

SECTION 5: TREATMENT OF INSOMNIA

A close-up photograph of various pills and capsules scattered on a blue background. The pills are in various colors (white, yellow, orange, red, black) and shapes (round, oval, rectangular). Some have embossed text like 'ESAV', 'SUN', 'PRN', and '4P.M.-6P.M.'. The background also has some faint text like '11A.M.-1P.M.' and '4P.M.-6P.M.'.

Formulary and
Prescribing Guidelines

5.1 Approved Drugs for the treatment of Short term Insomnia in ADULTS

Drug	Formulations	Comments
Zopiclone	Tabs 3.75mg, 7.5mg	'Z-drug'. 1st line.
Zolpidem	Tabs 5mg, 10mg	'Z-drug'. Alternative 1st line.
Daridorexant	Tabs 25mg, 50mg	Orexin receptor Antagonist. Alternative 1st line.*
Temazepam	Tabs 10mg, 20mg Liquid 10mg/5ml	Benzodiazepine. 2nd line Controlled drug
Promethazine	Tabs 10mg, 25mg Elixir 5mg/5ml	Antihistamine. 3rd line
Melatonin	M/R tabs 2mg	Only approved for use in Children and Adolescents

*Please see section on daridorexant for further information on transferring prescribing to primary care

Melatonin is non-formulary for use in adults and requires a non-formulary application for use in this patient group.

Treatment of insomnia in children is discussed in [section 12](#), whilst further information is provided in [section 11](#) in relation to drug use in older adults.

The Z-drugs are believed to have greater selectivity for the omega 1- benzodiazepine receptor (resulting in lesser anxiolytic, anticonvulsant and muscle relaxant effects, with purported lower potential for dependence and tolerance⁴). Additionally, zopiclone is reported not to cause REM rebound upon discontinuation, due to aforementioned (relative to BDZs) receptor selectivity⁶. Onset of activity for zopiclone is 30-45 minutes, and duration of action is quoted as 'short' (or 6 hours⁴). It is metabolised by the CYP3A4 system and thus, is subject to interactions with inhibitors such as erythromycin. Temazepam is a non-selective benzodiazepine, and consequently has some anxiolytic (and muscle-relaxant) activity in addition to the hypnotic action. It possesses an intermediate duration of activity (8-10 hours) and an onset of action of approximately 1 hour. It is not associated with the same degree of accumulation as seen with flurazepam or nitrazepam on chronic administration. It is not oxidized in the liver (it is conjugated and then excreted) and, thus, does not compete with other hepatically metabolized drugs¹⁻³.

As a benzodiazepine, temazepam normally increases stage 2 sleep, at the expense of REM, and stages 3 and 4 – resulting in REM rebound (manifested as vivid dreams) upon discontinuation⁴. As with all benzodiazepines, the risk of dependence and withdrawal syndrome should be considered when prescribing. See the BNF for further information and guidance relating to minimising such risks. Prescribers should be conscious of the risk of diversion when prescribing for leave/discharge or in an outpatient setting as benzodiazepines have abuse potential. The FDA has warned of a serious risk of death when benzodiazepines are used in combination with opioid analgesic or cough preparations.¹¹

People with borderline or antisocial personality disorders should only be prescribed sedative medication for short-term crisis management or treatment of comorbid conditions.

Both Z-drugs and benzodiazepines are associated with dependence, characterised by both tolerance and withdrawal symptoms. This possibility should be explained to patients so that a shared decision can be reached about the benefits and risks of treatment, including that missed doses or sudden cessation may lead to symptoms of withdrawal and that support will be provided at the time that withdrawal occurs.

Factors which may increase the risk of problems during withdrawal, such as long duration of use, high dose, history of withdrawal symptoms should be considered. NICE has published guidance on safe prescribing and withdrawal of medicines associated with dependence and withdrawal symptoms, Z-drugs and benzodiazepines.¹⁴

Daridorexant

Daridorexant is an orexin OX1 and OX2 receptor antagonist that blocks the action of orexin and decreases wakefulness. Daridorexant is recommended by NICE (TA922: Daridorexant for treating long-term insomnia)¹⁵ as a possible treatment for insomnia in adults:

- who have had symptoms for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected
- only if cognitive behavioural therapy for insomnia has not worked, or if it is unsuitable or not available.

