WITHDRAWAL OF BENZODIAZEPINES IN THE ELDERLY INPATIENTS: HOW TO DO IT?

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ABSTRACT

Benzodiazepines (BZDs) constitute the most widely used symptomatic treatment of insomnia and anxiety. Many of these drugs are associated with adverse effects, such as daytime sedation and dependence with continued use. There is a concern about the rationale for and extent of benzodiazepine (BZD) use in the elderly. The sedation due to BZD use is a main risk factor for falls and other accidents. Impaired cognitive function with continuous use appears to be a major side effect. There is a general awareness that BZD use is inappropriate in many patients, and therefore discontinuation should be recommended whenever possible. Moreover, long-term use of these drugs should be actively discouraged. Although no unanimous recommendations concerning the optimal duration of the withdrawal process exist, BZDs may easily be withdrawn during a short period in most patients who are habituated to a low dose, if an initial phase with dose reduction and psychological support are provided.

INTRODUCTION

For almost six decades, benzodiazepines have been used in clinical practice. Following their introduction into pharmacotherapy these drugs were welcomed because they were a valuable substitute for bromides and barbiturates. Due to their clinical efficacy benzodiazepines became by far the most frequently prescribed psychotropic drugs in the world[1].

Often, benzodiazepines are prescribed on a long-term basis. Frequently, inappropriately large doses of benzodiazepines are prescribed with minimal physician follow-up, especially among elderly patients.

The problems that arise with the use of benzodiazepines in the elderly may be subtle. Thus, clinicians, patients, and family members may have difficulty recognizing them or may assume that they are psychopathologic changes rather than drug induced effects.

The acute administration of benzodiazepines is associated with impairments in cognition, memory, coordination and balance. The long-term use, even at therapeutic dosages, has been associated with tolerance, dependence and in some patients withdrawal effects[2].

Knowledge of the adverse effects of benzodiazepine treatment of insomnia and anxiety in the elderly can be important for several reasons. First, the elderly have a much higher use of hypnotic medications than young individuals with insomnia and anxiety. Second, the elderly are at increased risk for toxicity and adverse effects from medication of all sorts. Third, the elderly have a greater potential for drug interactions because of concurrent treatment for other health problems[3].

Since the beginning of the eighties more attention has been paid to the problems arising from the widespread use of benzodiazepines. Apart from the risk of abuse and primary dependency, there is also the risk of "low-dose dependency", which is of special importance because of the high rate of long-term benzodiazepine treatment[2].

Treatment with benzodiazepines typically is initiated during periods of acute stress, medical illness, or hospitalisation, or simply when an old person can no longer cope with the daytime sequelae of chronic sleep disturbance. Despite the initial intent to limit their use to a short period, some people continue using hypnotics for prolonged periods of time. The onset of this pattern of prolonged usage is often insidious, with both psychological and physiological factors contributing to its maintenance. Some individuals continue using medications because of chronic insomnia or anxiety, but other may do so even after their sleep or mood disturbance have subsided. Sometimes, prescriptions of hypnotic drugs are renewed without adequate evaluations of continued need or sustained efficacy of the medication[4].

CLINICAL EFFECTS OF BENZODIAZEPINES

All BZDs are characterized by, in slightly varying degrees, 5 major effects: hypnosedative, anxiolytic, anticonvulsant, muscular relaxant and amnesic. In the short term, BZDs may be used safely in certain clinical conditions. With long-term use, tolerance, dependence and withdrawal effects may prove to be major drawbacks[5, 6].

Hypnotic effects. BZDs accelerate sleep onset, decrease nocturnal arousals, and increase total sleep time. Nevertheless, they change the normal sleep pattern: light sleep is prolonged, while the duration of slow wave sleep and rapid eye movement sleep is reduced. The onset of the

first rapid eye movement sleep episode may be delayed[7]. The aberrant sleep profile possibly results from unselective depression of both arousal and sleep mechanisms in the brainstem[8, 9].

Anxiolytic effects are present in doses that cause minimal sedation, although the hypnotic, muscular relaxant and amnesic actions may all provide relief of associated tension and insomnia[10]. The effect on anxiety is probably related to suppressive activity in limbic and other brain areas involved in anxiogenesis. The main clinical attribute of BZDs prescribed for anxiety is the rapid onset of action, usually visible after a single dose. BZDs provide only symptomatic treatment for anxiety. Nevertheless they may be indicated in the initial management of distressing anxiety, while awaiting enduring clinical effects from more specific non-drug measures.

