Summer 6-19-2022

Abuse of Benzodiazepines among the Elderly Population

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PHRE 5223: Drugs of Abuse

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Benzodiazepines, also known as Benzos, BZF, BDZ, and Bzs, are a class of psychoactive drugs, more specifically depressants [1]. The core structure is an infusion of a benzene ring with a diazepine ring. The name benzos come from the 1,2 positions of the two nitrogen atoms in the diazepine ring [1]. The common street names for these drugs include Benzos and Downers [2]. According to DEA.gov, benzodiazepines are defined as depressants that help relieve anxiety, and muscle spasms, and reduce seizures by producing sedation and hypnosis [2]. They are also used for general anesthesia, muscle relaxation, alcohol withdrawal, drug-associated agitation, sedation before medical and dental procedures (e.g., surgery), depression, panic attacks, nausea, and vomiting [4]. Due to its effectiveness in relieving anxiety, mixed anxiety-depression, and other conditions (e.g., insomnia), it was and still is a comparatively safe drug. Even if the person gets addicted to this drug and has an overdose, the chances of resulting in death are low [3] unless other drugs are involved. According to the 1984 data from the United States National Nursing Home Survey, about 41 percent of antianxiety drugs that were prescribed to patients aged 65 years or older were benzodiazepines [5]. Nevertheless, inappropriate use of this drug together with known risks such as cognitive impairment, delirium, and falls, makes the elderly population more inclined to suffer adverse effects when using them. As a result, benzodiazepines were added to the Beers List in the 1990s and stays on the newest list from 2019 as a drug to avoid in the elderly population [6]. This paper will examine the use of benzodiazepines among the elderly population and their abuse through various published articles that addressed these concerns.

Benzodiazepines work by enhancing the effect of a neurotransmitter in the brain called gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system that suppresses the activity of nerves [3]. It enhances the effect by altering the GABA receptor by changing its conformation, thus modulating the pharmacological properties of the $GABA_A$

receptor [1]. For example, 1,4 – BZDs and 2,3 – BZDs cause minor structural changes in the receptor that increase the effect of the endogenous neurotransmitter GABA, producing sedative effects along with antipsychotic characteristics for 1,4 –BZDs [2]. However, 2,3- BZDs produce anxiolytic characteristics. Benzodiazepines are categorized as either short-acting or long-acting. Short-acting benzodiazepines are used for anxiety, amnesia in critical care settings, medication before anesthesia, and treating insomnia [2]. Long-acting benzodiazepines are used in treating insomnia for patients with daytime anxiety [2]. Some examples of short-acting benzodiazepines are midazolam, flurazepam, estazolam, temazepam and triazolam [2]. As for long-acting benzodiazepines, this includes alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, prazepam, and quazepam [2].

Disregarding the addition of benzodiazepine to the Beers List since the 1990s, they are still used in clinical practice and critical examination for more than 4 decades now. Problems about the various adverse effects among the elderly population have increased immensely. Most studies revealed the common adverse effects that elderly patients faced are memory impairment, adverse cognitive and psychomotor effects, increased risk of harmful events, withdrawal symptoms, anxiety, and depression [7]. According to a report created by several authors, both short-acting and long-acting benzodiazepines can cause memory-related problems [8]. This happens after the completion of benzodiazepine therapy where peak benzodiazepine levels can cause the patient to be unable to learn new information due to anterograde amnesia [8]. Anterograde amnesia results where the information from temporary, short-term memory to long-term memory storage is disrupted [7]. In addition, this study revealed that young patients after completing a 7-to-10-day tapering protocol with the use of chlordiazepoxide (long-acting benzodiazepine) showed no symptoms of memory impairment as well as no symptoms of

withdrawal. However, the effects of chlordiazepoxide lasted for weeks among elderly patients due to their slow metabolism, resulting in underlying dementia and excessive morbidity [8]. As a result, family members of the patients as well as clinicians are unable to recognize memory problems related to drug-induced effects and would assume it may be attributed to aging instead. Some evidence suggests that discontinuation of benzodiazepine therapy among elderly patients can reverse the effects of memory impairment if not used long term, thus improving memory and cognitive functioning [7]. Additionally, elderly patients who stop benzodiazepine therapy after a brief period, are reported to be brighter, more energetic, less dysphoric, and more intellectually alert [9].

