SIDE EFFECTS OF TREATMENT WITH BENZODIAZEPINES

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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, treatment with benzodiazepines during pregnancy, dependence on benzodiazepines and risk of falling.

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

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 accusto-
med to the presence of a drug, may occur in patients taking therapeutic doses of benzo-
diazepines. 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). Benzo-
diazepines 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 sub-
stance 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 benzo-
diazepines 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
doctrine life has been suggested to contribute to
neonatal morbidity and some congenital malfor-
mations, 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 malfor-
mations 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 (Pariente 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. (Pariente 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.

**REFERENCES**