UPDATE
Module 1657

This module covers:

- The mechanism of action for hypnotics, including benzodiazepines, z-drugs and antihistamines
- The latest guidelines on which hypnotic should be prescribed
- Adverse effects of hypnotics, both by class and the overall effects of hypnotics therapy
- Key advice pharmacists can offer patients

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Hypnotics

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Hypnotics, used to treat insomnia, assist in getting to sleep quickly and sleeping through the night. While insomnia can be distressing and debilitating, non-pharmacological strategies should be tried first; hypnotics should only be considered if these are inappropriate or ineffective. This is because hypnotics can disturb the structure of sleep (sleep architecture), resulting in increased dreaming and waking unrefreshed, and prolonged use can lead to tolerance and dependence.

Hypnotics should be prescribed at the lowest possible dose on an as-required basis, preferably for no longer than seven nights. All hypnotics in the UK are licensed for short-term use only and should be taken for no longer than two to four weeks, including the tapering-off period.[1] The exception to this is prolonged-release melatonin, which may be taken for a maximum of 13 weeks.[2]

Withdrawal symptoms, especially rebound insomnia, may occur when a hypnotic is discontinued abruptly. This is not a reason to restart the therapy.

How hypnotics work

Hypnotics such as benzodiazepines, z-drugs, chloral derivatives and clomethiazole all bind to the GABAA (gamma-aminobutyric acid) receptor, enhancing the effects of GABA, the major inhibitory transmitter in the brain. The receptor has six subunits.

The alpha 1 subunit is responsible for sedation, the alpha 2 and 3 subunits mediate anxiolytic effects and may help induce sleep, and the alpha 5 subunit regulates memory. Benzodiazepines bind non-selectively to alpha 1 2, 3 and 5 and z-hypnotics to alpha 1 and 5; z-hypnotics also act selectively at all six subunits.

Antihistamines antagonise central histamine (H1) receptors and induce sleep in this way, while melatonin binds to melatonin receptor subtypes, MT1 and MT2.

Benzodiazepines

Benzodiazepines disturb sleep architecture and sleep duration is increased, mainly due to prolonged light sleep. Temazepam and lormetazepam are preferable to the longer-acting nitrazepam and flurazepam, which can cause next-day drowsiness and confusion resulting in poor daytime performance and impaired memory.

Benzodiazepines should be used with caution in the elderly or people with kidney or liver disease, as reduced hepatic and renal function can cause accumulation leading to increased side effects.[3]

Benzodiazepines are contraindicated in chronic obstructive pulmonary disease and, although generally safe in overdose, pronounced respiratory depression can occur when taken in combination with alcohol.

Z-drugs

Zopiclone has greatest affinity for GABAA alpha 1 and 5 subunits, leading to sedative and possibly adverse cognitive effects. This may account for its predominantly hypnotic rather than anxiolytic effect. The short elimination half-life of zopiclone and its active metabolite results in little next-day sedation. The maximum licensed dose of 7.5mg provides six to eight hours of sleep and does not disturb sleep architecture. No clinical benefit has been shown for higher doses, but side effects are more common and sleep architecture may be disturbed.

Zolpidem has highest affinity for alpha 1 subunits, accounting for its predominantly hypnotic effect. It is rapidly absorbed, with onset of action within 30 minutes. Overall sleep duration is up to six hours and, as there are no active metabolites, neither psychomotor nor cognitive function is impaired the next day.

Zaleplon also binds selectively at the alpha 1 subunit. It is rapidly eliminated and has no active metabolites. It is licensed for the treatment of sleep initiation problems at the beginning of the night[4], and its extremely short duration of action may allow a second dose later without risk of residual drowsiness the following morning. However, the data sheet does advise against this.[5]

Antihistamines

Scant evidence supports the use of antihistamines as hypnotics, but they may be advantageous where insomnia is exacerbated by a skin irritation. Most produce next-day sedation due to their long half-lives and can be toxic in overdose. Some are available over the counter without a prescription.

Chloral derivatives

As a result of adverse effects and abuse potential, these are now rarely prescribed. Clomethiazole is only recommended in those over 55 years, but the risk of confusion, accidental overdose and respiratory depression is high.[5]

Melatonin

The hormone melatonin is produced by the pineal gland, regulated by the hypothalamus and inhibited by light via the retina. Endogenous melatonin levels rise soon after dark, peak in the middle of the night and gradually decline towards the morning.

Melatonin serves as a physiological signal to re-set the biological clock in order to match the environmental day-night cycle and regulate the sleep-wake and other circadian rhythms.

Lower production has been identified in patients aged over 55 years who suffer from poor sleep compared to healthy people of the same age who sleep well.