Anticonvulsant effects. BZDs are effective in the treatment of status epilepticus and convulsions due to drug poisoning. These drugs can only be used in emergency situations and are not appropriate for the extended treatment of epi-lepsy, because of the development of tolerance in the majority of patients[11, 12].

Muscular relaxant effects of BZDs can sometimes be used in a variety of motor disorders (i.e. dystonias and involuntary movements, myoclonus, restless limbs syndrome) and muscle spasm associated with pain[13].

Amnesic effects. BZDs also cause dose related anterograde amnesia. These amnesic properties may be clinically significant, particularly in the elderly and in those with coexisting medical problems[14].

SIDE EFFECTS OF BENZODIAZEPINES

Although BZDs initially induce and prolong sleep, tolerance develops quickly. Sleep latency and duration regress to pre-treatment levels after a few weeks of continued treatment. Sleep quality, however, does not improve, since deep NREM sleep and REM sleep stages are partially replaced by stage 2 light NREM sleep[15]. Tolerance to the anxiolytic properties of BZDs develops more gradually than to the hypnotic effects. Nevertheless, the extended use over years helps little to control and may even worsen anxiety. Therefore, BZD use in most anxiety states should be restricted to short term (not more than 4 weeks) or intermittent courses[16, 17].

Rebound insomnia refers to an increase in the original symptom beyond the baseline level after withdrawal from BZDs. There have been inconsistent reports of rebound insomnia with short-acting BZDs. Population surveys and results from large treatment effectiveness studies

show rebound insomnia in 14-20% of patients treated with BZDs, a rate indistinguishable from that seen with over-the-counter drugs or placebo[18, 19].

BZDs frequently give rise to subjective hangover. Even those BZDs that are quickly eliminated may cause the impairment of psychomotor performance and memory the next day. The effects depend on type of BZD, dosage and duration of use[20, 21].

Residual effects occur mostly with slowly eliminated BZDs, particularly if used in the long term and when administered to the elderly[36]. Increased volume of distribution due to a gain in body fat, in combination with reduced clearance leads to accumulation of BZDs in the elderly and a marked prolongation of $t_{1/2}$[22].

Dependence on BZDs is a psychological or physical need to continue taking these drugs. It may be psychological, physical or both. Psychological dependence, also referred to as habituation, is characterized by an intermittent or continuous craving for BZDs[23, 24]. Physical dependence on BZDs is characterized by a need to take these drugs to prevent the occurrence of a withdrawal or abstinence syndrome. The need to continue taking a drug, as reported by the patient, is therefore not synonymous with pharmacological dependence. It is part of a complex clinical situation, composed by the patient's perception, negative conditioning, the personality structure, past and current psycho-pathology and also the pattern of chronic BZD use[25]. However, if the continuation of a drug is required because it prevents discomfort, this can be a sign of psychological dependence on a pharmacological basis[26]. Sporadically, the BZDs may provoke paradoxical stimulation, including excitement, irritability and even furious reactions[27].

SUSCEPTIBILITY OF THE ELDERLY TO BENZODIAZEPINES

In elderly, BZDs may induce a variety of CNS effects like sedation, lethargy, memory problems and deficient coordination, as well as impaired learning and impaired psychomotor performance. Utilization of BZDs in hospitalised elderly patients has been related to a higher risk of delirium compared with non-users. These drugs are, besides antihypertensive and anticholinergic agents, frequently cited as a cause of a dementia-like state[28]. A moderate recovery of some cognitive deficits in long-term users, six months after withdrawal from BZDs, has been reported[29].

The elderly in particular are vulnerable to adverse effects of hypnotic drugs. These patients are more sensitive to CNS depression, states of confusion and ataxia that can result in falls and fractures[30, 31]. They are as well susceptible to respiratory depression, diminished ventilatory response, hypercapnia and increased hypopnoeic episodes during sleep[31].

