



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Fracture risk associated with melatonin and other hypnotics

An observational cohort study 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. The study found that in a matched cohort receiving 2 or more prescriptions for 'Z drug' hypnotics was also associated with a similarly increased fracture risk.

In line with NICE guidance on [zaleplon, zolpidem and zopiclone](#) and [MHRA advice](#) if, 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 and only in strict accordance with their licensed indications.

Overview and current advice

Falls and fall-related injuries are a common and serious problem for older people with 30% of people older than 65 and 50% of people older than 80 falling at least once a year. Certain medication can increase the risk of falls in older people, for example drugs that cause drowsiness such as hypnotics. A [NICE guideline on falls in older people: assessing risk and prevention](#) was published in 2013.

Risks associated with the long-term use of benzodiazepine and 'Z drug' hypnotic drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. In 1988, 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 technology appraisal guidance on [zaleplon, zolpidem and zopiclone](#) supports this and 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.

As the MHRA reinforced in the [July 2011 edition of Drug Safety Update](#), for those who have been prescribed hypnotic drugs for a long period of time, reducing or stopping use of these drugs may be difficult. Various approaches to reducing hypnotic prescribing can achieve significant success. See the NICE 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.

A NICE [key therapeutics topic on hypnotics](#) discusses the evidence base and safety concerns associated with these drugs. See the NICE Clinical Knowledge summary on [insomnia](#) for a general overview of the condition.

Prolonged-release melatonin ([Circadin](#)) was launched in 2008 and 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. The NICE 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.

Prescribing of melatonin has increased over recent years; one possible reason for this could be due to safety concerns over benzodiazepine and 'Z drug' hypnotic drugs¹. Evidence for the safety of melatonin is less well described than for other hypnotics.

New evidence

A [retrospective](#) cohort study has assessed the fracture risk of melatonin and other hypnotic drugs in adults aged 45 years and over using data from 309 UK GP practices who contributed to The Health Improvement Network ([THIN](#)), a database of electronic medical records¹.

The study included 4 cohorts: people first prescribed melatonin between 1 July 2008 and 30 June 2013 who had not received hypnotic benzodiazepines or 'Z drugs' in the 6 months prior to their first melatonin prescription (n=1,377), people prescribed at least 2 prescriptions of hypnotic benzodiazepines between the same timescale (n=880), people prescribed at least 2 prescriptions of 'Z drugs' between the same timescale (n=1,148) and a control group. The 2 cohorts prescribed hypnotic benzodiazepines or 'Z drugs' were matched (for age, gender and practice) to the melatonin cohort. Participants in these 2 cohorts had no prescriptions for melatonin recorded in their electronic records and in the 6 months prior to their first prescription for hypnotic benzodiazepines or 'Z drugs' had not received either 'Z drugs' or hypnotic benzodiazepines respectively. The control group (n=2,752) were matched to the melatonin cohort and had never been prescribed melatonin, hypnotic benzodiazepines or 'Z drugs'.

The study outcome was any fracture following study entry (defined as first prescription of a study drug). Each person was followed from study entry to the date of first fracture, the date of leaving the GP practice or the end of the observation period (30 May 2013). Fracture risk for the study cohorts were presented as hazard ratios and these were adjusted for 26 covariates and potential confounding factors including gender, age, body mass index, smoking and alcohol status, concomitant medication and a variety of co-morbidities including cancer, respiratory and cardiovascular disease, diabetes, musculoskeletal conditions, epilepsy, sleep disorders, ophthalmic conditions, dementia, mental health conditions and pre-study fractures.

