

SIDE EFFECTS OF TREATMENT WITH BENZODIAZEPINES

Suzana Uzun¹, Oliver Kozumplik¹, Miro Jakovljević^{2,3} & Biserka Sedić⁴

¹University Department, Vrapče Psychiatric Hospital, Bolnicka cesta 32, 10090 Zagreb, Croatia

²University Department, Clinical Hospital Zagreb, Kišpatičeva 12, 10000 Zagreb, Croatia

³School of Medicine, University of Zagreb, Šalata 3b, 10000 Zagreb, Croatia

⁴University of Applied Health Studies, Mlinarska cesta 38, 10000 Zagreb, Croatia

SUMMARY

Background: The use of benzodiazepine anxiolytics and hypnotics continues to excite controversy. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term benzodiazepine use actually constitutes a problem. Although as a class benzodiazepines act rapidly and are well tolerated, their use presents clinical issues such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome. The aim of this article is to review literature regarding different side effects associated with treatment with benzodiazepines – effects on cognition, treatment with benzodiazepines during pregnancy, dependence on benzodiazepines and risk of falling.

Content analysis of literature: Literature research included structured searches of Medline and other publications on the subject of treatment with benzodiazepines, particularly effects on cognition, risk of falls, benzodiazepine dependence and treatment with benzodiazepines during pregnancy.

Conclusion: Results of investigations have revealed different side effects associated with treatment with benzodiazepines. Previous investigations showed that treatment with benzodiazepines may induce anterograde amnesia. Also, previous studies confirmed occurrence of physical dependence in high percentage of patients in long term treatment with benzodiazepines at therapeutic dosages. Some investigation suggested higher risk of oral cleft, the floppy infant syndrome, or marked neonatal withdrawal symptoms when using benzodiazepines during pregnancy. Investigations have shown increased risk of falling in elderly persons taking benzodiazepines.

Key words: benzodiazepines – treatment – cognitive decline - dependence

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INTRODUCTION

The use of benzodiazepine anxiolytics and hypnotics continues to excite controversy. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term benzodiazepine use actually constitutes a problem (Lader et al. 2009).

Benzodiazepines are frequently prescribed to patients with different psychiatric disorders, in part of these patients for longer periods of time, which makes even more important for the psychiatrist, general practitioners and other specialists to be aware of the long-term effects of benzodiazepines, and to discuss such issues with their patients. Although as a class benzodiazepines act rapidly and are well tolerated, their use presents clinical issues such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome (Chouinard 2004). The aim of this article is to review literature regarding different side effects associated with treatment with benzodiazepine – effects on cognition, treatment with benzodiazepines during pregnancy, dependence on benzodiazepines and risk of falling.

CONTENT ANALYSIS OF LITERATURE

Literature research included structured searches of Medline and other publications on the subject of treatment with benzodiazepines, particularly effects on cognition, dependence and abuse, treatment with benzodiazepines during pregnancy and risk of falling.

Cognitive decline

Benzodiazepines are known as "acquisition-impairing" molecules, and their effects on anterograde memory processes are well described (Beracochea 2006). The short-term use of benzodiazepines adversely affects multiple areas of cognition; most notably, it interferes with the formation and consolidation of memories of new material and may induce complete anterograde amnesia (Ballenger 2000). Following the ingestion of a benzodiazepine, short-term memory is not affected, but long-term memory is impaired. The memory loss may occur because events are not transferred from short-term memory to long-term memory and thus not consolidated into memory storage. Information stored prior to the ingestion of

a benzodiazepine is not affected (Mejo 1992). A major public health issue is to determine whether long-term benzodiazepine use may induce cognitive deficits persisting after withdrawal. As a large proportion of subjects are exposed to benzodiazepines, a small increase in the risk of cognitive decline may have marked deleterious consequences for the health of the general population (Verdoux et al. 2005). The results from a follow-up study of 1,389 people aged 60 to 70 years suggest that long-term use of benzodiazepines is risk factor of increased cognitive decline in the elderly (Paterniti et al. 2002). The association of exposure to benzodiazepines with an increased risk of incident cognitive decline has been examined in different prospective studies carried out in general population samples, with the discrepant findings obtained by studies (Verdoux et al. 2005). The question of differences between benzodiazepines in terms of their effects on cognition is a subject of investigations. A recent investigation reviewed evidence suggesting that certain benzodiazepines, especially lorazepam, differ in a number of respects, in particular with respect to their effects on cognition (Giersch et al. 2010).

Dependence and abuse

The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Although benzodiazepines are highly effective for some disorders, they are potentially addictive drugs (Denis et al. 2006).

Pharmacologic dependence, a predictable and natural adaptation of a body system long accustomed to the presence of a drug, may occur in patients taking therapeutic doses of benzodiazepines. However, this dependence, which generally manifests itself in withdrawal symptoms upon the abrupt discontinuation of the medication, may be controlled and ended through dose tapering, medication switching, and/or medication augmentation (O'Brien 2005).

