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Important New Evidence Service

In partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch® Rapid Update 3 – July 2025

Medicines optimisation: Systematic review and meta-analysis of interventions to deprescribe benzodiazepines

A systematic review and meta-analysis has been conducted as part of a wider European project to improve patient safety and prescription practices relating to use of benzodiazepines and closely related sedative hypnotic drugs (BSH) for the treatment of insomnia (BE-SAFE). Eligible trials were those that looked at strategies to deprescribe or discontinue the use of BSH in adult patients.

The review identified 58 publications of 49 trials with 39,336 participants. It found low certainty evidence suggesting that, compared with usual care, education of patients, medication review, and a pharmacist led educational intervention may increase the proportion of patients who discontinue BSH. None of the interventions described improved physical function, mental health, or signs and symptoms of insomnia. Factors like whether the age of patients or the duration of BSH use affected the results could not be tested due to insufficient data.

Useful information and advice on understanding polypharmacy, overprescribing and deprescribing is available from the Specialist Pharmacy Service and the Health Innovation Network Polypharmacy programme.

Reference: Zeraatkar D, Kumbargere Nagraj S, Ling M et al. Comparative effectiveness of interventions to facilitate deprescription of benzodiazepines and other sedative hypnotics: systematic review and meta-analysis. BMJ 2025;389:e081336

What do we know already?

- Benzodiazepines and other sedative hypnotics like the 'z' drugs (zopiclone, zaleplon and zolpidem) are commonly prescribed for the treatment of anxiety and insomnia, respectively. They are also well known as drugs associated with a risk of dependence and withdrawal symptoms. NICE recommends ensuring that all suitable management options, including non-pharmacological approaches and watchful waiting, have been discussed with and offered to a patient before starting or continuing with dependence forming medicines.
- Latest data for the levels of benzodiazepine prescribing are available for 2019/20 for Scotland where 5% of the adult population in Scotland (225,000 in total) received a benzodiazepine prescription in the last year, and 3.2% received 'z' drugs. In Scotland levels of benzodiazepine prescriptions are decreasing (down from 265,000 in 2010/11), whereas z drug prescribing increased from 120,000 people in 2010/11 to 145,000 in 2019/20.
- Similar data for England is available for 2017/18 where 3% of adults in England (1.4 million) received a prescription for benzodiazepines, and 2% (1 million) received a prescription for a z-drug. There is a continuing longer-term fall in prescription numbers for benzodiazepines. A longer-term increase in annual prescription numbers for z-drugs started to reverse in 2014.
- Prescribing analysis of dependence forming medicines using CPRD data has also shown a steep fall in the proportion of benzodiazepine prescribing periods exceeding 30 days (from about half of prescribing periods in 2000 to a third in 2014). Data on longer term prescribing of benzodiazepines over 6- or 12-month periods is less clear.

What does this evidence add?

- The study found low certainty evidence that some interventions may increase BSH discontinuation rates, but little evidence for an effect on patient-centred outcomes like physical function, mental health or the signs and symptoms of insomnia.
- It also found that multicomponent interventions may be more effective than single component approaches, but further high quality research is needed
- The study had limitations in that the authors anticipated that the effects of interventions may vary according to several characteristics of patients and interventions such as age and duration of BSH use, but were unable to do subgroup analyses owing to insufficient data. Fewer than half of the trials reported most patients to be using BSH for the treatment of insomnia. Whether the effects of interventions for deprescribing BSH may be different depending on the reason for its use is unclear. The authors also commented that key organisational aspects of interventions that may contribute to their success remain uninvestigated. Except for one trial that offered financial incentives to

physicians for doing medication reviews, the effectiveness of changes in financial and governance structures has not been studied.

Study details

- This systematic review and meta-analysis looked at studies that evaluated strategies to deprescribe or discontinue the use of BSH for insomnia in adult patients. The drugs that patients were taking included benzodiazepines (for example, diazepam, alprazolam) and nonbenzodiazepine "z-drugs" (for example, zolpidem, zaleplon).
- Outcomes of interest agreed by a panel included the proportion of patients who discontinue BSH, quality of life, physical function, mental health, cognitive function, signs and symptoms of insomnia, sleep efficiency, total sleep time, sleep onset latency, number of BSH prescriptions, drug-free nights, and dropouts of patients during the intervention. It was not possible to stratify patients by age or by duration of treatment because the information was not available in the trials.
- The evidence was assessed for biases in implementation using the Cochrane risk of bias 2.0 tool and the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to consider the certainty that outcomes reported were a true reflection of the effect of treatment.

Results

- The review included 58 publications, reporting on 49 unique trials with 39,336 patients. The interventions investigated in the trials included tapering, education of patients, education of physicians, combined education of patients and physicians, cognitive behavioural therapy, medication review, pharmacist-led interventions including a multicomponent intervention involving pharmacists, a pharmacist led educational intervention, and the introduction of a clinical pharmacy service to nursing homes, mindfulness, motivational interviewing, drug assisted tapering and withdrawal, and auricular acupuncture.
- Sixteen trials used a cluster randomised trial design, one a crossover by cluster design, and the remainder parallel randomised designs. The median duration of follow-up was 24 weeks (interquartile range 14 to 50.5). All trials were conducted in high income countries, apart from two trials conducted in Argentina and Brazil. Four trials were conducted in nursing homes and the remainder in the community. More than half of all trials were funded by government organisations, followed by not-for-profit organisations or hospitals and universities.
- Three trials targeted non-benzodiazepine hypnotics, seven a range of inappropriate drugs including BSH, and the remainder benzodiazepines including or excluding other related hypnotics. Trials included a median of 188 patients (interquartile range 70 to 528). Approximately one third of all patients were male. Twenty one trials with 5,848 patients reported that most of their participants (>60%) were using BSH for insomnia. The reasons for BSH use in other trials were not reported.
- The assessment of the quality of the trials defined in terms of the risk of bias found that nearly all data were rated as being at high risk of bias primarily owing to concerns about deviations from intended intervention that arose from lack of masking of patients and healthcare providers and potential for differential care across trial arms. Concerns about the randomisation procedures and allocation concealment also contributed to ratings of high risk of bias.
- Overall, low certainty evidence suggests that, compared with usual care, education of patients, medication review, and a pharmacist led educational intervention may increase the proportion of patients who discontinue BSH. The investigators did not find evidence that these interventions improve physical function, mental health, or signs and symptoms of insomnia.
- There was moderate certainty evidence that that education of patients probably has little or no effect on physical function, mental health, and signs and symptoms of insomnia. The study did not find evidence assessing these outcomes for medication review or the pharmacist led educational intervention.
- Low certainty evidence suggests that multicomponent interventions may increase the proportion of patients who discontinue BSH compared with single component interventions. The investigators did not find evidence that multicomponent interventions led to more dropouts during the intervention.

Level of Evidence: Level 2 according to the SORT criteria. **Study funding:** State (European Union and Swiss State Secretariat for Education, Research and Innovation)