

Insights on Benzodiazepine's Contribution to Neuroinflammation and Alzheimer's Disease Biomarkers

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Abstract

Benzodiazepines (BZDs) are a class of prescription medications widely used for their anxiolytic, hypnotic, and muscle relaxant properties. Prolonged use of BZDs has been shown to increase the risk of abuse, dependence, and relapse in patients. Elderly people are particularly more vulnerable to the effects of BZDs due to altered pharmacokinetics and pharmacodynamics, along with drug interactions resulting from polypharmacy. These processes initiated by BZDs may trigger the onset of cognitive pathologies such as Alzheimer's disease (AD). The present study focused on the relationship between BZD use and its contribution to neuroinflammation in AD. Moreover, it summarized some studies evaluating the effect of BZDs in the AD population.

Keywords: Benzodiazepines, Cognition, Neurotoxicity, Neuroinflammation, Alzheimer's disease

Introduction

In recent years, various drug classes with anticholinergic properties have been used to treat several pathological conditions such as different types of allergies, incontinence, and depression.^{1,2} According to World Health Organization (WHO) reports, benzodiazepines (BZDs) are critical medicines for the central nervous system (CNS) and are commonly used to treat numerous clinical disorders, including epileptic attacks, phobias, depression, excitation, agitations, and anxiety, among others.³ BZDs are often preferred for the treatment of anxiety and depression due to their fast-acting nature, efficiency, fewer side effects, and lower acute toxicity compared to the other pharmacological approaches.⁴ It is also reported that BZDs are highly effective in reducing symptoms of alcohol withdrawal and are helpful in anesthesia.⁵

While BZDs can be an effective treatment, their prolonged use in older adults increases the risk of falls, hip fractures, cognitive decline, and drug-related hospital admissions.^{6,7} Neurotoxicity is defined as any abnormal effect on both the structure and function of the CNS and peripheral nervous system caused by a variety of biological, chemical, or physical factors. The site and severity of neurotoxic damages can lead to neurocognitive impairments that significantly impact various aspects of daily life. Although neurotoxicity is a major concern in some neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), a comprehensive evaluation of the correlation between

neurotoxicity and such disorders is still necessary.⁸

The strength of the association between BZDs and neurotoxicity remains controversial. A case-control study reported potential neuroprotective effects of BZDs, indicating their protective role in cognitive functions.⁹ In addition, a literature review discussed different findings regarding long-term BZD use and its potential AD risk.¹⁰ However, the possible link between BZDs and specific features in the long term remains unclear. The majority of existing data suggests a higher risk of dementia among BZD users with long-term exposure to BZDs.¹¹

Nevertheless, various evidence suggests that several damages induced by BZDs can negatively impact neurocognitive conditions. Additionally, the activation of neurotransmitter systems, including dopamine and glutamate systems, mediated by BZD-induced neurotoxicity, represents detrimental effects on the brain.¹² From a molecular perspective, BZDs enhance the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA),¹³ facilitating the flow of chlorine ions through the ionotropic channel, resulting in neuronal membrane hyperpolarization.¹⁴ To provide strong evidence on whether long-term BZD use increases the risk of cognitive decline, we evaluated the association between BZD effects and preclinical dementia biomarkers.

Benzodiazepine Action and Underlying Mechanisms in the Central Nervous System

BZDs are clinically relevant drugs that enhance the binding of the inhibitory neurotransmitter GABA to GABA

receptors throughout the CNS. The pharmacokinetic profile of BZDs affects their onset duration of action. Following oral administration, BZDs are rapidly absorbed from the gastrointestinal tract and quickly distributed to the brain and CNS after intravenous administration. They have a high volume of distribution in the body because of their lipid solubility, leading to higher tissue concentrations compared to blood. These drugs are frequently classified based on their elimination half-life as short-acting, intermediate-acting, and long-acting BZDs (Table 1). BZDs are also characterized by relative potency. When prescribing BZDs, clinicians must consider individual factors such as lipid solubility, distribution, absorption, and elimination half-life. Numerous studies have evaluated the effects of BZDs on cognition, yielding different results. In the following sections, we discuss BZD contributions to neuroinflammation and AD biomarkers.

