Health Leadership and Quality of Life. 2025; 4:597
doi: 10.56294/hl2025597

ORIGINAL

Long-Term Benzodiazepine Consumption and Its Repercussions on Aged Brain Performance

Consumo prolongado de benzodiazepinas y sus repercusiones en el rendimiento cerebral en personas mayores

Prabavathy S[1], Salahuddin[2], Takveer Singh[3], Nyalam Ramu[4], Srimant Pattnaik[5], Lovish Dhingra[6]

[1]Department of Mental health Nursing, Kasturba Gandhi Nursing College, Sri Balaji Vidyapeeth (Deemed to be University). Puducherry, India.
[2]Noida Institute of Engineering and Technology Pharmacy Institute. Greater Noida, Uttar Pradesh, India.
[3]Centre of Research Impact and Outcome, Chitkara University. Rajpura- 140417, Punjab, India.
[4]Centre for Multidisciplinary Research, Anurag University. Hyderabad, Telangana, India.
[5]Department of Neurology, IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University). Bhubaneswar, Odisha, India.
[6]Chitkara Centre for Research and Development, Chitkara University. Himachal Pradesh-174103 India.

Cite as: S P, Salahuddin S, Singh T, Ramu N, Pattnaik S, Dhingra L. Long-Term Benzodiazepine Consumption and Its Repercussions on Aged Brain Performance. Health Leadership and Quality of Life. 2025; 4:597. https://doi.org/10.56294/hl2025597

Submitted: 31-05-2024 **Revised:** 10-12-2024 **Accepted:** 13-08-2025 **Published:** 14-08-2025

Editor: PhD. Neela Satheesh

Corresponding Author: Prabavathy S

ABSTRACT

Benzodiazepines, often known as BZDs, are widely used sedatives, hypnotics, and anxiolytics which are particularly frequent among older persons. The purpose of the research was to investigate the potential effects of benzodiazepines on cognitive skills in well-educated elderly persons. This research comprised 152 elderly those with a basic education of 15,8 years. The participants was split into three distinct categories: long-term, short-term, and non-users of BZD. Three statistical tests the evaluation of variance, chi-squared test, and the evaluation of variance was utilized to investigate demographic data and cognitive evaluations for the three groups. Using a multiple linear aggression technique, the relationship among BZD usage and cognition was examined. The Trail Making Test B (TMT-B) results showed that each of the three categories was substantially different from one another in terms of executive functioning. Long-term BZD (LTBZD) users exhibited substantial faults on TMT-B time, whereas short-term BZD (STBZD) users presented substantial flaws on TMT-B time and TMT-B errors. LTBZD users significantly outperformed STBZD users in terms of TMT-B mistakes. Other cognitive tests including general intelligence, linguistic fluency, verbal memory, and visual memory revealed no significant changes. Greater BZD usage over time were favorably correlated with results for the updated Brief Visuospatial Memory Test when demographic factors were taken into account. Among older persons with high levels of education, BZD usage may be strongly linked to lower executive functioning. However, there is no link between increasing cognitive impairments in older persons with high levels of education and the length of BZD usage.

Keywords: Benzodiazepines; Trail Making Test B; Short-Term BZD (STBZD); Long-Term BZD (LTBZD).

RESUMEN

Las benzodiazepinas, conocidas como BZD, son sedantes, hipnóticos y ansiolíticos de amplio uso, especialmente en personas mayores. El objetivo de esta investigación fue investigar los posibles efectos de las benzodiazepinas en las habilidades cognitivas de personas mayores con un alto nivel educativo. Participaron 152 personas mayores con un nivel educativo básico de 15,8 años. Los participantes se dividieron en tres categorías: consumidores de BZD a largo plazo, a corto plazo y no consumidores. Se utilizaron tres pruebas estadísticas:

la evaluación de la varianza, la prueba de chi-cuadrado y la evaluación de la varianza para analizar los datos demográficos y las evaluaciones cognitivas de los tres grupos. Mediante una técnica de agresión lineal múltiple, se examinó la relación entre el uso de BZD y la cognición. Los resultados de la Prueba de Trazado B (TMT-B) mostraron que cada una de las tres categorías presentaba diferencias sustanciales en cuanto al funcionamiento ejecutivo. Los usuarios de BZD a largo plazo (LTBZD) mostraron deficiencias sustanciales en el tiempo de TMT-B, mientras que los usuarios de BZD a corto plazo (STBZD) presentaron deficiencias sustanciales en el tiempo de TMT-B y errores de TMT-B. Los usuarios de LTBZD superaron significativamente a los de STBZD en cuanto a errores de TMT-B. Otras pruebas cognitivas, como la inteligencia general, la fluidez lingüística, la memoria verbal y la memoria visual, no revelaron cambios significativos. Un mayor uso de BZD a lo largo del tiempo se correlacionó favorablemente con los resultados de la Prueba Breve de Memoria Visuoespacial actualizada al considerar los factores demográficos. En personas mayores con altos niveles de educación, el uso de BZD podría estar fuertemente vinculado a un menor funcionamiento ejecutivo. Sin embargo, no existe una relación entre el aumento del deterioro cognitivo en personas mayores con altos niveles de educación y la duración del uso de BZD.

Palabras clave: Benzodiazepinas; Prueba de Trazado B; BZD de Corto Plazo (STBZD); BZD de Largo Plazo (LTBZD).

