# THE USE OF BENZODIAZEPINES IN THE AGED PATIENT: CLINICAL AND PHARMACOLOGICAL CONSIDERATIONS

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**ABSTRACT**
Benzodiazepines are widely used to treat anxiety and insomnia in elderly patients. The interest of this prescription is discussed in this article. The discussion is based on the pharmacological properties and adverse effects of benzodiazepines in the elderly subjects. The conclusions are that benzodiazepines should be rarely prescribed in elderly people; many patients treated by benzodiazepines should be withdrawn and other therapeutic strategies than benzodiazepines should be considered to treat anxiety and insomnia in the elderly patients.

**Keywords**: benzodiazepines, elderly patients, insomnia, anxiety disorders.

## INTRODUCTION

Since the introduction of chlordiazepoxide in 1961, benzodiazepines (BZDs) are the most commonly prescribed medications in anxiety and insomnia (as well as their use in a wide variety of other pathologies), in spite of a limited number of studies showing their efficiency for these two indications. It has been shown that the utilisation of these medications in aged patients represents 27% of the whole prescription treatment whereas the aged patients represent only 14% of the population. Otherwise, BZDs represent 38% of hypnotic prescriptions in the United States (Griffiths and Weerts, 1997; Katz and Winger, 1992). The follow-up examination of the EVA (Epidemiology of Vascular Aging) study in a sample of 1265 elderly subjects (aged 60 to 70 years) showed that the use of BZDs was reported by 23% of the participants (Lechevallier *et al*., 2003).

Despite the very large utilisation of BZDs, there is evidence to suggest that anxious disorders and insomnia are at times under-diagnosed and under-treated in aged patients [Sheikh 1996]. This poses the problem of their vast and very weak specificity of utilisation, which proves that these medications are relatively misused. Epidemiological studies show that among 25% of over 65 years old patients are in old folks residences and are often treated with BZDs. The anxious disorders are typically chronic disorders with remission periods and may be exacerbated stressful events. Few quality of life studies concerning aged people have been performed, although anxious symptoms have been associated with a mortality increase, all causes disconcerted and notably sudden cardiac deaths. It is also known that anxious people use the medical services more that others (Lindesay 1991). BZDs treatment efficiency and its impact on longevity, quality of life and utilisation of services in aged patients suffering with anxious disorders are not well known.

Moreover, BZDs have been prescribed to treat behavioural disorders associated with dementia (Bourin and Vercelletto 1999). These behavioural disorders can appear in more than 75% of patients suffering with dementia living in retirement homes and more than half of them show two, or more, problematic behaviours. Few short or long-term BZDs efficiency studies concerning sleeping problems and/or behavioural associated dementia symptoms in aged patients exist. Most of the studies included non-benzodiazepine molecules like meprobamate, barbiturates and antihistaminergics. Over-consummation and dependence definitions varied and studies that included aged patients have been associated with younger populations.

BZDs are widely used by elderly subject; this BZDs prescription is associated frequently with adverse effects and is inappropriate in many patients. The aim of this article is to propose a better utilisation of the BZDs in the geriatric population.

### *Benzodiazepine pharmacology in the aged patients*

Utilisation of BZDs poses a problem with aged patients due to their weak therapeutic index when considering the weak interval of doses between their sedative and anxiolytic properties, showing decreased interval in the aged patient (Greenblatt *et al*., 1991). Ever more so in the young patient, it is necessary to avoid the "sedation trap", i.e., over dosage that renders aged subjects more susceptible to tiredness, prevents them from being active and so decreases their socialisation faculties. Essentially the pharmacokinetics is modified at the time of the administration of medicines to aged patients. One essentially notes:

- a slowing of the speed of the digestive absorption
- a reduction of the fraction bound to plasma proteins
- a modification volume of distribution of the medication

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- a reduction of metabolism
- a reduction of the renal elimination.

Slowing of the gastro-intestinal absorption of BZDs is only slightly modified in the aged and is not, in any case troublesome in the utilisation of these medicines as anxiolytics. It avoids the apparition of a peak plasma concentration, which may as a consequence result in sedation. The reduction of plasma protein binding, which increases the liberated fraction and therefore pharmacologically active, does not have, in the precise case of BZDs, a therapeutic consequence. Indeed, the increased liberated BZD fraction of little importance when considering the relationship between bound and liberated fraction. For BZD employed as anxiolytics where the percentage binding is 80 to 90%, an increase of activity of some percentage of the liberated fraction implies an increase of activity, a part from the balance of equilibrium phenomenon is attenuated, with correct renal functioning. However, the BZD half-life is usually lengthened in aged patients, for two essential reasons:

- because the volume of distribution is increased
- because the clearance rate is decreased.

