



**WeMeReC Bulletin**  
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**Benzodiazepines and “Z” drugs for insomnia**

The most commonly prescribed drugs for the treatment of insomnia are the benzodiazepines and the newer non-benzodiazepine hypnotics, the so-called “Z” drugs (zaleplon, zolpidem, and zopiclone). The effectiveness of the benzodiazepines has led, historically, to over-prescribing and problems with dependence in some patients reluctant to stop taking them. Prescribing of these drugs remains a problem, with many patients taking them inappropriately and others being denied short-term effective treatment because of fears of “addiction”.

The level of prescribing of hypnotics in Wales is a matter of concern and has been identified by the All Wales Medicines Strategy Group as a key area for review. This bulletin discusses some of the problems associated with use of benzodiazepines for insomnia. It also considers the evidence for the use of non-benzodiazepine hypnotics and guidance for promoting appropriate use of these medicines in primary care.

All benzodiazepines have hypnotic and anxiolytic effects, however, they are classified separately under hypnotics and anxiolytics in the BNF. Indications for individual drugs are given in the table on page 4. The “Z” drugs are indicated only for insomnia.

**Indications for use of hypnotics**

Insomnia is common and can be debilitating. It is important that potential causes of insomnia should be sought and addressed if possible. These may include anxiety and/or depression, excessive alcohol use, physical causes, such as pain, as well as psychological or emotional distress.<sup>1</sup> Where intervention is required it is essential that patients are given advice on practical measures that promote sleep (sometimes referred to as sleep hygiene; for example, avoid daytime naps, strenuous exercise, heavy meals, alcohol and caffeinated drinks at night; develop a bedtime routine, and ensure a comfortable, quiet, dark environment).<sup>2</sup> Behavioural therapies, including relaxation and cognitive therapies, can produce effective and lasting improvements in sleep.<sup>3</sup>

**Summary**

- Insufficient sleep is associated with significant stress. Where it is a symptom of disease or an acute reaction to events, it is important that the underlying cause is sought and addressed.
- Practical, non-pharmacological measures can be effective in producing lasting improvements in sleep and all patients should be given advice on these.
- Drugs prescribed for insomnia are only indicated for short-term relief (for two to four weeks) of insomnia that is severe, debilitating or causing extreme distress.
- Patients should be advised of the risks associated with hypnotic use, including the potential for dependence. The non-benzodiazepine or “Z” drugs are subject to the same precautions as benzodiazepines.
- Non-prescription products are available for occasional insomnia, although the evidence for their value is often limited. Antidepressants should not be prescribed for insomnia; where insomnia is associated with depression, the underlying condition should be treated appropriately.
- Hypnotics should not be routinely added to repeat prescribing lists, especially following discharge from hospital. Patients, often the elderly, who remain on long-term therapy should be reviewed every three months.
- Gradual and supportive withdrawal measures should be followed when stopping hypnotic therapy.
- There is evidence that patient education and practice audit can reduce benzodiazepine use in primary care.

## Benzodiazepines

Benzodiazepines are effective for insomnia but may cause hangover effects or daytime drowsiness.<sup>4</sup> Associated psychomotor impairment can have serious consequences, for example, when the ability to drive or operate machinery safely is affected. Benzodiazepines with long half-lives have been implicated in road traffic accidents.<sup>5,6</sup> In the elderly, benzodiazepine use has been associated with diminished “functional status”<sup>7</sup> and memory impairment,<sup>8</sup> and with an increased risk of falls.<sup>9</sup> Studies of the risk of hip fracture have produced conflicting results.<sup>10,11</sup> These effects can be potentiated by concomitant use of other CNS-depressants, including alcohol. Paradoxical effects (restlessness, agitation and aggressiveness) have also been reported with benzodiazepine use.

The CSM advises that benzodiazepine therapy is only indicated for short-term relief (two to four weeks) of insomnia that is severe, disabling or subjecting an individual to extreme distress.<sup>12</sup>

### Tolerance, dependence and withdrawal

Patients who take benzodiazepines regularly are at risk of developing tolerance to the sedative effects and becoming dependent on their medicine. This can lead to a desire to increase the dose and to the development of withdrawal symptoms when therapy is stopped.