INTRODUCTION

Brain performance, encompassing cognitive skills including memory, attention, decision-making, and solving issues, is referred to as brain performance. Genomics, sleeping habits, exercise, stress, and environmental influences are just a few of the variables that might affect brain performance. There are several ways to increase the performance of the brain, involving regular physical activity, adequate sleep, a diet rich in antioxidants and omega-3 fatty acids, stress reduction through mindfulness practices, and mentally stimulating activities like picking up a new hobby or playing brain games. Avoiding behaviors that might impair brain function, such as smoking, binge drinking, and a sedentary lifestyle, is important. People may improve their brain function and sustain memory as they age by developing healthy habits and partaking in challenging and stimulating activities.[1] Aged brain performance describes the cognitive aptitudes and talents that a person demonstrates as they age. A person's capacity to think, learn, and recall knowledge may be impacted by changes that the aging brain experiences. Age-related changes that may affect brain function include a decline in processing speed, a decrease in working memory capacity, a shortening of attention span, and problems multitasking. It's important to understand that, even while these changes are common, they don't exclude older people from continuing to lead fulfilling lives or pick up new skills. Many senior people may keep their brains functioning well into their golden years with the correct techniques and assistance.[2]

One of the brain abilities most often impacted by aging is memory. Both short-term and long-term memory issues, including forgetfulness, difficulty picking up new knowledge, and recall issues, are common in older persons. The ability to multitask or complete complicated activities rapidly may be hampered in older persons due to a reduction in attention and processing speed. Brain alterations brought on by aging may also have an impact on one's ability to think and solve difficulties. When it comes to jobs that call for abstract thinking or the capacity to think about many factors at once, older folks might have trouble. Through the process of good lifestyle practices including exercise, a nutritious diet, social interaction, and mental stimulation, many older persons can preserve their cognitive performance. There are several cognitive training programs and therapies that may assist senior citizens keep their independence while enhancing their cognitive ability.[3] Gamma-aminobutyric acid, a chemical found in neurons that aids in calming the brain and central nervous system, is made more active when benzodiazepines are employed. Long-term benzodiazepine usage may have several negative side effects, including sleepiness, disorientation, memory issues, reduced coordination, and diminished libido. Especially for the elderly, benzodiazepines might make fractures and falls more prevalent.[4]

The reduction in brain function, including encompasses abilities such as attention, processing speed, and problem-solving, is the most significant effect of aging on brain function. Even while this deterioration may be slow, it may nonetheless have a big influence on every day activities by making it harder to do tasks that used to be simple or normal.[5] Memory loss is another typical effect of aging on brain functionality. The issue can show up in a variety of ways, such as having trouble recalling recent conversations or information as well as having trouble recalling people, locations, or events. Despite having a significant brain injury, some people function cognitively better than others. This clinic-pathological dissociation suggests that certain elements, including mental capacity, the lifelong intellectual stimulation reduce the deleterious impact of MS disease load on neuropsychological activity, and guard against brain loss.[6] Anxiety, sleeplessness, and other illnesses of this kind are often treated with benzodiazepines, a group of medications. Especially for older persons, prolonged

use of these medicines may have detrimental effects on brain performance. The fact that benzodiazepines may alter the anatomical makeup of the brain, especially in the hippocampus, and region essential for recall and learning, is one explanation for their detrimental effects on brain function.[7] The volume of the hippocampus has been observed to decrease with prolonged benzodiazepine usage, which may affect brain performance. Due to its functional heterogeneity along its dorsoventrally axis, the brain region is engaged additionally in cognitive processes including episodic storage and spatial referencing similar to the pathophysiology of anxiety and mood conditions.[8]

There are several therapeutic applications for benzodiazepines. Psychiatric conditions including anxiety spectrum disorders are often linked to sleeplessness and may speed up the aging of the brain. Additionally, sleep disturbance is linked to neurotoxicity throughout the AD trajectory, even in milder stages. Sleep seems to be inversely correlated with amyloid and tau build-up in the brain.[9] If individuals continue to practice certain healthy living practices throughout their lifetimes, attractive brain aging is achievable. The aspects of lifestyle include things like caloric intake, the composition, and quality of the diet, physical and mental activity, quitting smoking, maintaining an active social life, effectively utilizing technological advancements for communication with others, maintaining an active emotional life, and managing a stressful lifestyle.[10] The behavioral alterations compatible with the likely initiation of resistance and the glutamatergic system's contribution to its growth determined.[11] The adverse consequences linked to long-term misuse of ALP have emerged as a significant hurdle in pharmacotherapy, underscoring the unfulfilled desire to better explore their underlying molecular processes. The evaluated BZDs and hypnotics and the concurrent usage of these drugs' risks for the occurrence of memory in the future, with a focus on their half-lives demonstrated.[12] The consumption of benzodiazepines and z-hypnotics has significantly grown with population aging, the danger of BZDs and z-hypnotics in dementia development is still an important concern.[13] examined the incidence of benzodiazepine usage among older individuals with schizophrenia spectrum disorder as well as the clinical characteristics connected to such consumption. There are a few investigations on the use of psychotropic drugs by elderly people with schizophrenia spectrum illness. Particularly, there is virtually little data on benzodiazepine usage in elderly individuals with schizophrenia spectrum illness.[14] explored both established and cutting-edge CBT strategies that treat both the underlying problem and the drug use disorder, including Acceptance and Commitment Therapy. Review of the theoretical underpinnings and supporting data for various methods. Insomnia and anxiety have both been successfully treated with benzodiazepines. A significant risk-benefit conundrum about dependence, withdrawal symptoms, and possible adverse effects occurs in the context of long-term usage, even though it is generally regarded as safe when used for a short length of duration. The proportion does not reach 25 % to 30 % of patients, even with the assistance of a general practitioner, and only around 7 % of those patients can avoid using drugs for an extended period.

