



## Benzodiazepine use among older adults

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“the use of benzodiazepines is increasing among older adults and they form the largest group of users for these drugs. These agents are effective in treating some clinical symptoms, but their use is fraught with serious side effects and addiction potential among older adults.”

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Benzodiazepines are one of the most commonly prescribed psychotropic drugs in the developed world. Recent data from the 2015 to 2016 National Survey on Drug Use and Health show 30.6 million adults reported benzodiazepine use in the past year. The highest use of benzodiazepines of all age groups was reported by respondents aged 50–65 years at 14.3%, followed closely by the ≥65 years age group at 12.9% [1]. This is a change in trend from 2008 when the ≥65-year old age group was found to have the highest benzodiazepine use [2], although use in this age group has also increased in absolute terms. Prevalence of prescription benzodiazepine is also highest in the 50–65-year age group at 12.9%, although the misuse of prescription benzodiazepines in this group remains the lowest [3].

Similar trends for benzodiazepines have also been observed around the globe. Analysis of European databases between the years 2001 and 2009 shows prevalence of benzodiazepine use increased with age, and was consistently twice as high among women than men across all age groups [4]. This data is especially concerning, as several major medical and psychiatric organizations have cautioned against the use of benzodiazepines in the geriatric age group due to the seriousness of side effects related to them [5]. Furthermore, as the baby boomer generation enters the geriatric age group, prescription of psychotropics with addiction potential needs to be monitored carefully, as this cohort has a higher lifetime exposure to substances and has continued to use these drugs at higher levels when compared with previous older cohorts [6].

Prescription patterns of some psychotropics were studied in the community through a survey of a nationally representative cross-section of outpatient physician visits between 2003–2005 and 2010–2012 [7]. It shows the largest increase in primary care visits related to benzodiazepine prescription when compared with antidepressants and other sedatives-hypnotics, while benzodiazepine prescription remains stable among psychiatrists. An alarming proportion of benzodiazepine prescriptions to the elderly is carried out in the absence of a clearly diagnosed behavioral disorder or significant symptoms. In fact, based on current estimates, up to a third of all benzodiazepine prescriptions may not be clinically necessary [7]. Moreover, a third of the elderly patients who are prescribed benzodiazepines end up using them long term [2].

Educating prescribers on appropriate indications and the use of benzodiazepines in elderly individuals is necessary to prevent indiscriminate use of these agents that are likely to cause significant adverse effects in this population. Multiple professional guidelines exist to curb benzodiazepine use among the geriatric population. The 2019 update to the American Geriatrics Society (AGS) Beers Criteria<sup>®</sup>, the 2014 Screening Tool of Older Person's Prescriptions and Screening Tools to Alert Doctors to Right Treatment adopted in Europe, and by the American Psychiatric Association (APA) have all put benzodiazepines on a list of medications that should be avoided in adults

aged 65 years or older [5]. The Choosing Wisely international campaign, as well as country-specific Choosing Wisely campaigns based in the USA, Australia and Canada have tried to tackle the problematic trend of prescribing benzodiazepines to older adults.

Currently, benzodiazepines are US FDA approved for the treatment of anxiety disorders, insomnia, seizure disorders and status epilepticus and as muscle relaxants, and for the withdrawal symptoms of acute alcoholism. The most common reasons for benzodiazepine prescriptions among older adults are for the treatment of symptoms of anxiety and sleep problems [8]. In addition to these indications, they are commonly used off-label to treat agitation and other behavioral symptoms associated with dementia among the elderly [5]. However, data specific to their efficacy for these indications among older adults is sparse, while there is a plethora of literature advising caution with the use of these drugs due to adverse effects, especially for longer durations. In a recent systematic review studying the use of benzodiazepines to treat anxiety disorders in the elderly, we found that while these drugs were effective in the short term, long-term data are not available, with the longest trial being 8 weeks in duration. Benzodiazepines use also consistently showed higher prevalence of side effects when compared with placebo or the active comparator across all trials. There is also evidence for the efficacy of benzodiazepines for sleep problems among older adults, but the data is limited and it is difficult to draw definitive conclusions from the available data [9]. Two systematic reviews assessing the use of benzodiazepines in dementia reported two studies showing efficacy in treatment of aggression, while five studies showed worsening of cognition and none of the studies showing an effect on the quality of sleep [10,11].

The use of benzodiazepines among older adults is concerning because of the increased sensitivity to side effects, medication interactions and the potential for addiction. The AGS Beers Criteria for potentially inappropriate medication use in older adults, publishes an explicit list of potentially inappropriate medications every 3 years that are typically best avoided by older adults in most or under specific circumstances using a comprehensive systematic review and grading of the evidence on drug-related problems and adverse events in older adults. The 2019 update to the AGS Beers Criteria makes a strong recommendation to ‘avoid’ the use of benzodiazepines in older adults. According to the update, “older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase the risk for falls, cognitive impairment, delirium, fractures and motor vehicle crashes among older adults” [12]. Association between benzodiazepines and falls in the elderly is well established. Most common reasons for falls related to these drugs are due to sedation, gait instability and psychomotor incoordination. While some authors suggest long-acting benzodiazepines may have a higher likelihood of causing falls and that short-acting benzodiazepines should be chosen in elderly if needed, other authors, including the Beers Criteria, advise that both are equally culpable in causing falls. However, the Beers Criteria suggests that if a benzodiazepine is essentially needed for conditions such as seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, alcohol withdrawal, severe generalized anxiety disorder and periprocedural anesthesia, long-acting benzodiazepines should be used. Benzodiazepines have also been shown to cause cognitive dysfunction in the elderly, especially in verbal memory, learning, attention and visuospatial abilities. Some studies also indicate a possible irreversible decline in cognition following the long-term use of benzodiazepines. However, the role of benzodiazepines in increasing the risk for dementia remains controversial, as the results are mixed. Other adverse effects with benzodiazepine use include paradoxical agitation and disinhibition. The most significant, and potentially lethal risk with benzodiazepine use is respiratory depression [5]. This risk has led the FDA to issue a black box warning to advise patients of the risk of respiratory suppression and death from benzodiazepines, particularly in those on concurrent therapy with opioids or other sedatives and hypnotics [13]. There is also a reported increase in all-around mortality in older adults who use benzodiazepines, although causality cannot be established [14]. Suicide attempts have also been found to be associated with long-term benzodiazepine therapy among older adults, but it is not clear if there is a causal relationship. Given that suicide rates are highest in middle-aged and older adults of all age groups [15], it is important to further explore this finding, and screen the elderly for suicidal ideations prior to prescribing benzodiazepines.