Withdrawal, often characterised by rebound insomnia, is reported to occur in general practice in approximately 30% of patients who stop taking benzodiazepines.<sup>13,14</sup> Withdrawal symptoms may develop anytime from a few hours to up to three weeks after discontinuation of therapy, often depending on the half-life of the drug. They usually disappear after one or two weeks although they can persist after prolonged use. It is often difficult to distinguish withdrawal effects from the return of the original complaint and patients often seek to continue taking their medication. The difficulty in stopping therapy can reinforce a dependency that may be psychological and physical. The elderly who may suffer chronic insomnia, and who are more sensitive to the effects of these drugs, often experience the most difficulty.

Abrupt withdrawal of benzodiazepines can be dangerous, especially in patients who have been taking high doses for prolonged periods. The severity of withdrawal symptoms can be minimised by gradual reduction in drug therapy. It is

important that approaches to withdrawal are supportive and flexible. Gradual withdrawal is recommended in patients who have been on therapy for more than two weeks and, in difficult cases, may involve switching patients to diazepam (a long-acting drug) before reducing doses (see BNF).

The term “addiction” refers to a more severe state of drug dependence, usually involving drug misuse, extreme drug-seeking behaviour and escalation of dose, often in combination with alcohol and other drugs. The term does not apply to most patients and should be avoided as it may stigmatise patients unfairly. However, prescribers must be aware that benzodiazepines have a “street value” and are often abused by addicts. (They are also often utilised in drug and alcohol withdrawal or maintenance regimens and can now be prescribed by instalments for this purpose).<sup>15</sup>

### Duration of use and repeat prescribing

The biggest problem with hypnotics appears to be that these drugs are included on repeat prescriptions without adequate review to assess whether there is continued need for them. This often occurs when patients have been prescribed hypnotics during hospital stays. Such drugs are usually not required after discharge and should not be continued in primary care. Ongoing therapy without review is also a common problem in nursing homes.

### Non-benzodiazepine hypnotics

Zaleplon, zolpidem and zopiclone are essentially very similar to benzodiazepines and are licensed for short-term treatment of insomnia. Their short half-lives and preferential binding to specific sub-units of the benzodiazepine receptor complex were hoped to result in fewer adverse effects.<sup>16,17</sup> However, increasing clinical experience does not support clear superiority in this regard.

Comparisons of the “Z” drugs with benzodiazepines indicate that their hypnotic efficacy is similar, although effects on sleep duration are dependent on the half-life. Zolpidem and zopiclone both have a short duration of action (with half-lives of 2.4 hours and 5 hours, respectively).<sup>16</sup> Zolpidem is associated with minimal effects on daytime cognitive functioning and may be associated with less rebound insomnia,<sup>16,17</sup> however, zopiclone has been reported to cause hangover effects<sup>17</sup> and has been associated with an increased risk of road traffic accidents.<sup>5</sup> Misuse, dependence and withdrawal symptoms have been reported (mostly in patients with a history of addiction) with both agents.<sup>17</sup>

Zaleplon has been in clinical use for a shorter period. Zaleplon does appear to reduce the time to onset of sleep and because of its very short half-life (1 hour) it may be taken during the night when there are several hours of sleep time remaining. It is less suitable when sleep duration is a problem.

The Summaries of Product Characteristics for “Z” drugs list many of the same warnings and potential effects as those seen with benzodiazepines. These drugs should be subject to the same precautions when prescribing. Although there is no published discussion of the withdrawal of “Z” drugs, the recommendations for benzodiazepines are likely to apply. Costs for the “Z” drugs and benzodiazepines are given in the table on page 4.

### Alternative drugs

The roles of older hypnotics such as chloral hydrate and clomethiazole are now very limited because of the considerable toxicity of these drugs. They cause dependence and withdrawal effects and are more dangerous in overdose than the alternatives.

The **antihistamines**, diphenhydramine (*Dreemon*<sup>®</sup>, *Nytol*<sup>®</sup>, *Paxidorm*<sup>®</sup>) and promethazine (*Phenergan Nighttime*<sup>®</sup>, *Sominex*<sup>®</sup>, *Ziz*<sup>®</sup>) are available without a prescription for occasional insomnia but they can cause daytime drowsiness and may only be effective for a few days. Clinical trials evaluating the safety and efficacy of melatonin (an unlicensed product) and **herbal products**, such as *Valerina Night-Time*<sup>®</sup> and *Nytol Herbal*<sup>®</sup> are lacking.

