Benzodiazepines and hypnotics

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Abstract

Benzodiazepines and so-called 'Z' drugs are used as hypnotics. Their mode of action is to enhance the activity of central γ-aminobutyric acid. Adverse effects include anterograde amnesia and paradoxical reactions. Tolerance, dependence and withdrawal symptoms can develop, which can be minimized by intermittent dosing. Concurrent administration with central nervous system (CNS) depressants is not recommended as this produces additive CNS effects. Melatonin is also used as a hypnotic.

Keywords Benzodiazepines; hypnotics; melatonin; neurotransmitters; zaleplon; zolpidem; zopiclone

Key points

- The National Institute for Health and Care Excellence states there is no difference in efficacy between the 'Z' drugs and shorter acting benzodiazepines, so recommends prescribing the cheapest drug
- Do not prescribe one of the other 'Z' drug hypnotics if treatment with a previous medicine has not worked
- Long-acting diazepam given as a single dose at night can be useful if insomnia is associated with daytime anxiety
- Advise good sleep hygiene
- Non-pharmacological interventions are the preferred treatment option for the elderly. Use lower doses if medication is required

Insomnia

Insomnia is a disturbance of normal sleep patterns characterized by difficulty in falling asleep, maintaining sleep and early waking. Adverse consequences are distress and impairment of daytime functioning. Non-pharmacological strategies to manage insomnia should be considered first, alongside good sleep hygiene. Hypnotics are sleep-inducing drugs and include benzodiazepines (BZDs), 'Z' drugs and melatonin. The National Institute for Health and Care Excellence advocates the use of drugs with the lowest purchase cost as there is no difference in efficacy between the 'Z' drugs and shorter acting BZDs.[1] However, caution is required as sedative hypnotics are associated with increased mortality, although the mechanism of effect remains unclear.[2] Certain factors must be considered before prescribing hypnotics for insomnia, these are highlighted in Table 1.

Benzodiazepines

BZDs currently licensed in the UK for the treatment of insomnia are temazepam, loprazolam, lormetazepam (short-acting), diazepam (for insomnia associated with anxiety), flurazepam, nitrazepam (long-acting) and lorazepam. These should be used only for insomnia that is severe, disabling or causing extreme distress and prescribed for no longer than 2–4 weeks.[3] Lorazepam is also licensed for use in anxiety. Chlordiazepoxide and diazepam are used for the management of anxiety and alcohol withdrawal.

Mode of action

BZDs enhance the effects of γ-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter; they act as agonists at the allosteric modulatory BZD receptor on the $GABA_A$ receptors. The combination of a BZD binding to its BZD receptor site and GABA binding to its GABA receptor site on the $GABA_A$ receptor complex increases the frequency of opening of the $GABA_A$ central chloride channel to an extent not possible with GABA alone. Subsequent increased influx of chloride ions boost GABA's inhibitory action, which reduces arousal and promotes sleep. The onset of action for BZDs ranges from 20 to 60 minutes and there is a medium to long duration of action.

Adverse effects and interactions

BZDs may cause cognitive impairment, occasional 'paradoxical' reactions such as disinhibition (more common with short-acting hypnotics[4]), next-day 'hangover' effects (more common with long-acting hypnotics), tolerance and dependence with prolonged use, and withdrawal, and can adversely affect driving performance. They are contraindicated in respiratory depression. BZD-induced respiratory depression is reversed by flumazenil, a BZD antagonist. As flumazenil has a short half-life, additional doses may be needed. BZDs do not induce or inhibit microsomal enzymes so do not usually cause pharmacokinetic interactions with any other drugs.[4] (See Table 2 for interactions.)

'Z' drugs

Zopiclone, zolpidem and zaleplon are structurally unrelated non-BZD hypnotics that were developed in an attempt to overcome some of the disadvantages of BZDs, such as hangover effects and dependence.[1] It is advised that a patient who has not responded to one of the 'Z' drugs should not be switched to any of the others. 'Z' drugs also potentiate GABA activity by acting on the BZD receptor site of the $GABA_A$ receptor complex, but are more selective in their binding than BZDs.[5] 'Z' drugs can cause amnesia and dependence. Zolpidem has a rapid onset of action with minimal hangover effects. Zopiclone has a slower onset and medium duration of action. Zopiclone, zaleplon and zolpidem are metabolized by hepatic enzymes, so inducers or inhibitors of

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Essential prescribing considerations[3]

- Use the lowest effective dose for the shortest time (maximum 4 weeks)
- Aim for intermittent dosing (alternate nights or less) to reduce the risk of developing tolerance and dependence
- Short-acting hypnotics with a rapid onset of effect are better for patients who have difficulty falling asleep. However, there is increased potential for dependence
- Long-acting hypnotics are more effective in maintaining sleep throughout the night, but usually cause hangover effects the next day
- Avoid the use of hypnotics in individuals with respiratory disease or severe hepatic impairment
- Advise patients of the interaction with alcohol and other sedating drugs
- Discontinue slowly
- Be alert for withdrawal symptoms when benzodiazepines are discontinued

Table 1

these enzymes can decrease or increase the serum concentrations of these drugs (see interactions in Table 2).

Melatonin

Melatonin is a natural hormone secreted by the pineal gland and is involved in the regulation of circadian rhythms. In darkness, melatonin is released into the plasma. Once melatonin enters the brain, it acts on melatonin receptor MT_1 to promote sleep and on MT_2 to move the circadian sleep phase forward. It is an effective hypnotic for sleep onset.[5] A modified-release formulation of melatonin has been licensed for the management of insomnia in people over 55 years of age for up to 13 weeks. It is taken after food 1–2 hours before sleeping. Adverse effects include dyspepsia and dry mouth.[3] See Table 3 for the use of BZDs and hypnotics in vulnerable groups. ◆

BZDs and 'Z' drugs[1,3,5]

Drug	BZDs	Zaleplon	Zolpidem	Zopiclone
Adverse effects	Headaches, ataxia, confusion, blurred vision, muscle weakness, gastrointestinal disturbances, paradoxical excitement (rare), anterograde amnesia, disinhibition	Paraesthesia Sleep-walking Anterograde amnesia	Euphoria Sleep-walking Anterograde amnesia	Bitter metallic taste Sleep-walking Retro/anterograde amnesia
Symptoms upon abrupt withdrawal	**Psychological:** anxiety/insomnia, nightmares, decreased memory, impaired concentration, delusions and hallucinations, depression **Physical:** stiffness, weakness, flu-like symptoms, paraesthesia, visual disturbances, gastrointestinal disturbances	Tremor Anxiety, sweating, panic	Delirium Anxiety, insomnia, seizures	Dysphoria Anxiety, depression
Clinically relevant drug interactions	Additive effect with CNS depressants Methadone: risk of fatal overdose is greatly enhanced when methadone is taken concomitantly with respiratory depressant drugs Enhanced hypotensive effect of temazepam with antihypertensives, vasodilators and diuretics *Concentrations of diazepam, lorazepam and nitrazepam all increased by*: erythromycin, some SSRIs and ketoconazole *Concentrations of diazepam, lorazepam and nitrazepam all decreased by*: rifampicin	Additive effect with CNS depressants *Concentrations increased by*: erythromycin, fluconazole *Concentrations decreased by*: carbamazepine, omeprazole, phenytoin, rifampicin		
Cautions	Avoid alcohol: sedation is enhanced Drowsiness can persist the next day and impair ability to perform functions requiring mental alertness Muscle weakness and myasthenia gravis Respiratory disease: can cause respiratory depression			

BZD, benzodiazepine; CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor.

Table 2

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