Drug interactions are an important consideration in older age groups due to polypharmacy. Most benzodiazepines are metabolized in the liver via the cytochrome P450 system. Drugs that either inhibit (oral contraceptive pills, antifungals such as ketoconazole and itraconazole and some antibiotics including erythromycin, grapefruit juice) or induce (carbamazepine, phenytoin, rifampin, St John’s wort) cytochrome P450 enzymes will either increase or decrease the systemic levels of benzodiazepines. The use of benzodiazepines with other central nervous system (CNS) depressants such as alcohol and opioids can potentiate this effect, which can be fatal. Beers Criteria has issued new recommendations to avoid the use of opioids concurrently with benzodiazepines. Furthermore, it suggests

avoiding concurrent use of a combination of any three or more CNS agents (antidepressants, antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, antiepileptics and opioids) due to increased risk of falls [12].

The risks of abuse and chemical dependence have long been discussed in all patients taking benzodiazepines regardless of the clinical indication. Signs of dependency in older adults include strong desire to use, use of these drugs despite side effects, withdrawal symptoms and continued use of benzodiazepines despite physician's recommendations to discontinue [14]. While rates of prescription misuse are low in the older population, dependence can develop with use of both short- and long-acting benzodiazepines for as little as 2 months [16]. It is therefore important for healthcare providers to avoid indiscriminate and long-term use of benzodiazepines in this population to prevent dependence. Co-prescription rates of opiates along with benzodiazepines are also increasing in the elderly, which can foster dependence of both these drug classes. Multiple agencies including Center for Disease Control (CDC), the US FDA and Substance Abuse and Mental Health Services Administration (SAMHSA) have all issued caution against the concomitant use of opioids and benzodiazepines, as they can cause profound sedation, respiratory depression, coma and death.

Due to the risks and potential adverse effects of prescribing benzodiazepines among the older adult population, clinicians are advised to use caution when prescribing these medications. Because of the conflicting data on the use of benzodiazepines in older adults, it is recommended that providers avoid their use as much as possible. Providers should educate patients on the short- and long-term risks associated with benzodiazepine use and should attempt, when possible, to discontinue their use. There are several studies that outline the appropriate tapering protocols for the safe and effective discontinuation of benzodiazepine when applicable. Wherever appropriate, alternatives to benzodiazepines should also be considered. These alternatives are distinct for the specific clinical situation in question. For dementia-related agitation, appropriate alternatives include antidepressants or antipsychotics. For the treatment of insomnia, clinicians may utilize melatonin, non-sedative hypnotic agents, such as zolpidem or eszopiclone or antidepressants such as mirtazapine or doxepin [14]. Other alternatives for benzodiazepine therapy include nonpharmacological interventions such as improved sleep hygiene, constant supervision and care for older adults living at home and limiting polypharmacy wherever possible. Cognitive behavioral therapy is also emerging as an extremely effective alternative therapy for the treatment of both anxiety and insomnia [5]. Benzodiazepines reduce sleep onset latency, demonstrable both by polysomnography and sleep diaries and increase total duration of sleep [17,18]. The American Academy of Sleep Medicine guidelines for primary insomnia recommend initiating benzodiazepines only after careful consideration of nonpharmacological options such as sleep hygiene, stimulus control and relaxation [19]. Situational insomnia shows similar short-term response to short-acting benzodiazepines and behavioral interventions. Data are lacking on whether tolerance develops to the sleep-promoting effect of benzodiazepines on prolonged use [18]. Clinicians must be aware of the increased risks and possibilities for drug–drug interactions or adverse effects associated with prescribing benzodiazepines to older adults. Patients and families must also be carefully educated on these risks prior to initiating therapy. Consequently, benzodiazepines must be judiciously avoided wherever possible, with possible alternatives considered for therapy including non-addictive agents and nonpharmacological interventions.

In summary, the use of benzodiazepines is increasing among older adults and they form the largest group of users for these drugs. These agents are effective in treating some clinical symptoms, but their use is fraught with serious side effects and addiction potential among older adults. Despite recommendations from many national geriatric organizations to avoid the use of benzodiazepines among older adults, the prevalence of prescription benzodiazepines is highest in this population. Providers should be educated on the appropriate indications for the use of these medications, with recommendations to discontinue their use as quickly as it is possible. Alternative pharmacological and nonpharmacological measures should be employed wherever possible.

#### Author contributions

All the authors contributed equally to the development, researching and the writing to this commentary.

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