Benzodiazepine-Induced Neurotoxicity and Memory Impairment

Memory is divided into short-term and long-term spans according to duration, explicit and implicit processes based on content, and acquisition, consolidation, or retrieval based on the stage of memory formation. Explicit memory is a type of declarative memory in which past events (episodic memory) are consciously recollected. In contrast, implicit memory is related to the non-declarative system and refers to a nonconscious

(automatic or spontaneous) processing of information, as observed in procedural learning. Furthermore, explicit memory depends on the hippocampus and is vulnerable to organic amnesia.¹⁵

It seems that short-term memory is the most vulnerable type to BZDs.¹⁶ BZDs can exert a range of side effects, including drowsiness, confusion, dizziness, trembling, impaired coordination, and memory impairment. Of these adverse effects, disturbances in memory performance present significant limitations to BZD use in conditions such as anxiety, insomnia, and seizures.¹⁷ In other words, BZDs impair episodic memory, resulting in deficits in recalling personally experienced events. BZDs negatively affect memory acquisition, inducing anterograde amnesia. Through this mechanism, deficits in learning, which are responsible for building new associations and the disturbed acquisition of novel information, are caused by the negative effects of BZDs.¹⁶

Considerable evidence indicates that memory processes in mice are affected by a single administration of BZDs. For example, diazepam (DZ) and flunitrazepam (FNZ) exert detrimental effects on memory acquisition in the elevated plus maze and the novel object recognition memory tests. Surprisingly, these studies demonstrated differences in the action of nitric oxide synthases (NOS) inhibitors on memory loss after DZ or FNZ administration.^{18,19}

Additionally, BZDs inhibited passive avoidance performance which is mediated by the amygdala since microinjection of midazolam into the amygdala before inhibitory avoidance (IA) training impairs the acquisition of IA memory.²⁰ It is suggested that pre-conditioning administration of two anxiolytic BZDs, chlordiazepoxide (CDZ) and alprazolam, affected the acquisition of conditioned taste aversion (CTA) by causing a CTA that presented faster extinction in C57BL/6 mice. This evidence supports the finding that selective deficits in aversive learning caused by BZDs are relevant to their clinical anxiolytic actions.²¹

Although sedation and drowsiness, the most common negative effects of BZDs on cognition, often improve with tolerance of a large number of cognitive impairments, including attention, concentration, learning, working memory, episodic memory, semantic memory, verbal and nonverbal memories, procedural memory, general intelligence, problem-solving, motor performance, and psychomotor speed, persist with continued use.^{15,22,23} In the elderly, these symptoms may be mistaken for unrelated progressive dementia.¹⁵ However, BZD-related cognitive impairments can persist even after discontinuation and may cause dementia.⁷

Benzodiazepines and the Risk of Dementia

A growing body of research highlights the causal effect of BZDs on increased dementia risk. Although BZDs are widely used as effective treatments for anxiety, agitation, insomnia, and other mood-related conditions, they have been linked to an increased risk of AD and related

Table 1. Various BZDs and Their Characteristics

BZDs	Onset of Action (h)	Half-Life (h)	FDA-Approved Indication
Short Acting			
Midazolam	0.5-1.5	0.78-0.33	-Amnesia -Sedation
Triazolam	2	1.5-5.5	-Hypnotic -Insomnia
Intermediate Acting			
Alprazolam	1-1.5	11.2	-Acute anxiety disorder -Panic disorder
Estazolam	0.5	10-24	-Hypnotic -Insomnia
Lorazepam	2	12	-Anxiety disorder
Oxazepam	3	8.2	-Alcohol withdrawal -Anxiety disorder
Temazepam	1.2-1.6	8.8	-Hypnotic -Insomnia
Long Acting			
Diazepam	0.5	Up to 48	-Alcohol withdrawal -Anxiety -Amnesia -Sedation -Seizure
Flurazepam	0.5-1	50-100	-Insomnia
Clonazepam	0.33-0.66	30-40	-Panic disorder -Seizure
Chlordiazepoxide	3	24-48	-Alcohol withdrawal -Anxiety disorder