If the insomnia does not improve enough, daridorexant should be reviewed and stopped after 3 months. If treatment is continued after 3 months, there should be regular checks to make sure it is still effective, efficacy has been shown in trials for up to 12 months, however the effectiveness of longer term treatment is unknown.

In a study where treatment was continued up to 52 weeks, no withdrawal was reported on stopping daridorexant, and currently the data suggests a low risk of dependency. It is also associated with low levels of next day sedation and falls. Caution should be used if considering prescribing in patients with serious or uncontrolled mental health conditions or those who use alcohol or other substances as patients with suicide ideation/attempt, acute/unstable psychiatric conditions or alcohol/drug abuse were excluded from clinical trials.¹⁶

At the time of approval within EPUT daridorexant has not been approved for use in all ICBs therefore prescribing may not be able to be transferred to primary care and may have to remain within EPUT.

MELATONIN M/R tabs 2mg

Melatonin M/R is licensed for the short-term treatment of primary insomnia (characterised by poor quality of sleep) but only in patients who are aged 55 years old or over⁶. Its licence permits use for up to 13 weeks⁶. The British Association of Psychopharmacology (BAP) recommend the use of melatonin prolonged release therapy as first-line **medication** in the elderly for sleep problems (with endorsement of CBT as first-line **treatment**)⁸.

There are now a number of melatonin products that are licensed, melatonin M/R 2mg tablets are the preferred product and should be prescribed generically. The MHRA have produced guidance indicating that where melatonin is needed, the licensed product should be used wherever possible – including off-label use where deemed suitable by the clinician.

Melatonin M/R 2mg tablets may be crushed, but in doing so the product loses its controlled release profile and becomes identical to an immediate release product; near maximal release of melatonin is reached within the first hour. Crushed tablets may be administered to children in small portions of food, water, juice, yoghurt or jam. Using **Melatonin M/R 2mg** tablets either crushed (to obtain an immediate release profile) or halved (to obtain alternative M/R doses) offers a more cost effective method of obtaining specific doses/release profiles compared to using expensive ‘special’ formulations.

It should be noted that the prescription of Circadin is subject to a “Non-Formulary” request approval other than for use in children/adolescents.

A number of other licensed melatonin products are now available, if there is a specific requirement for a different product this can also be requested via a “Non-Formulary” request approval.

The table below indicates how patients stabilised on melatonin capsules, tablets or liquid which are not melatonin M/R 2mg tablets can be switched to or initiated onto the relevant melatonin M/R 2mg tablets dose and how the desired profile

Switch Melatonin capsules, tablets or liquid to Circadin as follow:

- Melatonin 1mg caps or tabs immediate release – half a tablet crushed
- Melatonin 1mg/1ml–half a tablet crushed per 1mg of liquid
- Melatonin 2mg immediate release caps or tablet-one tablet crushed
- Melatonin 3mg immediate release caps or tablets-one tablet & a half crushed
- Melatonin 3mg CR tabs or caps-one tablet & a half (do not crush)
- Melatonin 5mg immediate release-2 tablets and a half crushed

5.2 Treatment of insomnia

BAP endorse the use of CBT-based treatment packages (including sleep restriction and stimulus control) as ‘first line treatment for chronic insomnia because of efficacy (considered equivalent to prescription medications for short term treatment of chronic insomnia)⁸. BAP also endorses the need for increased availability of this therapy (within the UK). The ideal hypnotic has a rapid onset of effect (within 20 minutes), helps the patient sleep throughout the night, does not cause daytime impairment, and has no abuse potential. Currently, there is no such ideal hypnotic⁴.