Melatonin has been shown to be beneficial in alleviating sleep disorders in the elderly and young people with ADHD (attention deficit hyperactivity disorder). A prolonged-release formulation is licensed in the UK as monotherapy for the short-term treatment of primary insomnia in patients aged 55 years or

over. It is not recommended for use in those under 18 years due to insufficient data on safety and efficacy.[2]

Melatonin has also been shown to improve next day functioning and minimise jet lag. It does not disturb sleep architecture, affect dreaming or produce withdrawal effects.[6,7]

Adverse effects

All short-acting compounds acting at the GABAA receptor can give rise to disinhibition[9] and hypnopompic hallucinations – persistence of the imagery of a dream into the waking state. Such sensory disturbances can happen to anyone on waking unexpectedly, but are more common after a short-acting hypnotic. They may be frightening and result in bizarre behaviour, but are generally harmless.[10]

Prolonged use of benzodiazepines can lead to tolerance and dependence. Tolerance and rebound symptoms can be dealt with relatively easily with appropriate withdrawal programmes.

However, where dose-escalation has occurred and high doses are being used, the physiological withdrawal syndrome can be severe and include convulsions. Withdrawal should take place in an inpatient setting.

There is mixed evidence for z-hypnotic dependency and abuse.[11] Reports of misuse have been increasing but prevalence is uncertain;[12] manufacturers and Nice warn of tolerance, dependence and withdrawal symptoms after extended use.

The majority of cases involve patients who already have a history of drug, alcohol and particularly benzodiazepine misuse or who have been prescribed high doses over long periods of time. It would seem reasonable therefore to apply the same caution to prescribing z-hypnotics as to benzodiazepines.

Studies indicate that the risk of impairment when driving following hypnotic use is greater for the older, longer half-life compounds due to next-day sedation.

Nevertheless, a short half-life does not necessarily confer less risk: zopiclone increases the risk of involvement in a road traffic accident and this risk may be greater early in the course of treatment.[13,14]

A recent study found that those prescribed hypnotics had an increased risk of dying compared with the general population. An increased risk of death was seen even in those who took fewer than 18 doses a year.[15]

Management tips

Those with chronic insomnia have higher rates of psychiatric and medical illnesses and reduced quality of life. Insomnia is also a risk factor for depression.

Many patients are reluctant to seek help because they feel that nothing can be done, or that the only remedy is a sleeping tablet to which they might become addicted. Strategies such as herbal remedies, aromatherapy, relaxation and good sleep hygiene can be effective.

However, when these fail, it may be necessary to consider pharmacological treatment, ideally only on a short-term basis. Hypnotics can and do improve quality of life if used correctly.

Pharmacists should be able to:

- promote the use of non-pharmacological interventions for insomnia, such as relaxation techniques and good sleep hygiene
- encourage patients newly prescribed a hypnotic to take it on an intermittent basis, only if absolutely essential and for a minimum period of time
- make patients aware that hypnotics have the potential to become a psychological habit
- alert patients to the risks of tolerance and dependence with extended use of hypnotics
- caution about the risks of driving when a hypnotic has been taken the night before
- caution against combining alcohol with a hypnotic
- advise patients with repeat prescriptions for hypnotics to seek a review and to consider non-pharmacological strategies
- conduct regular audits of hypnotic use and prescribing
- remind prescribers of the recommendations concerning the use of hypnotics
- discourage doses in excess of maximum licensed doses
- signpost any patient who may be dependent on a hypnotic to an appropriate agency
- intervene if large quantities of an over-the-counter sleep remedy are purchased on a regular basis
- notify the prescriber of potential interactions with hypnotics.

Further resources

- Ashton CH. *Benzodiazepines: How they work and how to withdraw* (The Ashton Manual). 2002. http://tinyurl.com/hypnotics1
- Clinical Knowledge Summaries. *Benzodiazepine and z-drug withdrawal – Management*. http:// tinyurl.com/hypnotics2
- eGuidelines. *Diagnosis and management of chronic insomnia in primary care*. http:// tinyurl.com/hypnotics3
- Royal College of Psychiatrists. http:// tinyurl.com/hypnotics4
- National Sleep Foundation. http:// tinyurl.com/hypnotics5
- Teens and sleep. http:// tinyurl.com/hypnotics6
- Ageing and sleep. http:// tinyurl.com/hypnotics7
- Shift work. http:// tinyurl.com/hypnotics8

Information for the pharmacy team on managing insomnia, including OTC treatments, is available in the June issue of OTC and at otcmag.com

Box 1. Selecting a hypnotic

Nice[8] found no strong evidence to distinguish between z-hypnotics and shorter acting benzodiazepines and recommended that:

- the agent with the lowest purchase price should be prescribed, taking into account the dose and price.
- switching z-hypnotics is only appropriate if adverse effects occur, then a compound with a higher acquisition cost may be used.
- someone who has not responded to one z-hypnotic should not be switched to another.