Note. BZD: Benzodiazepines; FDA: Food and drug administration.

dementias in older adults.⁷ However, the underlying mechanisms behind these relationships are not fully understood, as some mixed results have been observed in the literature. For example, Joyce et al²⁴ found little evidence of a possible relationship between BZD treatment and dementia risk in their study.

Benzodiazepines-Induced Neuroinflammation Neuroinflammation, Alzheimer's Disease, and Gamma-Aminobutyric Acid Neurotransmission

From a pathologic point of view, AD, the most common type of dementia, is related to the accumulation of amyloid beta (A β) as senile plaques and hyperphosphorylated tau (hp-tau) as neurofibrillary tangles in the brain. Recent studies have reported that dysfunction in neurotransmitter GABA receptors could be a major contributor to AD pathology in animal models.²⁵ Components of the GABA-A receptor, including 2 α subunits, 2 β subunits, and 1 γ subunit, form a pentamer that surrounds the ligand-gated chloride channel. The active site of the GABAA receptor is the binding site for GABA, the primary inhibitory neurotransmitter of the CNS. When GABA binds to the GABA receptor, the chloride ion (Cl⁻) channel opens, allowing Cl⁻ ions to enter the cell. Therefore, the entry of chloride causes hyperpolarization of the cell, reducing its action potential and preventing the release of excitatory neurotransmitters.²⁶

The detection of increased inflammatory factors and the identification of AD risk genes related to innate immune function suggest that neuroinflammation plays a critical role in AD pathogenesis.²⁷ Microglia are key players in neuroinflammation and are associated with several pathways in AD that suppress or modulate the disease's progression.²⁷ Furthermore, the inhibitory effect of the GABAergic system is enhanced via BZDs.¹³ BZDs might adversely affect cognitive functions in aging AD patients. Long-term use of the moderate-effect BZD lorazepam can exert amnesiac effects due to the weakening of synaptic plasticity and impaired memory.²⁸

Effect of Benzodiazepine on GABAergic System

BZDs allosterically modulate GABA type-A receptors (GABAARs) to enhance inhibitory synaptic potency, leading to suppression of neural action in the CNS. Since BZDs reduce anxiety, insomnia, convulsions, and muscle tone, they have been extensively used as drugs with low toxicity and high efficacy. Nevertheless, prolonged use of BZDs leads to various side effects, including dependence, tolerance, and withdrawal effects.²⁹

Although the exact mechanism by which BZDs could exacerbate cognitive deficits and AD risk is not fully understood, some hypotheses can clarify this link. The α 1 subunit of the neurotransmitter GABA drives BZD-mediated cognitive loss. In preclinical models, increased activity at the α 1GABAA receptors modulated by BZDs causes spatial learning and memory deficits. Furthermore, in the hippocampus, activation of the α 5 subunit is

responsible for the memory deficits induced by BZDs. Thus, the administration of compounds targeting the α 5GABA subunit could improve cognition, suggesting their therapeutic potential in AD treatment.³⁰ Moreover, enhanced activity of the α 5GABAA receptor has been observed in the inflammatory process, which is probably crucial in the memory deficits induced by inflammation.³¹

Different studies have highlighted the association between BZD use in patients with AD, which is particularly important because AD leads to medial temporal lobe atrophy. The mechanisms underlying the cellular and molecular causes of BZD-induced anterograde amnesia and cognitive impairment are not entirely understood. Understanding these mechanisms could provide greater insight into how these drugs contribute to cognitive decline in aging and AD.³²