The evidence for neuroadaptive processes driving benzodiazepine tolerance, which includes alterations in the receptor, intracellular alterations brought on by transcriptional and neurotrophic factors, ionotropic glutamate receptors, other neurotransmitters, and the neurosteroid complex examined.[15] Despite decades of scientific and clinical learning, benzodiazepines tend to decrease their effectiveness with time. While it seems that tolerance to benzodiazepine's sedative and anticonvulsant effects develops rather fast, the tolerance to their anxiolytic and amnesic effects is not created properly. The comparison of baseline and post-mild traumatic brain injury cognitive assessments in athletes was examined.[16] Before and after MTBI, collegiate athletes underwent a neuropsychological questionnaire. The assumed variances in starting inspiration, the SMB group was anticipated to improve more than the HMB category. Regarding Tests A and B of Trail Making, Digit Span, and Stroop-Color Word assessments, the SMB subjects showed more progress than the HMB groups in an ongoing evaluation of correlation that eliminated accomplishment achievement. The aging brain's neuroplasticity, or its tendency to develop in response to repeated experience was examined.[17] They contend that, despite some age-related neuronal decline, the capacity of the cognitive system increases mental activity produces neural infrastructure to control cognitive process. While differences in activation might reflect approach changes instead of neural elasticity, rises in neurone size brought on by cognitive learning or expertise imply changes.

The use trends and related variables to identify the general population of the Health Region of Lleida's consumption trends for benzodiazepines and medications associated with BZDs was examined.[18] Due to the danger, they pose to those receiving treatment, benzodiazepines are a very prevalent and often-used kind of therapy. Despite the present knowledge of these medications' risk-benefit ratio, their usage is however quite high.[19] Investigated the wide variety of potential cognitive performance variables in older-age bipolar disorder. Self-report questionnaires and structured interviews were utilized to gather data on demographics, mental traits, and usage of psychotropic medications. Using data from physical examinations, lab tests, and organized conversations, the existence of cardiovascular risk factors was identified.[20] Provides an overview of the research that looked at how BZDs affected sleep organization. A pertinent medical problem is insomnia, which is characterized as experiencing sleep issues or maintaining sleep. Insomnia is often treated with the prescription drug benzodiazepines. Human sleep is divided into two phase's rapid eye movement sleep and non-

REM sleep. The continuous period of NREM and REM phases that make up physiological sleep is referred to as Sleep Architecture.[21] Evaluated and summarize existing synthesis studies on the connection between BZD and BZRD usage and dementia risk. Although the popular negative effects, which include acute effects on cognition, benzodiazepines, and related medications are often used to treat a variety of mental diseases owing to their anxiolytic, hypnotic, and sedative qualities. Recent research has also raised the possibility that dementia and long-term cognitive consequences might coexist, increasing the likelihood of dementia and memory loss. The relationships among LTBZD prescription, overall functioning, and cognitive functioning in PSD patients were investigated.[22] In individuals with psychotic spectrum disorders, cognitive impairments have a substantial influence on everyday functioning and general well-being. Multiple signs that long-term benzodiazepine usage harms cognition in several patient populations. To assess the effects of a decrease in benzodiazepine chronic usage on the projected dementia epidemic was examined.[23] A Monte Carlo technique centered on an illness-death model offered forecasts of many markers of dementia burden using estimates of dementia incidence, benzodiazepine usage, and national estimates of fatality and population growth. It examined the incidence of prescription long-term benzodiazepine use in the general population about sociodemographic and clinical variables. Information on the regularity of long-term benzodiazepine usage in the general population is scarce. The body of research on the connection between long-term benzodiazepine use and the risk of adult cognitive deterioration and was critically analyzed.[24] Even though they have negative side effects, benzodiazepines were utilized extensively for a very long time.

A strategy for fresh BZDR users to evaluate the prevalence of long-term benzodiazepine and related drug usage and variables related to the creation of long-term use was investigated.[25] Considering Cox proportional hazards models, LTBZDR usage is defined as repeatedly used for 180 variables related to long-term vs. short-term usage contrasted.[26] Individuals with schizophrenia who take benzodiazepines for short periods, long periods of time, or not at all are examined for potential changes in the impact on the disease's course features. The clinical course features of patients were additionally retrospectively monitored from the initial admittance date throughout the designated time to the conclusion of the period of monitoring. The reported cognitive function for executive function, intellect, attention, memory, and processing speed analyzed.[27] A large number of research found substantial impacts, indicating that TBI is linked to deficits in various cognitive areas. The explored rapid intoxication's relationship to clinical symptoms were examined.[28] The cognitive and on-road driving abilities of 31 long-term regular BZRA users and 19 long-term regular BZRA consumers having projected blood levels less than the therapeutic threshold was compared to individuals of 76 subjects. It determined the antagonistic neuropharmacological interactions between long-term benzodiazepine usage and the mechanism of action for antidepressants. The brain-age paradigm was increasingly relevant for examining diseases associated with aging and may forecast significant long-term health implications was examined.[29] The majority of brain-age studies employ functional neuroimaging to measure brain size.[30] Investigated the relationship between age, pre-morbid intelligence, and injury severity as determined by the length of post-traumatic amnesia in 109 people with complex mild-to-severe TBI. A competent control population of 63 people, 59 % were men, underwent the tests once. Participants with TBI fared considerably worse than the healthy control group at the first evaluation on every measure.