**Antidepressants** are not licensed for use as hypnotics and should not be used as such. Where insomnia is a symptom of depression, the underlying condition should be treated appropriately. Both tricyclic antidepressants and selective serotonin re-uptake inhibitors, have been associated with withdrawal effects and an increased risk of hip fracture in elderly patients.<sup>18</sup>

### Patient education and practice guidance

As previously discussed, it is important that need for use of an hypnotic is established. If prescribing a benzodiazepine for insomnia, an appropriate choice could be made from those that appear in the table on page 4. Note that nitrazepam has a prolonged duration of action and may not be an ideal first choice. Use of hypnotics “prn” is not appropriate, however planned intermittent courses can be useful clinically. Shiftworkers may benefit from such use (although regular use should always be avoided). When prescribing benzodiazepines, simple measures have been shown to reduce their use in primary-care patients.

Providing information about the problems of benzodiazepine use with or without a letter suggesting a gradual withdrawal process is successful in reducing use in long-term users. In a study in general practice, benzodiazepine use was reduced by about one third after six months; 18% of the patients who were issued information received no prescriptions during the study period compared with 6% of the control group.<sup>19</sup>

The net cost of a simple intervention involving letters to patients (including administrative and professional staff time) was calculated as less than £5.<sup>20</sup> It is noted that such letters, in addition to informing patients, can also serve to help meet medico-legal responsibilities, as well as audit and clinical governance goals.

Audit of hypnotic prescribing can be an effective tool for reducing prescribing. In an audit-driven study, patients taking benzodiazepines had their medication reviewed by GPs in 15 practices. Eight months later, 16% of patients had stopped receiving prescriptions for benzodiazepines.<sup>21</sup> Similar interventions implemented by multidisciplinary teams have successfully reduced prescribing.<sup>22,23</sup>

Examples of audit criteria that have been developed for benzodiazepine prescribing in primary care are available.<sup>24</sup> Key points include:



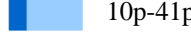
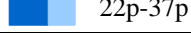
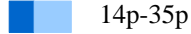
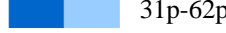




- New benzodiazepine prescriptions should be issued for no more than four weeks for severe insomnia (or anxiety).
- Patients (and their carers, where applicable) should be advised on non-drug therapies and on the risks associated with hypnotics, including the potential for dependence; this should be recorded in the patient’s notes.
- Appropriate withdrawal measures should be used (see the BNF).

Examples of patient education and practice guidance tools are available under “key documents” at: [www.neathporttalbotlhb.wales.nhs.uk](http://www.neathporttalbotlhb.wales.nhs.uk).

### Long-term use

There are situations in which long-term use of a benzodiazepine may be justified.<sup>25,26</sup> A clear example is in palliative care where the issue of dependence is irrelevant. Long-term use might also be justified, for example, in patients with severe anxiety states or those with multiple insoluble medical or mental health problems. Patients receiving benzodiazepines long-term should be reviewed at least three-monthly.

## Comparative costs of drugs for insomnia

Benzodiazepines for insomnia <sup>§</sup>	Dose range*	Cost per 7 nights supply <sup>†</sup>
		0 ————— £2.50
loprazolam 1mg tab	0.5mg-2mg	 56p-£2.23
lormetazepam 0.5mg, 1mg tab	0.5mg-1.5mg	 85p-£1.87
nitrazepam 5mg tab	2.5mg-10mg	 10p-41p
temazepam 10mg, 20mg tab	10mg-20mg	 22p-37p
<b>Benzodiazepines for insomnia associated with anxiety<sup>§</sup></b>		
diazepam 5mg, 10mg tab	5mg-15mg	 14p-35p
lorazepam 1mg tab	1mg-2mg	 31p-62p
oxazepam 10mg, 15mg tab	15mg-25mg	 29p-55p
<b>Non-benzodiazepines for insomnia</b>		
zaleplon 5mg, 10mg cap ( <i>Sonata</i> <sup>®</sup> ▼)	5mg-10mg	 £1.68-£2.02
zolpidem 5mg, 10mg tab	5mg-10mg	 73p-£1.06
zopiclone 3.5mg, 7.5mg tab	3.75mg-7.5mg	 77p-£1.12

§ Drugs identified from prescribing data for Wales as the most frequently prescribed.

\* Indications and relevant dose information taken from the BNF (Volume 45, March 2003).

† Costs calculated from the Chemist & Druggist, August 2003, and the Drug Tariff, August 2003.

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Summaries of Product Characteristics should be consulted for full prescribing information.