In fact, the half-life is the relationship between the volume of distribution and the clearance rate: $t\ 1/2 = 0,7 \times Vd/Cls$

Some recent studies show that BZDs metabolised by hepatic oxidation and/or conjugation had a reduced clearance rate in the aged subject, this phenomenon seemingly more notable in men than women.

The delay in the plasma elimination of a benzodiazepine is estimated as 5-6 folds the elimination half-life.

The list of BZDs metabolised by oxidation is indicated in the table. BZDs that are transformed into desmethyl derivatives correspond to this profile (diazepam, clorazepate, prazepam, clobazam, etc.) whereas lorazepam and oxazepam are not oxidised but conjugated before being eliminated. This oxidation capacity can be shown by a test with antipyrine, but it is of course simpler to decrease dosage in a preventive manner. In fact, renal clearance is of equal importance to hepatic clearance. Creatinine which reflects renal function provided that muscular lyses are not too important has to be also considered. An idea of the creatinine clearance would be ideal, however this is a parameter not easily obtained in ambulatory medicine. Otherwise, the volume of distribution (Vd) is increased in aged patients, more so in men than in women. This may explain the sedation decrease associated with a relative increase of fat in contrast to muscular mass that represents aqueous volume, in some patients.

Volume of distribution increase and total clearance (Clt = Cl hepatic + Cl renal) decrease results in a half-life increase. Theoretically, half-life increase is corrected by:

- decrease dosage,
- reduce frequency of dosing

In the case of BZDs with a long half- life, it may be wise to decrease the dosage, taking of medication every 2 or 3 days would be badly discerned by the patient and risk in resulting in inefficient concentrations. The search of the lowest effective dose lacking sedative effect is achieved initially by dividing the dose administrated to a young adult, while remembering that desmethyldiazepam or desmethylclobazam half-life increases by an hour per year.

The aged patient is often polymedicate, but medicinal interactions are rare with BZDs with the exception of the association of two BZDs which compete with each other to bind cerebral sites. BZDs metabolised by oxidation are suggested to effect medicines managed in a concomitant manner at the level of the cytochrome P 450 (CYP) hepatic system, particularly isoenzymes CYP 3A and CYP 2C19. Medicines inhibiting actions of metabolites of these isoenzymes can decrease the rate of clearance of these BZDs and so increase their half-life and therefore their plasma concentration and can in fact increase their clinical effects in the aged patient. The powerful inhibitors of the CYP 3A are essentially inhibitors of serotonin reuptake, anti-fungal such as the ketoconazole and itraconazole as well as antibiotics of the macrolides group such as azithromycin, erythromycin and clarithromycin. All BZDs are not affected in the same way by serotonin reuptake inhibitors. Indeed, a survey in healthy volunteers receiving alprazolam or clonazepam with a co-administration of fluoxetine or placebo, it was shown that fluoxetine prolonged the half-life of alprazolam and reduced its clearance rate but did not have an effect the half-life of clonazepam or its clearance. In a similar manner cimetidine inhibits the clearance of BZDs metabolised such as diazepam, chlordiazepoxide or clorazepate but not conjugated derivatives such as lorazepam and oxazepam. The most important interaction to consider in the aged patient is the interaction between the BZDs and alcohol, which has been mentioned previously. No problem of association in the aged patient receiving BZDs and neuroleptics exists (Bourin, 1989).

Another consequence of ageing, besides pharmacokinetic problems, is an increase sensitivity of the receptor to BZDs. Thus, it was showed that pharmacokinetics parameters of midazolam were similar in younger and elderly although a large decrease in half maximum concentration to reach sedation was observed in the elderly patients (Albrecht *et al*., 1999).