Psychomotor and cognitive impairment induced by benzodiazepines therapy for both short-term and long-term has been found as a huge risk factor among the elderly population. A 2017 Meta-analysis showed that visual-spatial ability and sustained attention were impaired among current long-term benzodiazepine users. These patients were unaware of their diminished ability in the areas of working memory, processing speed, divided attention, visuoconstruction, and expressive language [10]. The meta-analysis also reported that long-term users who stopped taking benzodiazepines still showed a significant impairment in all areas of cognitive function including working memory, perceptual-motor, visual perception, divided attention, and processing speed except for executive function's domain [10].

Due to impairment of psychomotor and cognitive functions, this will cause an increased risk of harmful events including impaired specific driving skills. The risk is significantly increased with high-dose regimens. In a 1992 study conducted in the United States, it was found that 2.9% of car accidents were associated with benzodiazepine users. A 1998 study conducted in Quebec, Canada revealed that users who were currently taking long-acting benzodiazepines had

an increased risk of a motor vehicle accident with injury compared to those who were taking short-acting benzodiazepines. The risk was even higher for those who began taking longer-acting benzodiazepines within the last seven days as well as those who were taking them for more than 61 days [11]. In a different study conducted in France, equivalent results to the 1998 Quebec study, also revealed that exposure to long-acting benzodiazepine was associated with an increased risk of car accidents, especially among elderly patients [12]. Other harmful events include an increased risk of falling and sustaining a hip fracture after the first 30 days of therapy [7]. Moreover, an elderly patient who is currently taking short-acting benzodiazepines has severe incapacitating psychomotor effects during the first few hours of administration, thus increasing the risk of falling [7].

Studies have shown that severe anxiety and depressive psychopathologic symptoms were found in elderly patients who were taking benzodiazepines for long-term use [7]. It also showed that deterioration in mood and social behavior were found among these patients [7]. However, if the long-term therapy was successfully withdrawn, it was reported that patients have reduced levels of anxiety and depression substantially [7]. On other the hand, if the treatment was abruptly discontinued, more than 90% of patients were reported to experience withdrawal symptoms including anxiety and depression. Compared to a low dose of benzodiazepines, it was revealed that a high dose can cause severe withdrawal symptoms. In addition, even if the dose of a benzodiazepine was gradually tapered after long-term use, it can cause a rebound of anxiety symptoms in more than 50 to 90% of patients [7].

According to FDA in 1960, Librium (chlordiazepoxide) was the first approved benzodiazepine after being discovered by Hoffmann-La Roche chemist Leo Sternbach [13]. By 1963, Librium was the most successful drug in pharmaceutical history [1]. At that time,

benzodiazepines were seen as less toxic and less likely to cause dependence among users compared to older drugs such as barbiturates [13]. Due to the skyrocketing popularity of Librium, a second benzodiazepine was marketed by Roche named Valium (diazepam) [1]. From the period 1963 to 1970, eight benzodiazepines were created and marketed, most of them being marketed by Roche [1]. A 1971 Fortune magazine reported that just Librium and Valium accounted for more than $200 million in sales in the United States alone [1]. By 1977, around 8000 tons of benzodiazepines were being consumed per year in the United States alone [1]. It was not until the 1980s, that benzodiazepines' specter of abuse and dependence started to rise at a rapid rate. By 1987, the American Psychiatric Association established a task force to gather all the available information about these drugs to then create guidelines for prescribing benzodiazepines [14]. Potential hazards from chronic therapeutic use of benzodiazepine started to arise in 1987 including rebound, recurrence, and withdrawal symptoms [14]. For example, in the American Psychiatric Association's report, rebound symptoms appeared after discontinuation of the drug, causing patients to have insomnia and anxiety to worsen, thus leading them to go back to benzodiazepine therapy [14]. The report also revealed the toxicity of benzodiazepines among the elderly population including risk factors such as cognitive impairment and increased predisposition to falling [14]. As a result, both short-acting and long-acting benzodiazepines were added to the 1990s Beers List.

Despite benzodiazepines being added to the BEERS List Criteria in the 1990s, in the period 2001-to 2010, benzodiazepine use increased from 8.9% to 19.3% among the elderly population [3]. Conversely, it has also been shown that inappropriate prescriptions for benzodiazepines decreased with increasing age among the elderly with around 10.7% accounting for patients aged 65 to 74 and 5.3% accounting for patients aged 85 years or older [15]. In the 2009