Chronic neuroinflammation is a common cause of pathological conditions observed in all neurodegenerative diseases. Research has shown that neuroinflammation induces alternations in the GABA neurotransmitter system, with GABAergic signaling influencing neuroinflammatory processes within the CNS. In addition, BZD action chemically induces GABAergic excitation, which leads to persistent neuroinflammation.³³

Benzodiazepine and Preclinical Markers of Dementia

It is well-established that the administration of BZDs exerts acute effects on cognition via the GABAergic system, which may persist for a long time after withdrawal.³⁴ Several observational studies have investigated the altered dementia risk in human users of BZDs. Recently, two meta-analyses have demonstrated an association between BZD use and increased risk of dementia, indicating that the harmful effects of BZDs outweigh any potential protective effects.^{35,36} BZDs are known to affect neuropathological hallmarks of AD, mainly through their impact on β -amyloid precursor protein (APP) mRNA levels and tau protein,³⁷ since BZDs may increase the risk of dementia in older people,^{38,39} several studies have concluded that these drugs can increase APP expression and tau phosphorylation. These mechanisms likely disturb cognitive performance, presumably by affecting synaptic plasticity, inducing neuroinflammation, and promoting the aggregation of A β plaques and neurofibrillary tangles.^{37,40}

The use of BZDs, probably by attenuating synaptic activity, has been associated with an elevated incidence of AD progression and experimentally disturbs synapses in AD transgenic mice.^{39,41} Likewise, researchers have focused on the frequent use of BZDs and their effects on tau phosphorylation, due to the strong involvement of tau in AD development. Indeed, tau oligomers in pathogenic soluble forms can promote neuronal dysfunction and cognitive impairment through several mechanisms at the early stages of AD.^{42,43}

It is well-known that the apolipoprotein E (APOE) 4 allele is a significant risk factor for AD.⁴⁴ The presence of this allele is associated with increased A β accumulation,

as well as increased cognitive decline and disease development compared to other APOE allelic variants. In this respect, Pomara et al reported that elderly carriers of the APOE4 allele exhibited increased sensitivity to the cognitive adverse effects of acute doses of lorazepam.⁴⁵ Thus, it seems that the APOE4 allele could also be a risk factor for psychotropic drug-mediated cognitive decline. Likewise, the same group suggested that individuals who carry the very long Translocase of Outer Mitochondrial Membrane 40 Homolog (TOMM40) Poly-T Length but do not possess the APOE4 allele might also be at increased risk for BZD-related cognitive loss. Therefore, the influence of the APOE genotype on hypnotics as a risk factor for AD seems relevant, and APOE4 genotyping could be useful in guiding clinicians to avoid BZD prescriptions in at-risk patients. Stonnington et al reported that a 2 mg acute dose of lorazepam given to middle-aged (50–65 years) cognitively normal adults resulted in a greater decline in verbal episodic memory and visuospatial memory/executive function in APOE4 carriers compared to non-carriers.⁴⁴

There is strong evidence that the APOE4 allele is a high-risk factor for AD development.⁴⁴ Increased presence of this allele is linked to elevated A β accumulation and also contributes to greater cognitive decline and disease progression compared to other APOE allelic variants. However, the impact of the APOE genotype on hypnotics and its relevance as a risk factor for AD is noteworthy.⁴⁵

Conclusions and Future Directions

BZDs are medicinal compounds widely used for pharmacological treatments due to their anxiolytic effects and muscle-relaxant properties. Furthermore, observational studies have reported a strong link between long-term BZD use and dementia, as cognitive deficits in BZD users may depend on preclinical dementia processes. The adverse effects of BZDs force clinicians to exercise caution when prescribing this class of drugs, especially in older individuals. More clinical studies should be designed to address the pharmacokinetics and pharmacological actions of BZDs and the side effects associated with increasing doses.

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Competing Interests

The author declares no conflict of interests, financial or otherwise.

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