METHOD

Subjects

Data was collected from 152 well-educated elderly participants (average 15,8 years of education), categorized into long-term, short-term, and non-users of BZDs. Demographic information and medication history were recorded. Cognitive function was assessed using standardized tests, including the Trail TMT-B for executive function, verbal and visual memory tests, and the BVMT-R. The informed approval was signed by everyone involved in the research project. A high school diploma or higher and be at least 65 years old were requirements for membership. Contributors were disqualified if they accomplished the Diagnostic and Statistical Physical of Mental Illnesses, diagnostic standards for the fifth edition Schizophrenia Spectrum Conditions along with other Neurocognitive Disorders, and Psychotic Disorders, were depressed or anxious, were taking medications that impair cognition, such as cholinesterase inhibitors and memantine, which had additional conditions of impaired cognition, including head trauma, or had failed cognitive tests. The subjects had to be free of any additional conditions that may have affected cognitive function, thus following exclusion requirements were established to achieve that. 152 adults over the age of 65 were screened and enrolled in the research.

Procedure

Screening

Participants were assessed for signs of both tension and despair consuming the Self-Rating Anxiety Scale and Geriatric Depression Scale after giving their permission. BZD users are more prone to feel anxiety and despair. Anxiety and depressive disorders, on the other hand, have a major impact on the way people do cognitive tests,

which might skew the findings of the research. Subjects having balanced signs of sadness or anxiety, according to ratings scores of ≥ 25 on the GDS and a score of ≥ 30, were eliminated from the research to lessen the effect of anxiety and disorders of depression on cognitive outcomes. In-person interviews with participants who did not experience depressive or anxiety symptoms followed to gather clinical and demographic information, age, education, sex, weight, height, smoking habits and drinking, use of medications, and previous history of chronic illnesses. They measured the participants' sizes and measurements to determine their body mass indices. During checking using the exclusion standards, 152 people were still present. Table 1, the demographic and medical details of those involved.

Table 1. Individual participant demographics

Demographic Variable	Category	Comparison Group (n = 51)	Short-Term Using Group (n = 50)	Long-Term Using Group (n = 51)
Age Group (years)	65-69	14 (27,5 %)	12 (24,0 %)	12 (23,5 %)
	70-74	16 (31,4 %)	17 (34,0 %)	17 (33,3 %)
	75-79	13 (25,5 %)	12 (24,0 %)	15 (29,4 %)
	80+	8 (15,7 %)	9 (18,0 %)	7 (13,8 %)
Gender	Male	25 (49,0 %)	23 (46,0 %)	25 (49,0 %)
	Female	26 (51,0 %)	27 (54,0 %)	26 (51,0 %)
Education Level	High School or Below	9 (17,6 %)	10 (20,0 %)	11 (21,6 %)
	Undergraduate Degree	21 (41,2 %)	22 (44,0 %)	22 (43,1 %)
	Postgraduate Degree	21 (41,2 %)	18 (36,0 %)	18 (35,3 %)
Smoking Habits	Never Smoker	28 (54,9 %)	26 (52,0 %)	25 (49,0 %)
	Former Smoker	15 (29,4 %)	15 (30,0 %)	15 (29,4 %)
	Current Smoker	8 (15,7 %)	9 (18,0 %)	11 (21,6 %)
Drinking Habits	Non-Drinker	25 (49,0 %)	23 (46,0 %)	24 (47,1 %)
	Occasional Drinker	17 (33,3 %)	17 (34,0 %)	16 (31,4 %)
	Regular Drinker	9 (17,6 %)	10 (20,0 %)	11 (21,6 %)
Use of Medications	Antihypertensives	17 (35,3 %)	19 (38,0 %)	20 (39,2 %)
	Antidepressants	19 (17,6 %)	14 (28,0 %)	18 (35,3 %)*
	Diabetes Medications	15 (21,6 %)	17 (24,0 %)	13 (19,6 %)
Chronic Illness History	Hypertension	20 (39,2 %)	21 (42,0 %)	22 (43,1 %)
	Diabetes	12 (23,5 %)	13 (26,0 %)	13 (25,5 %)
	Cardiovascular Disease	7 (13,7 %)	7 (14,0 %)	8 (15,7 %)
	Chronic Pain	12 (21,6 %)	9 (26,0 %)	8(31,4 %)

