The benzodiazepine hangover: Next-day residual effects on driving performance.

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Abstract

Context
Benzodiazepines (BZDs) are implicated in a considerable proportion of road crashes in Australia (behind only alcohol and cannabis respectively). In fact, BZD hypnotics are the pharmaceutical drug most commonly detected in driver fatalities and serious injuries in Australia. Based on epidemiological estimates, the road safety burden from BZDs is almost on par with the road safety burden relating to all illicit drugs combined.

Objectives
A review of reported patterns of BZD use, epidemiological studies of BZDs and crash risk, and laboratory studies of psychomotor and cognitive effects of BZDs was conducted.

Key Outcomes
BZD hypnotics provide clinically desirable effects (e.g. sedation and reduced alertness) at night for insomniacs. However, these same effects become adverse if experienced during the day. Ideally, a hypnotic should facilitate sleep at night (the typical time taken) but be free from residual sedative effects the following morning. Even relatively subtle residual effects may have serious consequences for daily activities and potentially devastating effects on road safety. Aside from the acute impairing effects of BZDs that may impair driving performance, there is a need to consider issues associated with longer-term use. BZDs are frequently used outside clinical guidelines (i.e. long-term), despite the absence of clinical evidence to inform this practice. It is now widely accepted that, even at normal therapeutic doses, BZDs have the ability to cause both physiological and pharmacological dependence. This is evidenced by the onset of withdrawal symptoms when the drugs are discontinued. Nevertheless, there is still considerable debate about whether BZDs effect any long-term impairment on sleep architecture and cognition.

Discussion and conclusions
This paper highlights gaps in the current knowledge relating to residual BZD effects on driving and cognitive performance with chronic use, and suggests approaches for future research to inform appropriate management of and advice relating to BZD use.
Introduction

Benzodiazepine (BDZ) hypnotics are primarily indicated to treat sleep-related disorders, a condition that is estimated to be prevalent in 10-40% of adults (Mai & Buysse, 2008). For sufferers of insomnia, the medications used to treat the condition, as well as the condition itself, have both been associated with compromised fitness-to-drive. In fact, BZDs are the prescription drug most commonly found in injured (~14%) and fatally-injured (~5%) drivers (Drummer et al., 2003; Griggs et al., 2007). They are also one of the most commonly prescribed psychoactive medicines in Australia, with script volumes remaining relatively constant over the last 10 years (Figure 1).

Figure 1: Pharmaceutical benefits scheme (PBS) script volumes for benzodiazepines from 2003 to 2012 (data sourced from Medicare Australia, 2013).

Residual impairment of driving performance after hypnotic BZD use

BZD hypnotics should facilitate sleep at night (the typical time when taken), with resolution of any sedative effects by the following morning. However, data from reported patterns of use, and epidemiological studies of crash risk and laboratory studies, together point to there being residual effects of the medication (Rapoport & Banina, 2007). This has implications for daytime functioning and alertness, and could result in impairment of cognitive and psychomotor skills, such as those required to safely drive a car. The strength of the residual effect is believed to be dependent on the type, dose, time since administration and frequency of dosing of the BZD, although this is not exclusively the case (Vermeeren, 2004). Hypnotics with short half-lives have also been shown to produce residual effects. As such, there is currently no clarity about which BZDs produce residual effects, how long these effects persist, and to what extent the effects influence cognitive functioning and driving skills.

Epidemiological studies have indicated that there is an increased risk of crash involvement the morning after administration of a BZD hypnotic, although the strength of this association

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remains unsubstantiated due to conflicting evidence (Rapoport et al., 2009; Smink, Egberts, Lusthof, Uges, & de Gier, 2010; Vermeeren, 2004). This is, in part, due to other consumer factors (such as age, comorbid medical or psychiatric disorders, other medications) rather than the BZDs themselves. As such, culpability is yet to be confirmed. A number of laboratory and driving simulator studies have demonstrated the potential for residual impairment of tracking ability, visual discrimination and reaction time, up to 11 hours after night-time administration of a BZD (Seppala, Korttula, Hakkinen, & Linnoila, 1976; Verster, Veldhuijzen, & Volkerts, 2004; Willumeit, Ott, & Neubert, 1984). This phenomenon has typically been more prominent with long-acting BZDs (Hindmarch & Subhan, 1983; Judice et al., 2002), although exceptions have been reported. Flunitrazepam (2mg) and lorazepam (1mg) are two examples of intermediate-acting BZDs that have demonstrated residual effects on on-road car handling, up to 17 hours post-dose, in insomniacs and anxious patients respectively (Hindmarch & Gudgeon, 1980; Verster, Veldhuijzen, Patat, Olivier, & Volkerts, 2006). Lorazepam has also been shown to impair on-road driving performance (tracking ability) in both anxious patients and healthy volunteers treated with 2mg lorazepam twice daily for 7 days (Verster et al., 2004; Verster, Veldhuijzen, & Volkerts, 2005).