The average age of participants in the study was 65 years and the average time of study follow-up was 2.6 years. The average time to fracture was 1.04 years. There was no significant difference in average time to fracture between the cohorts. Over the observation period 6.0% of participants in the melatonin cohort, 5.8% of participants in the hypnotic benzodiazepine cohort, 5.9% of participants in the 'Z drug' cohort, and 3.2% of participants in the control group had a fracture. After adjusting for covariates, both the melatonin cohort and the 'Z drugs' cohort were associated with an increased risk of fracture (adjusted hazard ratio [HR] 1.44; 95% [confidence interval](#) [CI] 1.01 to 2.04; p=0.04 and adjusted HR 1.52; 95% CI 1.04 to 2.23; p=0.03 respectively). However, after this adjustment the

hypnotic benzodiazepine cohort was not associated with an increased risk of fracture (adjusted HR 1.26; 95% CI 0.82 to 1.92; p=0.29).

The majority of the melatonin prescriptions (71%) were for the prolonged-release formulation and 79% of those prescribed melatonin were prescribed it once or twice. For the 21% of participants who received 3 or more melatonin prescriptions, the average number of prescriptions was 11.9. The study authors report that only people who received 3 or more melatonin prescriptions had an increased risk of fracture; further data are not provided in the paper.

Commentary

Commentary provided by Narinder Bhalla, Consultant Pharmacist – Medication Safety, Cambridge University Hospitals NHS Foundation Trust

This observational study found that in people aged 45 years and over, receiving prescriptions for melatonin was associated with an increased risk of fracture (adjusted HR 1.44). The study also found that in a matched population group receiving 2 or more prescriptions for 'Z drug' hypnotics was also associated with a similarly increased fracture risk (adjusted HR 1.52). The study authors reported that an increased risk of fracture was only seen in people who received 3 or more melatonin prescriptions. This is longer than the recommended duration of treatment which is an initial 3 weeks, followed by a further 10 weeks if a response is seen.

Risks associated with the long-term use of hypnotic drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. Since its launch in 2008, prescribing of melatonin has increased in recent years; one possible reason for this could be due to safety concerns over benzodiazepine and 'Z drug' hypnotics. However, this study suggests that melatonin may also have similar risks when prescribed as a hypnotic in older people.

We know that hypnotics should be used only if insomnia is severe, using the lowest dose that controls symptoms and only for short periods of time. The NICE Clinical Knowledge Summary on [insomnia](#) states that pharmacological therapy is generally not recommended for the long-term management of insomnia. Caution is recommended when prescribing hypnotics for older people. The results of this study would suggest that it would be prudent for prescribers to exercise the same degree of caution when considering melatonin as a hypnotic for older people. Indeed, the NICE guideline on [falls in older people: assessing risk and prevention](#) recommends that older people on any psychotropic agent should have their medication reviewed, with specialist input if appropriate, and discontinued if possible to reduce their risk of falling.

In this study, hypnotic benzodiazepines were not associated with an increased risk of fracture. However, this does not mean hypnotic benzodiazepines are 'safer' than melatonin or 'Z drug' hypnotics for fracture risk due to the limitations of the study. The study authors noted that the hypnotic benzodiazepine cohort was smaller than the cohort for melatonin and the 'Z drugs' (880 compared with 1,377 and 1,148 respectively) and that this may have affected the statistical power. As outlined earlier, there are also other safety concerns with hypnotic drugs apart from fracture risk.

This was an observational study so it is prone to [confounding](#) and [bias](#), in that any outcome (in this case fracture risk) may be due to the particular characteristics of the study population rather than the treatment being studied. For instance, the melatonin, 'Z drug' and hypnotic benzodiazepine cohorts had a higher prevalence of mental health conditions and other co-morbidities compared with the control group. In addition, the melatonin cohort had a higher prevalence of sleep disorders and dementia than the 'Z drug' and hypnotic benzodiazepines groups. However, the study aimed to reduce the risk of confounding by adjusting for several covariates and potential confounding factors including

age, body weight, gender, pre-study fractures, concomitant medication, sleep disorders and a variety of co-morbidities.

Study sponsorship

This observational study was supported by an unrestricted educational grant from Flynn Pharma to the School of Pharmacy, Keele University.

References

1. Frisher M, Gibbons N, Bashford J et al. (2016) [Melatonin, hypnotics and their association with fracture: a matched cohort study Age and Aging](#) DOI:10.1093/ageing/afw123

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