Cognitive performance

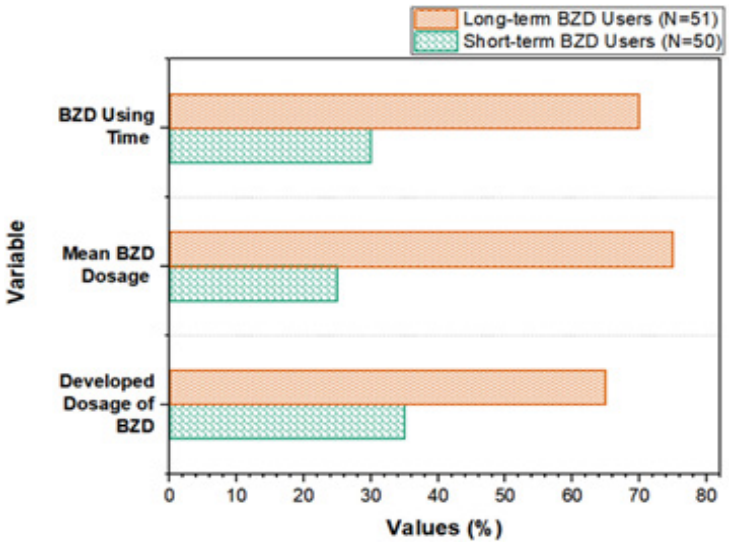

Figure 1. BZD utilizes participant information

Memory, focus, executive function, and verbal proficiency were the four different subsystems of cognition that made up the six tests that made up the cognitive function assessment procedure. A popular tool for assessing cognition is the Mini-Mental State Examination assessment. It encompasses the evaluation of several aspects of cognition. Patients suffering from dementia were not included in the assessment, which was designed to evaluate people's basic mental capacities. The Rey Auditory Verbal Learning Test is straightforward to perform and also provides a wide range of memory ratings. The verbal memory abilities of the individuals were assessed using this test. The Trail Making Task is the frequently utilized executive function detection test that aids in the earlier diagnosis of cognitive decline and dementia. The TMT-A evaluates interest and vasomotor computation speed, while the TMT-B measures these same traits along with memory capacity and visual-motor ability. The test's objective is to assess a subject's ability to produce words on demand in a constrained period. The test is cognizant of linguistic ability. The Digit Span Test is extensively utilized in geriatrics studies and is regularly utilized to assess short-term attentional capacity. Visual memory tests including the Brief Visuospatial Memory Test-Revised are frequently employed in a variety of clinical applications. Figure 1 shows the BZD utility information.

BZD controls and use groups

Anxiolytic, hypnotic and sedative, antiepileptic, and relaxant benzodiazepines were all included in this investigation. Additionally mentioned were hypnotic substances linked to or deriving from benzodiazepines. They converted every participant's total BZD dose and daily average BZD amount to comparable amounts of diazepam. Using their self-reported medication usage from their interviews and prescribing information from their electronic health record system. Three BZD usage categories was created by dividing people into three categories: LTBZD users, STBZD users, and nonusers depending on the BZD usage patterns described in the participants' medical records.

Data analysis

The ongoing demographic variables have been assessed using the ANOVA tests. Chi-square comparisons were executed to evaluate two BZD usage categories, the control group, and secret information demographic characteristics and chronic situations and heritage of illness. Three BZD usage categories were the focus of the statistical analyses on the demographic data, which sought to uncover possible confounders. Descriptive statistics were used to determine BZD consumption data. Analysis of covariance (ANCOVA) was used to compare cognitive task outcomes across the three BZD usage categories, with the BZD usage group being treated as a fixed factor and the demographic factors being taken into account. Additionally, utilizing participant data on BZD consumption duration and results from the cognitive tests, to test whether or not BZD usage duration is a predictor of memory efficiency, they conducted a bivariate and multivariate multiple linear regression evaluation, comparing those in the long-term in addition to STBZD usage categories. Age, gender, education level, and BMI were all incorporated as factors in the design. All tests of significance were performed at a 0,05 threshold of significance.

RESULTS

Demographic information is presented in table 1 in a descriptive manner, while use data for BZD is included in TMT-B results between groups table 2. There were a total of 152 participants: 57 females and 94 men. The normal age across all courses was 75,69 years, 18,84 years, while the normal number of years in school was 15,76 years, 5,19 years. The three categories were balanced in terms of age, gender, education level, smoking, alcohol use, also the heritage of chronic illnesses. In contrast, BMI among the categories was statistically interesting. In contrast to non-users as well as STBZD users, the BMI of the categories of hourly BZD consumers is substantially lower. The standard each day of BZD were 0,78 corresponding to diazepam, the median frequency of therapy was 659,79 days, and the median overall dosage among the 103 individuals was 523,13 corresponding to diazepam. The remainder of 82 individuals took BZD to treat insomnia, and 22 individuals used it to treat anxiety. The results of this ANCOVA, which used BMI as the covariant to examine differences in rational task accomplishment, are shown in table 3. The three categories proved substantial variations in TMT-B moments and TMT-B error performance, the results of any additional assessments. The time it takes for non-users for the TMT-B time was 197,28±62,65 s, which was much quicker than the times of short-term users (523,13±98,72 s) and LTBZD users (238,48±116,54 s). Regarding TMT-B mistakes, STBZD consumers has 1,90 ± 1,95 errors which was significantly more than either non-users or long-term users. Multiple linear regression analyses supported our hypothesis by demonstrating that extended BZD usage did not significantly affect performance on the AVLT, COWAT, TMT, MMSE, and DST cognitive tests. Longer BZD usage was positively connected with improved results on the BVMT-R N1 test. The BVMT-R N1 scores of BZD users continued a connection to BZD across the years when demographic factors were taken into account.

BZD Usage and Altered Cognitive Functions in Elderly Educated Persons

The three categories only demonstrated major variations in the TMT-B test's completion period and mistake rate in the ANCOVA finding for variations in cognitive tasks. Previous studies have demonstrated that, although both Timing and TMT-B errors may serve as indicators of their ability to make important decisions, TMT-B time has a better link with vision, and TMT-B mistake performance has a greater association with memory retention. A strong association between the BZD usage periods also the BVMT-R N1 score, which measures immediate visual memory, was found in the regression.

The findings suggest that executive function may be where the effect of BZD applies to the reasoning purpose of very well-educated older persons who are more likely to be seen, which includes working memory and visual motor function, and immediate visual recall performance.