Tips for your CPD entry on hypnotics

Reflect **Which hypnotics act on the gamma-aminobutyric acid receptors? Why are the side effects of z-hypnotics less than those of benzodiazepines? How does melatonin work?**

Plan **This article describes the use of hypnotics for insomnia and includes information about benzodiazepines, z-hypnotics and melatonin. Nice guidelines, adverse effects and the role of the community pharmacist in the management of insomnia are also discussed.**

Act **Read the article and the suggested reading, then take the 5 Minute Test. Update and Update Plus subscribers can then access their answers and a pre-filled CPD logsheet.**

Find out more about sleeping problems and their treatment from the Royal College of Psychiatrists website http://tinyurl.com/hypnotic11
Revise your knowledge of hypnotics from the BNF Section 4.1.1 Hypnotics.
Read more about benzodiazepine and z-drug withdrawal on the Clinical Knowledge Summaries website http://tinyurl.com/hypnotic12
Think about the advice you could give to patients complaining of insomnia, or to those who present with regular prescriptions for hypnotics. Identify any who might benefit from an MUR

Evaluate **Are you now confident in your knowledge of hypnotics and how they should be used? Could you give advice to patients about insomnia and the cautions and side effects associated with hypnotics?**

5 minute test

■ Sign up to take the 5 Minute Test and get your answers marked online: www.chemistanddruggist.co.uk/update

Take the 5 Minute Test

1. Hypnotics should not be taken for longer than two to four weeks.
True or false?
2. Benzodiazepines act more selectively than z-hypnotics at the GABAA receptors.
True or false?
3. Benzodiazepines are contraindicated in chronic obstructive pulmonary disease.
True or false?
4. A 7.5mg dose of zopiclone provides four to five hours of sleep.
True or false?
5. Zolpidem has an onset of action of within 30 minutes.
True or false?
6. Clomethiazole is only recommended for those aged over 55 years.
True or false?
7. Melatonin is licensed for use in children aged 12 to 18 years.
True or false?
8. Nice recommends that if one z-hypnotic does not work, another should be tried.
True or false?
9. Short-acting hypnotics can cause disinhibition and hypnopompic hallucinations.
True or false?
10. Studies have shown that zopiclone increases the risk of involvement in a road traffic accident.
True or false?

References

1. Committee on the Safety of Medicine. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems* 1988: 21; pp. 1-2.
2. *Circadin : Summary of Product Characteristics (SPC).* www.medicines.org.uk/emc/medicine
3. *Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits.* Glass J et al. www. bmj.com/cgi/reprint/331/7526/1169
4. *Zaleplon: Summary of Product Characteristics (SPC).* www. medicines.org.uk/emc/medicine
5. *Heminevrin Summary of Product Characteristics (SPC).* www. medicines.org.uk/emc/medicine
6. Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J. Sleep Res 2007. 372-380
7. Wade A, Ford I, Crawford G, NcMahon AD, Nire T Laudon M, Zisapel N. Efficacy of prolonged-release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness. CurrMed Res Opin: 2007: 23 (10) 2598-2604
8. National Institute of Health and Clinical Excellence (NICE). *Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia.* 2004. Technology Appraisal 77
9. Paton C. *Benzodiazepines and disinhibition: a review.* Psychiatric Bulletin (2002) 26, 460-462
10. Olsen LG. *Hypnotic hazards: adverse effects of zolpidem and other z-drugs.* Australian Prescriber 2008. 31. (6) December 146-149 www. australianprescriber.com/magazine/31/6/146/9/
11. Law, F. *How abusable are the Z drugs?* Pharmag 2005: Vol 6; (1); pp. 1-3
12. Reed, K et al. *The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England: A structured review of published English and international evidence and available data to inform consideration of the extent of dependence and harm.* 2011. www. appgita.com/wp-content/uploads/2011/05/Report-1-NAC-Benzos-and-z-drug-addiction.pdf
13. Vermeeren A et al. *Residual effects of zaleplon and zopiclone versus the effects of alcohol on actual car driving performance.* European Neuropsychopharmacology 2005, 10, Supp 3 394
14. Gustavsen I, et al. *Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam.* Sleep Med 2008;9:818-22
15. Kripke DF, Langer RD, Kline LE. *Hypnotics' association with mortality or cancer: a matched cohort study.* BMJ Open 2012: 2: e000850. Doi:10.1136/bmjopen-2012-000850