In case benzodiazepines are applied during short period of time (1-2 weeks) in moderate dosage, such treatment usually doesn't induce tolerance, dependence or withdrawal symptoms (Uzun et al. 2005). Various studies have shown between 20–100% of patients prescribed benzodiazepines at therapeutic dosages long term are physically dependent and will experience withdrawal symptoms (Ashton 1997). Benzodiazepines differ in their dependence potential (Higgitt et al. 1988). Also, patients taking daily

benzodiazepine drugs have a reduced sensitivity to further additional doses of benzodiazepines (Potokar et al. 1999). According to results of previous research withdrawing elderly people from benzodiazepines leads to a significant reduction in doctor visits per year, presumably due to an elimination of drug side effects and withdrawal effects (Longo & Johnson 2000). Benzodiazepines have many benefits for persons with severe mental disorders, but they may also lead to or exacerbate substance abuse (Clark et al. 2004). Because use of benzodiazepines may exacerbate existing substance use disorders or become abused substances, prescription of benzodiazepines for patients with severe mental illness (schizophrenia or bipolar disorder) and co-occurring substance use disorders (abuse or dependence) is controversial (Brunette et al. 2003). Furthermore, it is important to keep in mind the risk for non-medical use of benzodiazepines in persons with illicit drug use (Verbanck 2009). In the study that aimed to examine benzodiazepine use and associated psychiatric, substance abuse, and institutional outcomes in a six-year longitudinal study of patients with co-occurring disorders, almost one-half of the patients reported taking prescribed benzodiazepines at the time of at least one assessment. Patients taking prescribed benzodiazepines were more likely to have high scores on measures of overall symptoms and affective symptoms (anxiety and depression) and low ratings for general quality of life throughout the study. Benzodiazepine use was unrelated to remission of substance use disorder or hospitalization, but a greater proportion of patients who were prescribed benzodiazepines developed benzodiazepine abuse, compared with those who were not prescribed benzodiazepines (Brunette et al. 2003).

Treatment with benzodiazepines during pregnancy

Exposure to Benzodiazepines (BZD) during foetal life has been suggested to contribute to neonatal morbidity and some congenital malformations, for example, orofacial clefts (Wikner et al. 2007). An earlier meta-analysis that aimed to determine if exposure to benzodiazepines during the first trimester of pregnancy increases risk of major malformations or cleft lip or palate it was concluded that pooled data from cohort studies showed no association between fetal exposure to benzodiazepines and the risk of major malformations or oral cleft. On the basis of pooled data from case-control studies, however, there was a

significant increased risk for major malformations or oral cleft alone (Dolovich et al 1998). In the investigation that aimed to study the neonatal outcome and congenital malformations in neonates whose mothers reported use of benzodiazepines and/or hypnotic benzodiazepine receptor agonists during pregnancy, an increased risk for preterm birth and low birth weight was detected in the exposed population. The rate of relatively major congenital malformations was moderately increased among infants exposed in early pregnancy, not explained by known teratogenic maternal co-medication. A higher than expected number of infants with pylorostenosis or alimentary tract atresia (especially small gut) was found. This was, however, based on only seven infants for each group of malformation without association to any specific benzodiazepine or hypnotic benzodiazepine receptor agonist. The earlier proposed increased risk for orofacial clefts was not confirmed (Wikner et al. 2007). Late third trimester use and exposure during labour seems to be associated with much greater risks to the fetus/neonate. Some, but by no means all infants exposed at this time, exhibit either the floppy infant syndrome, or marked neonatal withdrawal symptoms. Symptoms vary from mild sedation, hypotonia, and reluctance to suck, to apnoeic spells, cyanosis, and impaired metabolic responses to cold stress. These symptoms have been reported to persist for periods from hours to months after birth. This correlates well with the pharmacokinetic and placental transfer of the benzodiazepines and their disposition in the neonate (McElhatton 1994). An earlier search of the literature with aim to review data about the effects of benzodiazepine therapy on the fetus and on nursing infants led to conclusion that minimizing the risks of benzodiazepine therapy among pregnant or lactating women involves using drugs that have established safety records at the lowest dosage for the shortest possible duration, avoiding use during the first trimester, and avoiding multidrug regimens (Iqbal et al. 2002).

Risk of falling

Benzodiazepines are frequently used medications in the elderly, in whom they are associated with an increased risk of falling, with sometimes dire consequences (Pariante et al. 2008).

The sedation due to BZD use is a main risk factor for falls and other accidents (Petrovic et al. 2003). In the investigation that aimed to estimate

the impact of benzodiazepine-associated injurious falls in a population of elderly persons, the results showed that benzodiazepine use was significantly associated with the occurrence of injurious falls, with a significant interaction with age. (Pariante et al. 2008). In the investigation that aimed to assess if some of the risk factors for falls are associated with new benzodiazepine prescriptions in elderly persons, the results showed that several risk factors for falls were associated with statistically significant increases in the risk of receiving a new benzodiazepine prescription including the number of prescribing physicians seen at baseline, being female or a diagnosis of arthritis, depression or alcohol abuse. The strongest predictor for starting a benzodiazepine was the use of other medications, particularly anti-depressants. It was concluded that patients with pre-existing conditions that increase the risk of injurious falls were significantly more likely to receive a new prescription for a benzodiazepine (Bartlett et al. 2009). To evaluate the role of different types of benzodiazepines in determining falls in a hospitalized geriatric population, a prospective study was conducted among 7908 patients. It was concluded that the findings suggest that benzodiazepines with short and very short half-life are an important and independent risk factor for falls and their prescription to elderly hospitalized patients should be carefully evaluated (Passaro et al. 2000).

CONCLUSION

Results of investigations have revealed different side effects associated with treatment with benzodiazepines. Previous investigations showed that treatment with benzodiazepines may induce anterograde amnesia. Also, previous studies confirmed occurrence of physical dependence in high percentage of patients in long term treatment with benzodiazepines at therapeutic dosages. Some investigation suggested higher risk of oral cleft, the floppy infant syndrome, or marked neonatal withdrawal symptoms when using benzodiazepines during pregnancy. Investigations showed increased risk of falling in elderly persons taking benzodiazepines.

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Correspondence:

Suzana Uzun, PhD, MD
Vrapce Psychiatric Hospital
Bolnička cesta 32, 10090 Zagreb, Croatia
E-mail: suzana.uzun@bolnica-vrapce.hr