Hypnotics

Key therapeutic topic
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nice.org.uk/guidance/ktt6

Key points

- The risks associated with hypnotics (including melatonin) such as falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised.
- **Options for local implementation:**
  - Only use hypnotics if insomnia is severe, using the lowest dose that controls symptoms for the shortest period of time.
  - A tool to support 'deprescribing' of hypnotics produced by the Bruyère Research Institute Deprescribing Guidelines Research Team in Canada and endorsed by NICE can help support the optimal use of hypnotics.

Evidence context

Risks associated with the long-term use of benzodiazepine and 'Z drug' hypnotic drugs have been well recognised for many years. Recent data also suggest a similar safety concern with melatonin. These risks include falls, accidents, cognitive impairment, dependence and withdrawal symptoms, and an increased risk of dementia.

The prolonged-release melatonin preparation (Circadin) is licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in people aged 55 years or over, for a maximum duration of 13 weeks treatment. NICE's clinical knowledge summary on managing long-term insomnia recommends that if prolonged-release melatonin is prescribed that the initial duration of treatment should be 3 weeks. If there is a response to treatment, it can be

continued for a further 10 weeks. An observational study discussed in NICE's medicines evidence commentary on fracture risk associated with melatonin and other hypnotics has found that in people aged 45 years and over, receiving 3 or more melatonin prescriptions was associated with an increased risk of fracture compared with no use of any hypnotic drugs. Prescriptions for 'Z drugs' were also associated with an increased fracture risk.

An observational study discussed in NICE's eyes on evidence commentary on benzodiazepines and the risk of dementia suggested that benzodiazepines and 'Z drugs' (zolpidem and zopiclone) are associated with an increased risk of dementia. A case-control study discussed in NICE's medicines evidence commentary on benzodiazepine use and risk of Alzheimer's disease found that past benzodiazepine use was associated with an increased risk of Alzheimer's disease. The study suggests that taking benzodiazepines for more than 3 months and the use of agents with longer half-lives strengthen the association, but potential biases in the study limit the conclusions that can be drawn. Another observational study discussed in NICE's medicines evidence commentary on psychotropic drugs and risk of motor vehicle accidents examined the relationship between exposure to psychotropic drugs and motor vehicle accidents and found that benzodiazepines and 'Z drugs' (and antidepressants) were associated with a significantly increased risk of motor vehicle accidents. In the May 2014 edition of Drug Safety Update, the MHRA warned about the risk of drowsiness and reduced driving ability the next day with zolpidem. Another study discussed in NICE's eyes on evidence commentary on prescriptions for anxiolytics and hypnotics and risk of death found that people who were prescribed anxiolytic and hypnotic drugs had a significantly increased risk of death from any cause over a 7-year period.

As long ago as 1988, in the January issue of Current Problems in Pharmacovigilance, the committee on safety of medicines advised that benzodiazepine hypnotics should be used only if insomnia is severe, disabling or causing the person extreme distress. The lowest dose that controls symptoms should be used, for a maximum of 4 weeks and intermittently if possible.

NICE's technology appraisal guidance on zolpidem and zopiclone recommends that when, after due consideration of the use of non-pharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. A meta-analysis discussed in NICE's eyes on evidence commentary on small benefits of Z drugs over placebo for insomnia found that 'Z drugs' reduce the time taken to fall asleep by 22 minutes compared with placebo but this may not be clinically significant. NICE's technology appraisal guidance states that there is no compelling evidence of a clinically useful difference between the 'Z drugs' and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. There is no evidence to

suggest that if people do not respond to one of these hypnotic drugs, they are likely to respond to another.

The MHRA reinforced the issues about addiction to benzodiazepines in the July 2011 edition of Drug Safety Update. Various approaches to reducing hypnotic prescribing can achieve significant success. See NICE's clinical knowledge summary on benzodiazepine and z-drug withdrawal for advice on assessing a person who is being prescribed long-term benzodiazepines or 'Z drugs', and on managing withdrawal of treatment.

An e-learning programme, Addiction, misuse and dependency: A focus on over-the-counter and prescribed medicines, has been developed jointly by the Centre for Pharmacy Postgraduate Education and the Royal College of General Practitioners. The programme aims to provide healthcare professionals with a better understanding of how to recognise people who may have an addiction to prescribed or over-the-counter medicines and how to approach and help them.

In August 2016, the US Food and Drug administration announced new labelling requirements for prescription opioids (indicated for pain or cough) and benzodiazepines. These concern the serious risks of respiratory depression, coma and death associated with the combined use of certain opioids and benzodiazepines.

The European Economic Area subsequently made similar labelling variations, and in February 2018, the Co-ordination Group for Mutual Recognition and Decentralised Procedure (CMDh) agreed on a proposed text warning about concomitant use of benzodiazepines or benzodiazepine like products ('Z drugs') and opioids. A corresponding text for opioids has also been agreed.

A new offence of driving with certain controlled drugs, above specified limits in the blood, came into force in March 2015. Prescription drugs covered by the new offence include amphetamine (for example dexamphetamine or selegiline), clonazepam, diazepam, flunitrazepam, lorazepam, methadone, morphine or opioid-based drugs (for example codeine, tramadol or fentanyl), oxazepam and temazepam. This list doesn't include all benzodiazepines and opioids. However, all benzodiazepines and opioids can impair driving ability. See the July 2014 edition of Drug Safety Update and the Drugs and driving: the law government web page for more details.

Prescribing data, metrics or supporting resources

Bruyère Research Institute Deprescribing Guidelines Research Team has produced a benzodiazepine and Z-drug deprescribing algorithm that supports recommendations in the NICE guidance on the use of zolpidem and zopiclone for the short-term management of insomnia, and

medicines optimisation.

The selection of metrics to support key therapeutic topics is overseen by the NHS England Medicines Optimisation Intelligence Group, and work is ongoing in this area. At this point, the following metrics and prescribing data have been identified by this group to support this topic.

A medicines optimisation key therapeutic topic prescribing comparator is available – Hypnotics ADQ/STAR PU (ADQ based).

The Medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes this comparator. It helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Prescription Cost Analysis data of prescriptions dispensed in the community in England show that in 2017, 834,793 items of melatonin were dispensed at a cost of approximately £34 million. These data relate to all melatonin preparations, including 'specials', for all indications.

Update information

March 2019: This topic was retained for the 2019 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence where appropriate.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic that has been identified to support medicines optimisation. **It is not formal NICE guidance.**

For information about the process used to develop the key therapeutic topics, see the integrated process statement.

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