EPIDEMIOLOGY OF INSOMNIA AND ANXIETY AND BENZO-DIAZEPINE USE IN THE ELDERLY

The prevalence of insomnia increases steadily with age. A literature review mentioned a gradually rise from approximately 5% in the age group between 18 and 30 years to a prevalence of 40-60% in the subjects aged over 65 years[32]. Prevalence rates of anxiety differ between studies and age ranges under observation[33, 34]. It has been estimated that the prevalence is about 3% in the general population. Among the patients seen by general practitioners a pre-valence of 15-20% has been reported[33, 34]. Most studies in regard to both disorders only report data for individuals over 65 years as one group. Individuals over 65 receive 30% of all prescriptions for BZDs and non-BZD minor sedatives. One-year exposure to BZD use for the elderly averages 32% (range 9-54%)[35]. Current prevalence of BZD use in the institutional setting varies between 11 and 42%[35-37]. In comparison, current prevalence of BZD use in the community setting among the elderly varies between 10 and 37%[35, 38]. A prototype of a long-term user is an aged widowed female with various health problems and a moderate psychiatric disorder[23,39]. Widespread BZD use is particularly common in nursing homes. Sleep disturbances and changes in sleep-wake cycle are frequent in patients with Alzheimer's dementia. This clinical picture has also been referred to as "the sundown syndrome"[40--42]. The changes in sleep behaviour include spending more time in bed, sleeping less than usual, trouble getting the patient out of bed, a day/night reversal of sleep pattern and nightmares upon awakening[43].

Rationale for prescription

It is essential that the practitioner develops a treatment plan when utilizing benzodiazepines to treat older patients. There is a growing agreement with the view that most patients currently taking benzodiazepines should discontinue them whenever possible[44]. If physical dependence exists without other adverse effects, the clinician and the patient can decide whether to detoxify from benzodiazepines and attempt alternative treatments. If benzodiazepine may be a factor in exacerbating the patient's problem, withdrawal is preferred, and observation of benzodiazepine therapy should be continued for at least 6 weeks to allow the possible effects of withdrawal or rebound to be evaluated. It has been shown that there is a significant improvement of memory and cognitive functioning following discontinuance, not necessary associated with increase in anxiety, agitation or sleeplessness[44]. Before initiating discontinuation of hypnotics, it is essential to evaluate the patient's readiness and motivation concerning the undertaking of this program. Discontinuation of a hypnotic drug is more likely

to be successful if motivation is intrinsic, rather than extrinsic. Providing information about the risks (i.e. memory impairment, falls and hip fractures) may be useful, but ultimately the patient should make the decision on his or her own. Some patients are apprehensive about withdrawal symptoms and rebound insomnia. Information about the tapering schedule and about the transient nature of most withdrawal symptoms should alleviate some of those concerns. Other patients may have very low self-confidence regarding their ability to discontinue medication. They should be encouraged to view this program as an opportunity to achieve greater self-control over their sleep and their life in general.

Guidelines for withdrawal

There is a general agreement on the notion that most patients who take BZDs regularly should try to discontinue treatment[45, 46]. Many patients who have taken BZDs for years can have these drugs withdrawn successfully. Older women with anxious symptoms and personality disturbance respond less successfully to withdrawing[23].

The factors presumed to affect withdrawal are personality profile, dose and half-life of BZDs, duration of treatment and mode of withdrawal[23, 47]. In contrast, there are reports sharing the observation that with the exception of age, withdrawal outcome is not related to any particular variable[46]. Withdrawal symptoms, if any, occur most often after 3 months of habitual use. They may include anxiety, restlessness, sleep disturbance, headache, muscle cramps, nausea, delirium or convulsions.

The treatment of BZD withdrawal includes suitable psychological support together with a gradual dosage tapering. In most of the cases, sleep symptoms progressively improve after withdrawal. It has been demonstrated that the elderly tolerate withdrawal as well as, if not better than young individuals[48].

There are no unanimous recommendations in the literature regarding the optimal duration of the withdrawal process. Hence, a variable withdrawal period ranging from 2 to 12 weeks may be allowed. The size of the stepwise lowering in dosage that should be utilized is arguable as well. Certain investigators use a fixed tapering schedule, while others claim that the reduction rate should be titrated against the patient's withdrawal symptoms[49]. Only five studies have evaluated withdrawal severity and outcomes in an elderly group[29, 49, 50, 48, 43]. Table 1 summarizes these studies.