- Hypnotics should not be prescribed indiscriminately/routinely but only after non-pharmacological methods have failed and where the insomnia is so severe that it is interfering with normal daily life⁸. Hypnotics should only be prescribed after consideration of non-drug therapies, including CBT.⁹
- Use should be short-term only (2-4 weeks, as per licensed indications). Hypnotics which have been prescribed in hospital should not normally be continued on discharge.
- The lowest possible dose should be used, and, where possible, use should be intermittent.

- Longer acting benzodiazepines, such as nitrazepam (non-formulary) should be avoided.
- A patient should only be switched from one hypnotic to another if they experience adverse effects (considered directly related to a specific hypnotic)
- A patient who has not responded to zopiclone should not be prescribed zaleplon (non-formulary) or zolpidem
- Benzodiazepines and the Z-drugs¹² should be avoided, as much as possible, in the elderly who are at risk of side effects such as ataxia, and confusion leading to falls and injuries. They should only be prescribed following a falls risk assessment
- Treatment should be tapered off gradually⁵.
- Patients should not routinely be prescribed hypnotics on discharge without a discontinuation plan communicated to the GP.
- NICE have published an overview about hypnotics¹³ It includes a tool to support 'deprescribing' of hypnotics, produced by the Bruyère Research Institute Deprescribing Guidelines Research Team in Canada and endorsed by NICE. This can help support the optimal use of hypnotics. A copy of the tool is shown in Appendix 1.

5.3 Sleep hygiene

This term refers to ways of promoting satisfactory sleep. Sleep hygiene on its own is not considered effective but is seen as a useful adjunct to CBT (cognitive behavioural therapy) or pharmacological therapy.

The environment should be conducive to sleep, e.g.

- Familiar setting
- Comfortable bed
- Correct temperature (not too warm and not too cold)
- Darkened, and quiet (that is, non-stimulating) room

Encourage:

- Bedtime routines
- Going to bed only when tired
- Regular daily exercise, exposure to sunlight, and general fitness
- A warm bath or hot milky drinks may promote sleep
- Reassurance to elderly patients that 5-6 hours sleep a night is normal as one gets older

Avoid

- Overexcitement near bedtime
- Late evening exercise
- Caffeine containing drinks late in the day
- Smoking and excessive alcohol
- Large meals late at night
- Thinking about problems and plans at bedtime
- Excessive or late napping during the day
- Too much time awake in bed (especially distressed)