Table 2. TMT-B results between groups Post-comparison

Group	TMT-B Errors	TMT-B Time (s)
Long-term BZD use group	0,5	275
Short-term BZD use group	2,0	310
Comparison group	0,5	290

Strengths and Limitations

It is to support clinical decision-making when giving BZD to older persons. Although BZDs' therapeutic effectiveness is generally accepted, there is significant worry about their possible deleterious effects on patients' cognitive abilities, particularly in elderly individuals. With the higher education sector being more accessible and BZD prescriptions becoming more common, it is anticipated that there will be a rise in the number of older persons who are well-educated and who use BZD. The particular strength and therapeutic significance of this research are provided by its forward-looking viewpoint. When examining the cognitive impact of BZD, this targeted the group of highly educated older persons and adjusted for several demographic and clinical variables. All other demographic data about the groups, except BMI, were closely matched. However, there are also a few limitations. Firstly, the cross-sectional, it has not been possible to conclusively determine the causative connection between BZD use and the way the impact of the drug on cognition changed over time. However, LTBZD and STBZD consumers were separated to examine the connection between the frequency of BZD use and its cognitive impacts. They failed to take sleep into account when analyzing the cognitive effects of BZD. The connection between sleep and cognitive function in older persons, according to prior studies while BZD is often used by seniors to treat insomnia. The quality of the individuals' sleep was not evaluated in this research.

As a result, the three groups' varied sleep quality may be to blame for the disparities in cognitive results. It is necessary to do further to rule out the impact of sleep. Additionally, certain other aspects of cognition in older persons, such as employment and regular physical activity, may have affected the findings. The usage of BZD and cognitive function were the subjects of the present investigation. In the background of those with advanced education, another negative impact of BZD usage, for example, addictive consequences, also need to be evaluated. Figure 2 shows the outcome of multiple linear regression.

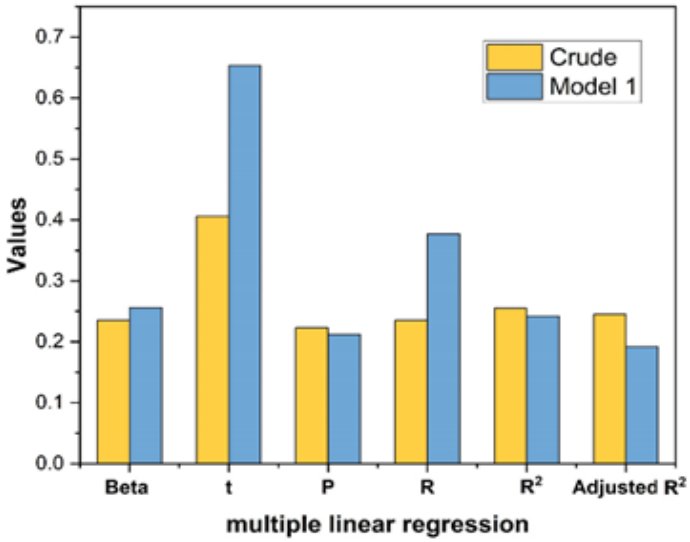

Figure 2. Analysis using regression for the elements affecting BVMT-R N1 scores in BZD users

BZD Using Time and the Cognition Decline in Highly Educated Older Adults

STBZD users demonstrated a substantial expansion of TMTB mistakes correlated to non-users and LTBZD users, demonstrating worse working memory performance. In addition, the absence of discernible variance among LTBZD users and non-users. Additionally, it was discovered that LTBZD users had much fewer TMT-B mistakes than STBZD users, and there was no discernible variance among LTBZD users and non-users. The three categories' BVMT-R scores did not vary significantly from one another, however, the significant relationship between the aggregate amount of BZD users' BVMT-R N1 scores and their cumulative use of the drug. The results imply that BZD's detrimental cognitive impacts did not worsen with continued use in older persons with high levels of education. LTBZD usage has been linked to physical dependency, and patients who become dependent on the drug might suffer cognitive impairment to a severe degree. To avoid serious cognitive impairment and to enhance a person's prognosis, it may be helpful to investigate the secure variables across the progression of cognitive deterioration in people with addiction. The findings of our research could open up a fresh window into how high levels of learning protect against BZD dependency. Although there are no follow-up data and this research is cross-sectional, it must be evaluated with care.

Table 3. Findings from an ANCOVA of variations in the performance on cognitive tests with BMI as a covariate

Test	Variable	Non-users	Short-term BZD users	Long-term BZD users	F-value	P-value
TMT	TMT A time	73,49 ± 51,85	91,08 ± 52,17	83,15 ± 57,77	0,62	0,542
	TMT A errors	0,62 ± 2,27	0,61 ± 0,99	0,64 ± 1,17	0,12	0,886
	TMT B time	187,28 ± 71,61	249,46 ± 94,53	227,48 ± 113,52	5,23	0,006*
	TMT B errors	0,64 ± 0,96	1,85 ± 1,86	0,87 ± 1,24	9,68	0,000*
AVLT	AVLT N1	3,98 ± 1,53	3,43 ± 1,80	3,51 ± 1,60	1,18	0,311
	AVLT N2	5,30 ± 1,60	5,11 ± 2,08	4,91 ± 1,91	0,49	0,612
	AVLT N3	6,40 ± 1,88	6,09 ± 2,50	5,77 ± 1,90	1,06	0,349
	AVLT N4	4,94 ± 2,65	4,00 ± 2,55	4,11 ± 2,43	1,53	0,221
	AVLT N5	19,80 ± 5,33	18,96 ± 5,57	19,64 ± 3,91	0,17	0,841
MMSE	Total scores	27,48 ± 2,64	25,90 ± 4,79	27,30 ± 2,60	1,71	0,186

