Benzodiazepines and the risk of dementia

An observational study suggests that use of an array of hypnotics and anxiolytics (mainly benzodiazepines and ‘Z drugs’) are associated with an increased risk of dementia.

Overview: Dementia is associated with a major social burden worldwide. Because treatment options are limited, identifying the factors contributing to dementia is important. The role of hypnotics in people with dementia is controversial because they are associated with cognitive impairment as well as other well recognised adverse effects. As long ago as 1988, the Committee on Safety of Medicines advised that benzodiazepine should be used only if insomnia is severe, disabling or causing the patient extreme distress.

The Medicines and Healthcare products Regulatory Agency (MHRA) reinforced the issues regarding addiction to benzodiazepines in the July 2011 edition of Drug Safety Update and point to a structured review by the National Addiction Centre. Overall prescribing of hypnotics decreased from May 2008 onwards, but the overall rate remains relatively high and this is a key priority area for medicines optimisation as highlighted in the NICE Medicines and Prescribing QIPP Key Therapeutics Topics document.

Current advice: NICE guidance on managing insomnia advises that after non-drug therapies have been explored, hypnotics should be used in the lowest dose possible for no more than 4 weeks with benzodiazepines, or 2–4 weeks with Z drugs (zopiclone, zolpidem, and zaleplon). NICE guidance on generalised anxiety disorder (GAD) in adults recommends that benzodiazepines should not be offered for the treatment of GAD in primary or secondary care except as a short-term measure during crises.

The NICE Pathway on dementia brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A prospective population based cohort study assessed whether there was an association between starting benzodiazepines, and similar drugs, and risk of subsequent dementia in 1063 people aged 65 years and over (mean age 78.2 years). The total study duration was 20 years, including a 5 year observation period and a 15-year assessment period. Patients were eligible for the study if they were dementia free at 5-years and did not start taking hypnotics until at least year 3 (Billioti de Gage et al. 2012).

During the 15-year follow-up, 253 (23.8% of the cohort) cases of dementia were confirmed: 30 (32%) in benzodiazepine users (n=95) and 223 (23.0%) in non-users (n=968). After adjusting for potential confounders, new use of benzodiazepines was associated with about a 60% increased risk of dementia (adjusted hazard ratio [HR] 1.60, 95% CI 1.08 to 2.38) compared with non-users, and when further adjusted for depressive symptoms the results were unchanged (HR 1.62, 95% CI 1.08 to 2.43).
Incident dementia was confirmed by applying validated criteria (The Diagnostic and Statistical Manual of Mental Disorders) ascertained by neurologists blinded to the study hypothesis. The study attempted to adjust for a number of potential confounders (for example, educational level and marital status). It also used a run-in and follow-up period to adjust for factors strongly associated with benzodiazepine use. However, the conclusions drawn are limited by several other methodological limitations (for example, lack of separately adjusting for anxiety and sleep disorders, both important prodromal symptoms of dementia). Furthermore, the study only included a small number of new users of hypnotics (n=95). This number may be too small to assess differences between different drugs such as, benzodiazepines versus 'Z drugs'.

Commentary: "This is yet another study that highlights important adverse effects with benzodiazepines and related drugs. Although this study cannot prove cause and effect, it does add to the concerns regarding the use of benzodiazepines and hypnotic agents. These include falls, accidents, cognitive impairment, longer term clinical effectiveness as well as dependence associated with prescribing benzodiazepines and related medicines.

"There are still a significant number of long-term users of hypnotic agents, despite gradual reductions in use in recent years. Clinicians should ensure that any new prescriptions are in line with NICE and MHRA advice and reserved for the short-term relief of anxiety or insomnia that is severe, disabling and causing unacceptable distress to patients. Interventions to reduce the use of these drugs are having an impact and need to continue, whether simple reminder letters, advice from pharmacists, GPs or others as well as other interventions such as cognitive behavioural therapy. These are detailed further in the NICE Medicines and Prescribing QIPP Key Therapeutics Topics document." – Nigel Barnes, Director of Pharmacy and Medicines Management, Birmingham and Solihull Mental Health Foundation Trust