**Table**: Metabolic ways of benzodiazepines (Bourin 1989)

| Initial medication | Metabolic pathway | Active substances in blood | Elimination half life (hours)[Schulz, 2003] |
|---|---|---|---|
| Chlordiazepoxide | oxidation (DM) | Chlordiazepoxide<br>Desmethyldiazepam<br>Oxazepam | 6-24<br>40-80<br>6-20 |
| Clobazam | oxidation (DM) | Clobazam<br>Desmethylclobazam | 10-32 |
| Clorazepate | oxidation (DM) | Desmethyldiazepam<br>Oxazepam | 40-80<br>6-20 |
| Diazepam | oxidation (DM) | Diazepam<br>Desmethyldiazepam<br>Oxazepam | 24-48<br>40-80<br>6-20 |
| Flunitrazepam | conjugation | Flunitrazepam | 10-20 |
| Lorazepam | conjugation | Lorazepam | 10-40 |
| Medazepam | oxidation | Medazepam<br>Diazepam<br>Desmethyldiazepam<br>Oxazepam | 2-5<br>24-48<br>40-80<br>6-20 |
| Nitrazepam | oxidation | Nitrazepam | 20-30 |
| Oxazepam | conjugation | Oxazepam | 6-20 |
| Prazepam | oxidation | Desmethyldiazepam<br>Oxazepam | 40-80<br>6-20 |
| Halazepam | oxidation (DA) | Halazepam<br>Desmethyldiazepam | 30-40<br>40-80 |
| Ketazolam | oxidation (OH) | Desmethyldiazepam | 40-80 |
| Alprazolam | oxidation (OH) | Alprazolam | 6-20 |
| Temazepam | Conjugation | Temazepam | 6-25 |
| Lormetazepam | Conjugation | Lormetazepam | 10-15 |
| Clotiazepam | Oxidation (OH, DM) | Clotiazepam<br>Hydroxyclotiazepam<br>Desmethylclotiazepam | 3-15 |
| Midazolam | Oxidation (OH) | Midazolam | 1.5-3 |
| Triazolam | Oxidation (OH) | Triazolam | 2-5 |
| Brotizolam | Oxidation | Brotizolam | 4-10 |

DM = desmethylation DA = dealkylation OH = hydroxylation

All these data contribute to decrease BZDs dosage in aged patients. Prudence is necessary for the association of benzodiazepine and alcohol, the latter considerably potentialises the effects of this medicinal class. Caution is also advised when considering the reputation of good tolerance of BZDs, which may be decreased in the elderly due to the risk of accumulation.

***Prevalence and use of BZDs***

Rates of prevalence and utilisation of BZDs differ extensively according to the studied populations and according to definitions and usual utilisation in precise indications. In a cohort of 2792 community-dwelling subjects 65 years of age or more living south western part of France prevalence rate of BZDs use was 31.9% at baseline (Fourrier *et al.,* 2001). The annual prevalence of BZDs prescription dispensed in Ontario for older people decreased slightly between 1993 and 1998 (25.1% versus 22.5%). In this population, BZDs dispensing prevalence increased with increasing age (approximately 20% to those age 65 to 69 to approximately 30% to those age superior or equal to 85). There is also a trend of dispensing relatively more short-acting than long-acting BZDs (Tu *et al.,* 2001). However, long-acting BZDS are still used although long half-life BZDs are not generally recommended in the aged patient as an increase of side effects as a result of the accumulation of these medicines may occur. Thus, in the cohort of the EVA study 48 % of the BZDs used were long acting compounds (Lechevallier *et al.,* 2003).

Because of the heterogeneity of the normal utilisation and abuse definition, there are problems in the interpretation of the long-term risks and advantages of BZDs utilisation

in aged patients. The categorisation of the utilisation of BZDs has been proposed as acute, intermittent, as well to short, long-term and continuous in an attempt to standardise definitions of utilisation (Llorente *et al.*, 2000).

*Acute utilisation* usually of about 7 days or less duration and consist generally of only one dose. Examples include acute treatments in emergency services for a psychotic agitation, pre-operative utilisation or if amnesia is wished, the treatment of the insomniac in the hospital and the treatment of alcoholic withdrawal.

*Intermittent utilisation* is when the BZDs is taken sporadically, generally two or three times per week and for periods not exceeding 60 to 90 days. One can also speak of long term with intermittent utilisation in the measure where the treatment lasts 4 months and more. The treatment of insomnia and anxious disorders with BZDs is very frequent in the aged subject with an intermittent utilisation of these products. When one finely analyses the utilisation in this type of category one perceives that the aged subject is going to use some relatively weak doses and discovers a beneficial effect on morning activity. This is why subjects take doses of 0,5 to 1 mg of lorazepam to facilitate falling to sleep or to decrease their anxiety and are going to indicate to the medicated physician that in fact it permits them to have a better morning. Studies achieved with healthy volunteers demonstrate that small doses of BZDs improved young adult psychometric performance (Bourin *et al*., 1995; Bourin *et al*., 1998). A Swedish survey showed that BZDs can have a protective effect against Alzheimer's illness (Fastborn, 1998). Authors compared chronic BZDs users versus non-users after a period of 3 years. They showed that there was a weaker impact of Alzheimer's illness in the BZDs group than in the non-consumers. This negative correlation persists when age, sex, instruction level, utilisation of the anti-inflammatory non- steroids and estrogens are controlled.