DISCUSSION

Compared cognitive execution of tasks for LTBZD users, STBZD users, and non-users to examine the connection between the usage of BZD and the cognitive abilities of well-educated older persons. The two BZD usage categories in our investigation, and the control category, whose genders had been matched. Education level, age, smoking, and alcohol consumption, as well as other demographic factors. BZD user categories had the smallest BMI ratings among the three groups, however, there existed a considerable variation between them. Demographic data from participants in prior examination on BZD usage are congruent with the findings. The demographic data were discordant when compared to those from prior research on BZD usage and cognitive performance. For instance, in several earlier research, the BZD use group had a higher proportion of female participant's non-use category. In our investigation, there was no discernible variation in the gender shipping among the BZD use and non-use categories. The demographic characteristics of the total patient group may not fully reflect the modest sampling size of our investigation. The particular participant group in our research may be another reason for the discrepancy. In the smaller groupings of STBZD users, LTBZD, and non-users, the number of highly educated people may take a comparable gender ratio overall. Therefore, the need for high academic achievement in choosing samples decreased the disparity in demographic data across the BZD circumstance categories.

CONCLUSIONS

The investigation of how BZD use affected cognitive function in older adults with advanced degrees and obtained useful clinical findings. According to the findings, STBZD use in older adults with high levels of education is significantly linked to inferior executive function, but not to general cognition or other cognitive abilities like verbal memory, Fluency in a language, attention, or visual memory. Furthermore, the length of BZD usage had no influence on the BZD effect on cognition in highly educated older people. The outcomes of this research may help advance the conversation on the safety of BZD usage among older individuals and provide direction for clinical practice in the coming years.

BIBLIOGRAPHIC REFERENCES

1. Bagarinao E, Watanabe H, Maesawa S, Mori D, Hara K, Kawabata K, Yoneyama N, Ohdake R, Imai K, Masuda M, Yokoi T. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. Scientific reports. 2019 Aug 6;9(1):11352. https://doi.org/10.1038/s41598-019-47922-x

2. Spreng RN, Turner GR. From exploration to exploitation: A shifting mental mode in late life development. Trends in Cognitive Sciences. 2021 Dec 1;25(12):1058-71. https://doi.org/10.1016/j.tics.2021.09.001

3. Valkenborghs SR, Noetel M, Hillman CH, Nilsson M, Smith JJ, Ortega FB, Lubans DR. The impact of physical activity on brain structure and function in youth: a systematic review. Pediatrics. 2019 Oct 1;144(4). https://doi.org/10.1542/peds.2018-4032

4. Jung ME, Metzger DB, Hall J. The long-term but not short-term use of benzodiazepine impairs motoric function and upregulates amyloid ß in part through the suppression of translocator protein. Pharmacology Biochemistry and Behavior. 2020 Apr 1;191:172873. https://doi.org/10.1016/j.pbb.2020.172873

5. Mancuso P, Bouchard B. The impact of aging on adipose function and adipokine synthesis. Frontiers in endocrinology. 2019 Mar 11;10:137. https://doi.org/10.3389/fendo.2019.00137

6. Lopez-Soley E, Solana E, Martínez-Heras E, Andorra M, Radua J, Prats-Uribe A, Montejo C, Sola-Valls N, Sepulveda M, Pulido-Valdeolivas I, Blanco Y. Impact of cognitive reserve and structural connectivity on cognitive performance in multiple sclerosis. Frontiers in neurology. 2020 Oct 30;11:581700. https://doi.org/10.3389/fneur.2020.581700

7. Salmanzadeh H, Ahmadi-Soleimani SM, Pachenari N, Azadi M, Halliwell RF, Rubino T, Azizi H. Adolescent drug exposure: A review of evidence for the development of persistent changes in brain function. Brain research bulletin. 2020 Mar 1;156:105-17. https://doi.org/10.1016/j.brainresbull.2020.01.007

8. Kontic MZ, Dragic M, Martinovic J, Mihajlovic K, Brkic Z, Mitrovic N, Grkovic I. Prolonged Alprazolam Treatment Alters Components of Glutamatergic Neurotransmission in the Hippocampus of Male Wistar Rats—The Neuroadaptive Changes following Long-Term Benzodiazepine (Mis) Use. Pharmaceuticals. 2023 Feb 21;16(3):331. https://doi.org/10.3390/ph16030331

9. DeKosky ST, Williamson JB. The long and the short of benzodiazepines and sleep medications: short-term benefits, long-term harms?. Neurotherapeutics. 2020 Jan;17(1):153-5. https://doi.org/10.1007/s13311-019-00827-z

10. Mora F. Successful brain aging: plasticity, environmental enrichment, and lifestyle. Dialogues in clinical neuroscience. 2013 Mar 31;15(1):45-52. https://doi.org/10.31887/DCNS.2013.15.1/fmora

11. Carton L, Auger F, Laloux C, Durieux N, Kyheng M, Potey C, Bergeron S, Rolland B, Deguil J, Bordet R. Effects of acute ethanol and/or diazepam exposure on immediate and delayed hippocampal metabolite levels in rats anesthetized with isoflurane. Fundamental & Clinical Pharmacology. 2022 Aug;36(4):687-98. https://doi.org/10.1111/fcp.12764

12. Tseng LY, Huang ST, Peng LN, Chen LK, Hsiao FY. Benzodiazepines, z-hypnotics, and risk of dementia: special considerations of half-lives and concomitant use. Neurotherapeutics. 2020 Jan 1;17(1):156-64. https://doi.org/10.1007/s13311-019-00801-9

13. Schuster JP, Hoertel N, von Gunten A, Seigneurie AS, Limosin F, Csa Study group. Benzodiazepine use among older adults with schizophrenia spectrum disorder: prevalence and associated factors in a multicenter study. International psychogeriatrics. 2020 Apr;32(4):441-51. doi:10.1017/S1041610219000358