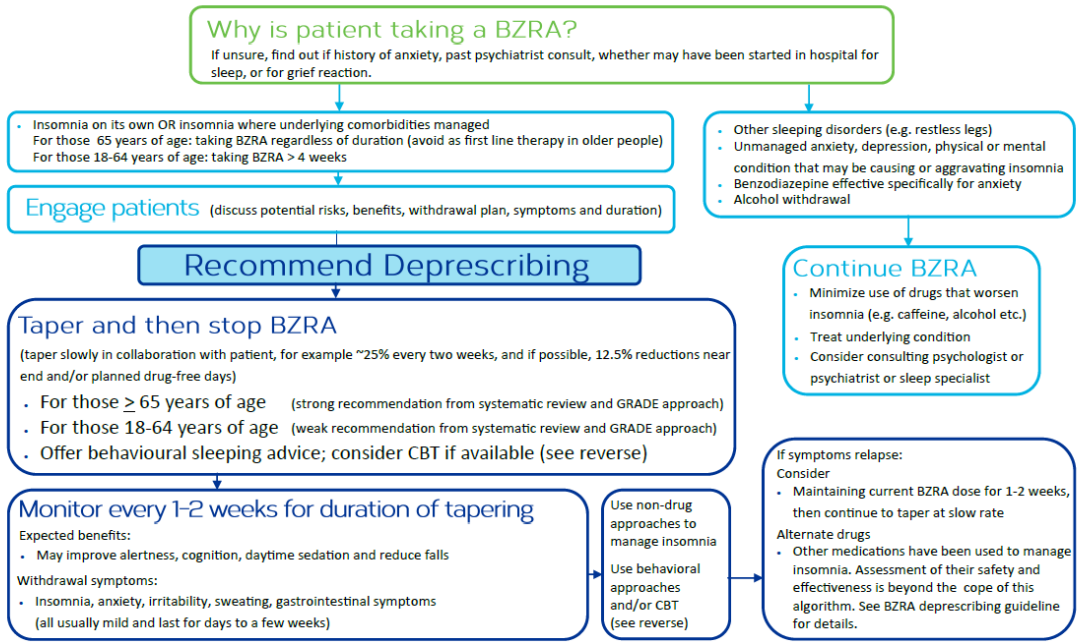
References

1. Terzano M G et al. New Drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; 26(4): 261-282.
<http://www.ncbi.nlm.nih.gov/pubmed/15291009>
2. Montgomery P et al. Cognitive Behavioural Interventions for sleep problems in adults aged 60+. *Cochrane Database Systematic Review* 2003 (1). Art no: CD003161.
<http://www2.cochrane.org/reviews/en/ab003161.html>
3. Dolpheide J et al. Sleep Disorders in 'Applied Therapeutics: the clinical use of drugs' 9th Edition edited by Koda-Kimble et al.
4. BNF: 72nd Current edition, Sep 2017
5. Summary of Product Characteristics (for individual drugs)
<http://www.medicines.org.uk/emc/>
6. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust Prescribing Guidelines: 12th edition Wiley Blackwell
7. NICE Guidelines. TA77, December 2005 - Insomnia.
<http://guidance.nice.org.uk/TA77>
8. BAP Consensus guidelines – insomnia
9. NICE eyes on evidence – prescriptions for anxiolytics and hypnotics and risk of death – June 2014
10. Nice QS 88 June 2015 Personality Disorders: Borderline and Antisocial
[Personality disorders: borderline and antisocial | Introduction | Guidance and guidelines | NICE](http://www.nice.org.uk/guidance/qs88)
11. <http://www.fda.gov/Drugs/DrugSafety/default.htm> Accessed September 2016
12. Appropriate and cost-effective prescribing of short acting hypnotics. PrescQIPP, February 2017
13. NICE Key therapeutic topic: Hypnotics. Published: 15 January 2015.
nice.org.uk/guidance/ktt6
14. NICE NG215: Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults. Published date: 20 April 2022. Accessed 16/03/23.

15. NICE TA 922: Daridorexant for treating long-term insomnia. Published 18th October 2023 <https://www.nice.org.uk/guidance/TA922> Accessed 24/11/23
16. Kunz D, Dauvilliers Y, Benes H, García-Borreguero D, Plazzi G, Seboek Kinter D, Coloma P, Rausch M, Sassi-Sayadi M, Thein S. Long-Term Safety and Tolerability of Daridorexant in Patients with Insomnia Disorder. *CNS Drugs*. 2023 Jan;37(1):93-106. doi: 10.1007/s40263-022-00980-8. Epub 2022 Dec 9. PMID: 36484969; PMCID: PMC9829592.

Appendix 1: Deprescribing tool.

deprescribing.org | Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm February 2019



© Use freely, with credit to the authors. Not for commercial use. Do not modify or translate without permission.
This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. Contact deprescribang@bruyere.org or visit deprescribing.org for more information.

Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B. Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Can Fam Physician 2018;64:339-51 (Eng), e209-24 (Fr)

This algorithm and accompanying advice support recommendations in the NICE guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia, and medicines optimisation. National Institute for Health and Care Excellence, February 2019

deprescribing.org | Bruyère | CIHR IRSC

deprescribing.org | Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm February 2019