**Long-term BZD use and cognitive impairment – A question of tolerance?**

Estimates from the National Health Survey 2007–2008 revealed that over 200,000 Australians had used BZDs to treat a sleep disorder (i.e. BZD hypnotics) in the 2 weeks prior to being surveyed, with approximately 30% of those having used the medications on more than three occasions per week for six months or longer (Australian Bureau of Statistics, 2009). There are very few, if any, accepted medical indications for such long-term use. Despite this, BZDs are commonly used outside therapeutic guidelines (Mant & Walsh, 1997). A recent thesis by Hansen (2012) demonstrated a strong relationship between sedative prescriptions and risk of motor vehicle crash (hazard ratio = 2.23, n = 676,694), with the highest risk group being those who had 121–240 days of continuous prescription fills (Hansen, 2012). This long-term use has implications for the safe and effective conduct of complex daytime activities such as driving. However, to date, only two experimental driving studies have endeavoured to address the question of driving impairment after chronic BZD hypnotic use (>3 months for at least 4 nights per week) the morning after use, and these were done in a population comprised of older drivers (T.R.M Leufkens, Ramaekers, de Weerd, Riedel, & Vermeeren, 2011; Tim R. M. Leufkens, 2009). The placebo-controlled crossover study found significant residual impairment of zopiclone (7.5mg) on highway driving in unmedicated insomniacs, chronic users of hypnotics and normal sleepers, while the parallel design cohort study revealed no significant differences between highway driving performances of unmedicated insomniacs, chronic users of hypnotics and normal sleepers.

**Directions for future experimental research**

Despite the existence of epidemiological research relating the use of BZDs with an increased risk of road crashes (Orriols et al., 2011), limited experimental evidence exists to confirm a causative role, particularly when considering chronic use and/or residual effects. The research that does exist remains inconclusive. There are a number of key limitations that could account for the disparity in previous experimental findings. Namely, these studies either utilised only laboratory-based psychomotor tests (as opposed to on-road or driving simulator tests), or adopted an acute dosing regime (e.g. single dosing or repeated dosing up to a maximum of 17 days), and in most cases examined the phenomenon in healthy volunteers rather than a patient population (e.g. insomnia patients) (Rapoport et al., 2009; Vermeeren, 2004). Two studies by Leufkens and colleagues are the only exceptions. Both these on-road
studies investigated the chronic and residual effects of benzodiazepine use in a patient population, compared to age-matched healthy controls and unmedicated insomniac controls. Only one found significant differences in driver performance, and that was after zopiclone administration. It should be noted, however, that the age range of the participants in both studies was 52 to 73 years, with the mean age of over 60 years in each experimental group. Age is of particular importance to both driving and cognitive performance, particularly when considering that cognitive degradation increases with increasing age and the proclivity of certain age groups to be involved in road crashes (age <25 and >65 being at highest risk). Although the prevalence of chronic benzodiazepine use does peak in the elderly, use/misuse remains considerable in the younger populations and has been shown to increase steadily in those aged in their mid-20s onwards (Hollingworth & Siskind, 2010). Despite this, there is continued neglect in the experimental literature of the effects of benzodiazepine use in younger age groups.

**Conclusion**

The evidence base regarding benzodiazepine-induced residual driving impairment is currently tenuous as described above, and hence clear guidelines in relation to driving while taking these medications have not been developed. Despite a number of epidemiological studies relating the use of benzodiazepine hypnotics with road crashes, limited experimental data exists to confirm a causative role. Indeed, the absence of a systematic assessment of the impairing effects in patients suffering from insomnia compared to a control sample, has recently been identified as a major gap in our understanding (Rapoport et al., 2009). As such, further high impact experimental research is required to quantify the impairing effects of BZDs on driving and cognitive task performances the next day following night-time use. The outcomes of such research will subsequently inform appropriate management of and advice relating to BZD use and the implications for safe driving.

**References**


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