharmacologic strategies to improve sleep, common causes of sleep problems in dementia and common causes for nighttime awakenings and are given assistance in developing sleep plans. A trial of sleep education resulted in significant reductions in caregiver ratings of resident wandering, inappropriate behaviors at night and in excessive daytime napping. Unanswered questions The use of benzodiazepines and other sedative-hypnotic drugs in older adults is frequent and associated with adverse outcomes. Given the paucity of safety and efficacy data supporting the long-term use of non-benzodiazepine sedative-hypnotic agents, should use of these medications be approached by clinicians as a problem to be managed, similar to benzodiazepine use? Furthermore, despite evidence for the efficacy of cognitive behavioural therapy and brief behavioural therapy for the management of chronic insomnia and benzodiazepine discontinuation, these modalities are not readily available to patients. The question remains regarding how best to translate this evidence into practice.

References


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