study conducted by Can J Hosp Pharm, around 4.2 % of the 8975 patients (accounts for 374 patients) were reported to fall during their stay at the hospital [15]. For the total amount of falls of these patients, 280 (around 74.9%) had one fall each while 20 patients (around 5.3%) had 4 or more falls. It also reported that in around 35.4% of these 574 falls (around 203 cases), at least one benzodiazepine has been prescribed for the patient (accounting for both appropriate and inappropriate use of benzodiazepine) [15]. Of these 203 cases of the 574 falls (around 35.4%), the inappropriate prescribed benzodiazepine accounted in 30 cases out of the 203 (around 14.8) [15]. The most common benzodiazepine prescribed in relation to these falls was lorazepam, which accounted 62.6% of the 203 cases, followed by a combination of lorazepam and oxazepam (18.7%) or oxazepam alone (14.8) [15]. Additionally, it reported that the use of inappropriate benzodiazepines was associated with a patient staying a longer time in the hospital than usual (around 7 days) [15]. According to the Centers for Disease Control and Prevention (CDC), there was an increase of 24% from 2019-to 2020 alone involving overdose of benzodiazepines, around 7,000 deaths [16]. More than 90% of the overdoses came from prescription-based benzodiazepines. According to a recent study from 2020, the use of long-acting benzodiazepines has decreased, but this concept cannot be applied to short-acting benzodiazepines [17]. Most of the health hazards were associated with short-acting benzodiazepines during the first weeks of treatment [17]. The study revealed that both long- and short-term benzodiazepine were discontinued only if mortality or excess risk of mortality has been associated with its use.

To combat the abuse of benzodiazepines among the elderly, guidelines were created for healthcare professionals on how to safely and effectively taper doses of benzodiazepine to avoid abuse or rebound symptoms [18]. In the 2019 Centre for Effective Practice (CEP) Benzodiazepine Guideline, benzodiazepines are not the preferred treatment for treating anxiety, insomnia, or

panic attacks among elderly patients [18]. For example, the guideline demonstrates that cognitive behavior therapy for insomnia is more effective than pharmacological therapy for both short-term and long-term management among the elderly [18]. If a pharmacological therapy is needed, the guideline suggests using doxepin or trazodone as opposed to benzodiazepines as there are minimal risks of physical dependence when using them [18]. The guidelines also recommend using short-acting benzodiazepines rather than long-acting ones to reduce the severity of withdrawal symptoms if a benzodiazepine needs to be used in an elderly patient [18]. According to the 2007 BEERS Criteria, there is an alternative regimen to benzodiazepine to be used in the elderly [19]. For example, rather than using long-acting benzodiazepines for anxiety, try using short-acting benzodiazepines instead such as alprazolam [19]. Keep note that alprazolam must be appropriately dosed before prescribing. For insomnia, try incorporating temazepam 7.5 mg or zaleplon (Sonata®) 5mg [19].

Another way to combat abuse of benzodiazepines among the elderly is incorporating a pharmacist-physician collaboration model to prevent and lessen benzodiazepine abuse as well as to optimize the use of the drug without it being abused. A 2017 study publicized that around 40% of benzodiazepines were prescribed inappropriately among elderly patients in the outpatient setting [20]. The study also revealed that physicians are misdosing benzodiazepines in various age groups especially the elderly for chronic use where the BEERS criteria has recommended benzodiazepine use for short term only [20]. In addition, physicians are aware of some risks associated with the use of benzodiazepines but are not aware of all risks associated with it [20]. Moreover, physicians do not have time to educate patients about potential risks when using this drug as well as a transition for patients to use more effective and safer alternative therapies [20]. Incorporating the pharmacist-physician collaboration can help lessen the burden for primary care

physicians in optimizing the use of this drug. Based on this approach, it would help initiate using alternative and more preferred therapies rather than relying on the use of benzodiazepines [20]. As a result, there was a vast improvement in treatment efficacy, improving patient safety, and the lack of regression among the patient population including the elderly [20].

As mentioned previously, there are higher risk factors including memory impairment, cognitive and psychomotor effects, risk of harmful events (e.g., falling or car accidents), withdrawal symptoms (e.g., rebound effects), anxiety, and depression among elderly patients. The risks rise significantly when these patients used a long-acting benzodiazepine compared to short-acting benzodiazepines use. Given the drug class was added to the Beers List in the 1990s, it's still used today in treating anxiety symptoms and insomnia in the elderly. To lessen the abuse of both short-acting and long-acting benzodiazepines, healthcare providers should use guidelines to find safer and more effective alternative therapies before prescribing as well as knowing all the risks associated with benzodiazepines if they need to be used. More outpatient settings including hospitals should incorporate the pharmacist-physician collaboration model to prevent and lessen benzodiazepine abuse while knowing how to optimize their use when needed. Further research is needed to assess the effectiveness of pharmacist-physician collaboration in optimizing the use of benzodiazepines and improving current guidelines for tapering benzodiazepines properly to then help overcome the abuse of once world prescribed drugs.

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