Studies in the United States are in progress in the aged subject in the same state of mind to try to understand what underlines the intermittent use of BZDs.

*Continuous utilisation* is defined by the fact that the subject is going to use the medicine every day, these patients are going to take anxiolytics in a chronic manner and it is especially for anxious disorders, often generalised anxiety and insomnia. The aged subjects and prescribers continue to take these products in a chronic manner in spite of recommendations of a short-term utilisation. Among usual users of BZDs, one finds 21% of users in an action anxiolytic capacity, but 17% in the capacity of a hypnotic action. It corresponds to a rate of prevalence of 3% of continuous utilisation in the general population between 18 and 80 years.

Compared to subjects not using BZDs, continuous users are most often older and most often women, who often take this type of medicine after suffering a bereavement. Indications are often as a result of such a prescription, in fact this prescription causes indirect cardiovascular disorders or rheumatologic disorders whatever the nature of these chronic illnesses their treatment is accompanied with a prescription of BZDs.

85% of continuous users do not have any support or professional mental health help i.e. these medicines are considered as being in themselves support for the aged patient. Even though no long term efficiency survey of BZDs has been conducted in the aged patient, tolerance to diazepam or other BZDs doesn't develop itself until after 22 weeks of treatment, which is relatively reassuring, i.e., after practically six months most patients have a continuous treatment at a steady dosage that can last effectively for months and years.

Only one survey of efficiency has been conducted in the aged patient to evaluate the continuous utilisation of BZDs in the treatment of chronic insomnia (Morin *et al*., 1999). This survey shows that BZDs and behavioural treatments are quite interesting for the treatment of insomnia in the last weeks of life. After 24 months, benefits obtained by the group that did not take the medicine and that therefore had not undertaken behavioural therapy was totally lost, i.e. the basal level was reached. The long-term negative effects of continuous utilisation of these medicines remain unknown other than that of physical dependence. There are some studies that have been carried out concerning the secondary risks such as falls and fractures, cognitive performance reduction which are presented in the next paragraph.

***Adverse effects of BZDs in the elderly population***

Elderly patients are more likely to experience adverse effects from BZDs than their younger patients due to age-related changes in pharmacodynamic and pharma-cokinetic parameters. Impaired cognitive function appears to be major side effects of BZDs (Pomara *et al*., 1998). A follow-up study of 1389 people aged 60 to 70 years showed that long-term use of BZD was a risk factor of increased cognitive decline in the elderly (Paterniti *et al*., 2002). Gray *et al*. (2003) showed also that older women who used BZDs were at risk for decline in physical performance. Subgroup analyses indicated that risk was greater with use of higher than recommended doses for long duration. These results are confirmed by the results from the Canadian Study of Health and Aging. In this work, BZDs appear to be associated with a number of adverse outcomes including impaired cognitive function (Hogan *et al*., 2003).

This cognitive and physical decline suggest a potential relationship between the risk of fall and the use of BZDs. Wang *et al* (2001) showed that the risk of hip fracture was increased in elderly patients treated with BZDs. Patients appear to be particularly vulnerable immediately after initiating therapy and after more than 1 month of continuous use. BZDs with shorter half-lives appear to be no safer than longer half-life agents. This result is partly consistent with results of Pierfitte *et al* (2001). They showed that the presence of BZDs in plasma was not associated with an increased risk of hip fracture except for lorazepam. In a recent review of this relationship between BZDs use and risk of hip fracture in older people, the authors explained this inconsistency by the difference in the design of these studies (Cumming and Le Couteur, 2003). The studies that did not show an association were nearly all hospital-based case-control studies, a type of study that often lacks validity because of the difficulty of finding an appropriate control group. However, Cumming *et al* concluded that the epidemiological evidence strongly suggests that the use of BZDs by older people increases their risk of hip fractures by at least 50%.

Moreover, the role of BZDs in elderly suicides suggests that BZDs should be prescribed with caution for these patients. Carlsten *et al* in Sweden observed that BZDs, especially the hypnotic's flunitrazepam and nitrazepam are common in drug poisoning suicides in the elderly during the period 1992-1996 (Carlsten *et al.,* 2003). Similarly, BZDs appear to be among the drugs most commonly used in overdose in England and Wales during the period 1993-1999 (Shah *et al.,* 2002).