BZRA Availability

BZRA	Strength
Alprazolam (Xanax®) T	0.25 mg, 0.5 mg, 1 mg, 2 mg
Bromazepam (Lectopam®) T	1.5 mg, 3 mg, 6 mg
Chlordiazepoxide C	5 mg, 10 mg, 25 mg
Clonazepam (Rivotril®) T	0.25 mg, 0.5 mg, 1 mg, 2 mg
Clorazepate (Tranxene®) C	3.75 mg, 7.5 mg, 15 mg
Diazepam (Valium®) T	2 mg, 5 mg, 10 mg
Flurazepam (Dalmane®) C	15 mg, 30 mg
Lorazepam (Ativan®) T,S	0.5 mg, 1 mg, 2 mg
Nitrazepam (Mogadon®) T	5 mg, 10 mg
Oxazepam (Serax®) T	10 mg, 15 mg, 30 mg
Temazepam (Restoril®) C	15 mg, 30 mg
Triazolam (Halcion®) T	0.125 mg, 0.25 mg
Zopiclone (Imovane®, Rhovane®) T	5 mg, 7.5 mg
Zolpidem (Sublinox®) S	5 mg, 10 mg

T = tablet, C = capsule, S = sublingual tablet

BZRA Side Effects

- BZRAs have been associated with:
 - physical dependence, falls, memory disorder, dementia, functional impairment, daytime sedation and motor vehicle accidents
- Risks increase in older persons

Engaging patients and caregivers

Patients should understand:

- The rationale for deprescribing (associated risks of continued BZRA use, reduced long-term efficacy)
- Withdrawal symptoms (insomnia, anxiety) may occur but are usually mild, transient and short-term (days to a few weeks)
- They are part of the tapering plan, and can control tapering rate and duration

Tapering doses

- No published evidence exists to suggest switching to long-acting BZRAs reduces incidence of withdrawal symptoms or is more effective than tapering shorter-acting BZRAs
- If dosage forms do not allow 25% reduction, consider 50% reduction initially using drug-free days during latter part of tapering, or switch to lorazepam or oxazepam for final taper steps

Behavioural Management

Primary care:

- Go to bed only when sleepy
- Do not use bed or bedroom for anything but sleep (or intimacy)
- If not asleep within about 20-30 min at the beginning of the night or after an awakening, exit the bedroom
- If not asleep within 20-30 min on returning to bed, repeat #3
- Use alarm to awaken at the same time every morning
- Do not nap
- Avoid caffeine after noon
- Avoid exercise, nicotine, alcohol, and big meals within 2 hrs of bedtime

Institutional care:

- Pull up curtains during the day to obtain bright light exposure
- Keep alarm noises to a minimum
- Increase daytime activity & discourage daytime sleeping
- Reduce number of naps (no more than 30 mins and no naps after 2 pm)
- Offer warm decaf drink, warm milk at night
- Restrict food, caffeine, smoking before bedtime
- Have the resident toilet before going to bed
- Encourage regular bedtime and rising times
- Avoid waking at night to provide direct care
- Offer backrub, gentle massage

Using CBT

What is cognitive behavioural therapy (CBT)?

- CBT includes 5-6 educational sessions about sleep/insomnia, stimulus control, sleep restriction, sleep hygiene, relaxation training and support

Does it work?

- CBT has been shown in trials to improve sleep outcomes with sustained long-term benefits

Who can provide it?

- Clinical psychologists usually deliver CBT, however, others can be trained or can provide aspects of CBT education; self-help programs are available

How can providers and patients find out about it?

- Some resources can be found here: <http://sleepwellns.ca/>

© Use freely, with credit to the authors. Not for commercial use. Do not modify or translate without permission.
This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. Contact deprescribang@bruyere.org or visit deprescribing.org for more information.

Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, Holbrook A, Boyd C, Swenson JR, Ma A, Farrell B. Evidence-based clinical practice guideline for deprescribing benzodiazepine receptor agonists. Can Fam Physician 2018;64:339-51 (Eng), e209-24 (Fr)

This algorithm and accompanying advice support recommendations in the NICE guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia, and medicines optimisation. National Institute for Health and Care Excellence, February 2019

deprescribing.org | Bruyère | CIHR IRSC