Prescriptions for anxiolytics and hypnotics and risk of death

Overview: Anxiolytics and hypnotics are often prescribed for people who have anxiety disorders or insomnia, as well as for several other indications. More than 16 million prescriptions for anxiolytics and hypnotics were written in general practice in England and dispensed in 2013. Benzodiazepines accounted for 58% of these prescriptions and ‘Z drugs’ (zaleplon, zolpidem and zopiclone) accounted for 39% (NHS Business Services Authority: personal communication April 2014). In addition to concerns about benzodiazepine dependence (Medicines and Healthcare Products Regulatory Agency 2011), anxiolytics and hypnotics have been associated with several risks, including falls, accidents and cognitive impairment (NICE 2013). A NICE Medicines Evidence Commentary discusses a case–control study that found that psychotropic drugs, including benzodiazepines and Z drugs, were associated with a significantly increased risk of motor vehicle accidents.

See the NICE Evidence Services topic pages on anxiety and insomnia for a general overview of these conditions.

Current advice: NICE guidance on generalised anxiety disorder (GAD) in adults advocates a stepwise approach to management, offering or referring for the least intrusive, most effective intervention first. Therefore, non-drug interventions should be the mainstay of treatment for many people, with drugs generally reserved for more severe illness or when symptoms have failed to respond to non-drug interventions. NICE recommends that benzodiazepines are not offered for GAD in primary or secondary care except as a short-term measure during crises.

NICE guidance on Z drugs for managing insomnia recommends that when, after due consideration of the use of non-drug 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 (4 weeks for benzodiazepines, 2–4 weeks for Z drugs; see the relevant summary of product characteristics). The Medicines and Healthcare Products Regulatory Authority advice for benzodiazepines recommends that the lowest dose that controls symptoms should be used, for a maximum of 4 weeks and intermittently if possible.

The NICE Pathways on GAD and common mental health disorders in primary care bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A UK retrospective cohort study assessed the risk of death in people aged over 16 years who were taking anxiolytic or hypnotic drugs, or both (Weich et al. 2014). Patients permanently registered with one of 273 GP practices were identified from the General Practice Research Database. The cohort included 34,727 patients who had received at least 2 prescriptions for an anxiolytic or hypnotic drug (see sections 4.1.1 and 4.1.2 of the British National Formulary) between January 1998 and December 2001. These were compared with 69,418 controls matched by age, sex and general practice who were not prescribed these drugs. People who were prescribed study drugs
had more physical and psychiatric comorbidities, more prescriptions for other drugs, and were more likely to be smokers than those who were not prescribed study drugs.

After an average of 7.6 years, prescription of an anxiolytic, a hypnotic or both was associated with double the risk of death from any cause compared with no prescription for these drugs (hazard ratio [HR] adjusted for sex, age, sleep disorders, anxiety disorders, other psychiatric disorders, comorbidities and prescription of other drugs=2.08, 95% confidence interval [CI] 2.02 to 2.15, p<0.001). Benzodiazepines were the most commonly prescribed class of drug (76% of patients), followed by Z drugs (39%) and other drugs (21%), but many people (32%) were prescribed more than 1 anxiolytic or hypnotic.

To reduce the likelihood of bias from the prescription of study drugs to people who were terminally ill, the analysis was restricted to patients who were prescribed these drugs only in the first year after recruitment but survived for more than 12 months. These people had lower rates of physical and mental health problems than the overall cohort, but prescription of an anxiolytic, a hypnotic or both was still associated with a significant increase in the risk of death (adjusted HR=1.75, 95% CI 1.65 to 1.85, p<0.001). The authors estimated that these drugs were linked to 4 excess deaths per 100 people followed for an average of 7.6 years after their first prescription. Risk generally increased with dose for all 3 classes of study drug.

Limitations include that this study was observational and was unable to adjust for all confounding factors, such as socioeconomic status. It did, however, attempt to adjust for sex, age, sleep disorders, anxiety disorders, other psychiatric disorders, comorbidities and prescription of other drugs. Nevertheless, there was likely to be some residual confounding from the inability to quantify illness severity and from misclassification of diseases. Also, causes of death were unknown.

Commentary: “This carefully conducted UK cohort study from Weich et al. (2013) found an association between anxiolytics and hypnotics and mortality after accounting for pre-existing psychiatric disorders, other diseases and other prescribed drugs.

“A number of previous studies have suggested that insomnia is associated with an increase in mortality (Cappuccio et al. 2010; Gallicchio and Kalesan 2009). A previous US cohort study by Kripke et al. (2012) also found hypnotics to be associated with increased risks of death and cancer. However, Kripke et al. (2012) were not able to control for certain pre-existing psychiatric diseases, such as anxiety or depression. The current study adjusted for psychiatric comorbidities in addition to other diseases and prescriptions, but it was not able to adjust for important confounders such as socioeconomic or functional status.

“The current study shows association not causation. Despite this, it reinforces guidance that anxiolytics and hypnotics should be prescribed only after consideration of non-drug therapies, including cognitive behavioural therapy (CBT). Access to CBT for anxiety and depression has improved, which should reduce the pressure to prescribe anxiolytics and hypnotics in the long term (Sirdifield et al. 2013). Further efforts are also needed in primary care to manage insomnia with non-drug treatments.” – Professor A Niroshan Siriwardena, Professor of Primary and Prehospital Health Care, Community and Health Research Unit, University of Lincoln

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