Another difficulty in the use of BZDs is the risk of dependence. When BZDs are stopped abruptly, a withdrawal syndrome can appear. The prevalence of these withdrawal syndromes has been estimated between 0 and 100% according to studies depending of the time course of the prescription; it is interesting to note that roughly 40% of patients treated for at least 6 months with a BZD can present with some withdrawal syndromes after abrupt cessation. Withdrawal symptoms are essentially tremors, confusion, anxiety and insomnia. Severe symptoms such as convulsions and psychotic reactions can occur as well as an appreciable increase of arterial pressure and a myocardial ischemia, which can occur at the time of abrupt cessation. Few withdrawal studies in the aged have been carried out, the aged patients when compared with young adults present less severe withdrawal symptoms, however it was observed that post withdrawal psychotic reactions seem more notable in the aged than the young patient. It is suggested that withdrawal is linked to a hyperactivity of the noradrenergic, serotonergic and cholinergic systems that have been inhibited by the chronic administration of BZDs. The fact that BZDs plasma concentrations decrease more slowly can perhaps explain the fact that symptoms of withdrawal in the aged patient seem less severe. It seems that risks of withdrawal are increased particularly with the abrupt cessation of BZDs having a short half-life and presenting a rapid reduction of plasma concentrations, as well as elevated doses, elevated daily dosage and the long-term utilisation. BZDs having a short or intermediate half-life, at the time of their cessation, can generate symptoms of withdrawal that appear between 24 and 36 hrs after the cessation, whereas BZDs with a long half-life can induce withdrawal symptoms after practically one week and in this case BZDs cessation is not always incriminated. It seems that other factors can contribute to the severity of the withdrawal syndrome, such as a premorbid personality, and notably passive-dependent personalities. Obviously important physiological differences exist, but the previous consumption of alcohol and a low level of education can facilitate a notable withdrawal syndrome.

All these results indicate that the benefits of BZDs for older people are unclear. Given the high morbidity/ mortality associated with BZDs use in this population Cumming *et al* concluded that older people should be rarely prescribed BZDs and that many older people already taking these drugs should have them withdrawn under appropriate supervision mainly at the hospital (Cumming and Le Couteur, 2003). Different studies tried to define designs to withdraw BZDs in elderly subjects. Baillargeon *et al* presented a method based on a combination of cognitive-behavioural therapy and BZDs tapering (Baillargeon *et al* 2003). They concluded that this combination was superior to gradual tapering alone in the management of patients with insomnia and chronic BZDs use. Petrovic *et al* proposed an initial replacement therapy with low-dose BZDs (lormetazepam 1 mg) [Petrovic *et al* 2002]. This therapy is preferred over placebo since the latter alternative is associated with worse sleep quality and a lower success rate.

## CONCLUSION

Problems posed by BZDs in the aged patient are both of a pharmacodynamic and pharmacokinetic order. In comparison to young adult users, BZDs users in the aged are essentially women; the latter take these medicines during important periods in their lives and often have a strong comorbidity, such as cardiovascular or rheumatologic problems or even psychiatric problems such as depression or panic disorders.

Aged patients who take BZDs at high doses can also consume other drugs such as alcohol and have often a psychiatric history. Some important secondary effects are associated with the utilisation of BZDs; essentially concerning falls and it has been noticed for some years that problems posed by aged car drivers can be effectively raised by BZDs. It is difficult to know if continual users of BZDs really have an advantage to other users.

However, instruments like an indicator in the form of an algorithm were developed to identify the appropriateness of prescribing of BZDs in elderly patients [Batty *et al* 2000]. It is certain that it is necessary in every possible measure to have a recourse strategy for cessation, to use as much as possible BZDs with a short half-life that are not oxidised, i.e. essentially BZDs that are not metabolised in the strictest sense of the term such as lorazepam or temazepam. Daily doses must be extremely limited and duration of use does not have to surpass 2 or 3 months in young patients. Other types of anxiolytics are advised for prescription to the aged patient and a good experience with anti-depressants such as clomipramine, which does not have the licence in France for this indication, but can sometimes be very useful for the aged patient. A new medicine, venlafaxine can be prescribed at doses that induce too many secondary effects.

Recent data showing an increase in studies and cardiovascular events in BPSD in Alzheimer's dementia patients with antipsychotics and the warnings that they should be used cautiously, it perhaps a new opportunity to use BZDs in such patients.

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