Recently Petrovic et al. showed that a short-term BZD withdrawal program is possible in the hospital setting[49]. Most geriatric patients who are habituated to a low dose of BZDs may wean during a short period, if an initial phase with dose reduction and psychological support is

included in the withdrawal programme. Two-thirds of chronic elderly users can thus successfully be withdrawn from BZDs by a single step of dose reduction, maintained during 1 week[49, 50]. The authors conclude that a faster taper should be encouraged, as it may fit in a short-term admission to the ward. Withdrawal symptoms, if any, will not pass unrecognised and may be sufficiently treated. The general practitioners should be involved in the decision to stop the treatment with BZDs, in addition to the follow-up after discharge from the hospital.

The study of Salzman regarding BZD discontinuation in the elderly showed no increase in anxiety, agitation and sleep disturbances in those who discontinued BZDs as compared with baseline levels. In addition, measures of memory and cognitive function revealed an important improvement following disconti-nuation[44]. Several lines of evidence thus point to the feasibility and advantages of eliminating BZDs from treatment regimens in elderly. The uneventful withdrawal that is obtained in many cases reflects the fact that the use of BZDs in the elderly is more habitual and sometimes based on an indulgence of the treating physician to meet the request of prescribing "something for sleep or nerves".

These findings lend support to the hypothesis that a short-term benzodiazepine withdrawal programme is feasible in the hospital setting. Most geriatric patients who are habituated to a low-dose benzodiazepine treatment may wean in one or two weeks, provided that an initial phase with dose reduction and psychological support is included in the withdrawal programme. A faster taper is advantageous, as it may well fit in a short-term admission to the ward. Withdrawal symptoms, if any, will not go unnoticed and may be adequately treated. Psychological rather than physical dependence proved to be the main reason for relapse in our patients group. To cope with this problem remains a considerable challenge in programmes aimed at weaning from psychotropic drugs.

A profound discriminatory history should identify a real cause of insomnia and/or anxiety among diverse somatic, psychological and situational factors in order to line up a problem oriented treatment strategy.

As to future perspective, non-pharmacological programs should be given a priority in respect of avoiding the use of hypnotic drugs. Psychological support and follow-up of the patient make herein an important task for caregivers. Patients already using benzodiazepines should be advised to discontinue these medications. Before initiation of a withdrawal programme, caregivers should inform the patient that withdrawal from benzodiazepines in combination with psychological support, could consolidate sleep and enhance the restorative value of sleep, but will not change the depth and duration of sleep. Participants in a withdrawal

programme should have ample access to conversational assistance from the psychologist, nurse or physician on the ward. They should be encouraged to continue, though a formal request for cessation of the programme should not be declined. Caregivers should combine this ancillary care with non-pharmacological interventions.

Finally, the role of the general practitioner in the non-pharmacological approach of insomnia and anxiety must not be neglected. The primary care physician may intervene at different care providing levels to improve psychological and social support of elderly patients. Such interventions may obviate the need for symptomatic sedation. Herewith, it is important that the general practitioner and hospital caregivers should respect the same approach.

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Table 1. Benzodiazepine withdrawal studies in geriatric patients

Study	N	Age	Population	Study design	Description of taper	BZD dose (mg)*	Outcome measure	% Completed
Schweizer et al (1989)	41 19 22	 66.4 34.4	Outpatients	Open-label gradual taper	25% reduction per week	16.4 16.6	Withdrawal symptoms BZD plasma levels	50% BZD free at 7 weeks
Salzman et al (1992)	25	86	Nursing home	Single-blind gradual taper	2 weeks of gradual taper then discontinued	10	Cognition, sleep, mood	60% BZD free at 12 months
Habraken et al (1997)	55	84	Nursing home	Randomised, double-blind, gradual taper	Reduction by 25% for 3 weeks, then by 12.5% for 2 weeks, then placebo for 12 months Control lorazepam for 12 months	10	Daily function, sleep quality	63% BZD free at 6 weeks
Petrovic et al (1999)	49	81.4	Geriatric medicine inpatients	Randomised, single blind	Brief educational intervention Replacement with either lormetazepam	10	Sleep quality	67.9% BZD free at 6 weeks

					or tradozone for 1 week, then discontinue all sedatives			
Petrovic et al (2002)	40	81.5	Geriatric medicine inpatients	Randomised, double blind	Brief educational intervention Replacement with either lormetazepam or placebo for 1 week, then discontinue all sedatives	12.5	Sleep quality, withdrawal symptoms	65% BZD free at 4 weeks, 30% BZD free at 12 months

BZD = benzodiazepine. * Mean daily dose in diazepam equivalents.