14. Chapoutot M, Peter-Derex L, Bastuji H, Leslie W, Schoendorff B, Heinzer R, Siclari F, Nicolas A, Lemoine P, Higgins S, Bourgeois A. Cognitive behavioral therapy and acceptance and commitment therapy for the discontinuation of long-term benzodiazepine use in insomnia and anxiety disorders. International journal of environmental research and public health. 2021 Sep 28;18(19):10222. https://doi.org/10.3390/ijerph181910222

15. Lim B, Sproule BA, Zahra Z, Sunderji N, Kennedy SH, Rizvi SJ. Understanding the effects of chronic

benzodiazepine use in depression: a focus on neuropharmacology. International clinical psychopharmacology. 2020 Sep 1;35(5):243-53. DOI: 10.1097/YIC.0000000000000316

16. LeBlanc J, Seresova A, Laberge-Poirier A, Tabet S, Correa JA, Alturki AY, Feyz M, de Guise E. Cognitive-communication skills and acute outcome following mild traumatic brain injury. Brain Injury. 2020 Sep 18;34(11):1472-9. https://doi.org/10.1080/02699052.2020.1802669

17. Park DC, Bischof GN. The aging mind: neuroplasticity in response to cognitive training. Dialogues in clinical neuroscience. 2013 Mar 31;15(1):109-19. https://doi.org/10.31887/DCNS.2013.15.1/dpark

18. Torres-Bondia F, De Batlle J, Galván L, Buti M, Barbé F, Piñol-Ripoll G. Trends in the consumption rates of benzodiazepines and benzodiazepine-related drugs in the health region of Lleida from 2002 to 2015. BMC Public Health. 2020 Dec;20:1-9. https://doi.org/10.1186/s12889-020-08984-z

19. Beunders AJ, Kemp T, Korten NC, Oudega ML, Beekman AT, Kupka RW, Stek ML, Schouws SN, Dols A. Cognitive performance in older-age bipolar disorder: investigating psychiatric characteristics, cardiovascular burden and psychotropic medication. Acta Psychiatrica Scandinavica. 2021 Oct;144(4):392-406. https://doi.org/10.1111/acps.13342

20. de Mendonça FM, de Mendonça GP, Souza LC, Galvão LP, Paiva HS, de Azevedo Marques Périco C, Torales J, Ventriglio A, MaurícioCastaldelli-Maia J, Sousa Martins Silva A. Benzodiazepines and sleep architecture: a systematic review. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2023 Feb 1;22(2):172-9.

21. Ferreira P, Ferreira AR, Barreto B, Fernandes L. Is there a link between the use of benzodiazepines and related drugs and dementia? A systematic review of reviews. European Geriatric Medicine. 2022 Feb;13(1):19-32. https://doi.org/10.1007/s41999-021-00553-w

22. Savić B, Jerotić S, Ristić I, Zebić M, Jovanović N, Russo M, Marić NP. Long-Term Benzodiazepine Prescription During Maintenance Therapy of Individuals With Psychosis Spectrum Disorders—Associations With Cognition and Global Functioning. Clinical neuropharmacology. 2021 May 1;44(3):89-93. DOI: 10.1097/WNF.0000000000000442

23. Jacqmin-Gadda H, Guillet F, Mathieu C, Helmer C, Pariente A, Joly P. Impact of benzodiazepine consumption reduction on future burden of dementia. Scientific Reports. 2020 Sep 4;10(1):14666. https://doi.org/10.1038/s41598-020-71482-0

24. Nader D, Gowing L. Is long-term benzodiazepine use a risk factor for cognitive decline? Results of a systematic review. Journal of addiction. 2020;2020(1):1569456. https://doi.org/10.1155/2020/1569456

25. Taipale H, Särkilä H, Tanskanen A, Kurko T, Taiminen T, Tiihonen J, Sund R, Tuulio-Henriksson A, Saastamoinen L, Hietala J. Incidence of and characteristics associated with long-term benzodiazepine use in Finland. JAMA network open. 2020 Oct 1;3(10):e2019029-. doi:10.1001/jamanetworkopen.2020.19029

26. Ekinci O, Ekinci A. Short-term, but not long-term, beneficial effects of concomitant benzodiazepine use on clinical course in patients with schizophrenia. International Clinical Psychopharmacology. 2022 Jul 1;37(4):143-50. DOI: 10.1097/YIC.0000000000000392

27. Kohler MJ, Hendrickx MD, Powell-Jones A, Bryan-Hancock C. A systematic review of cognitive functioning after traumatic brain injury in individuals aged 10–30 years. Cognitive and behavioral neurology. 2020 Dec 1;33(4):233-52. DOI: 10.1097/WNN.0000000000000236

28. Vinckenbosch FR, Vermeeren A, Vuurman EF, van der Sluiszen NN, Verster JC, van de Loo AJ, van Dijken JH, Veldstra JL, Brookhuis KA, De Waard D, Ramaekers JG. An explorative approach to understanding individual differences in driving performance and neurocognition in long-term benzodiazepine users. Human Psychopharmacology: Clinical and Experimental. 2021 Jul;36(4):e2778. https://doi.org/10.1002/hup.2778

29. Cole JH. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiology of aging. 2020 Aug 1;92:34-42. https://doi.org/10.1016/j.neurobiolaging.2020.03.014

30. Fraser EE, Downing MG, Biernacki K, McKenzie DP, Ponsford JL. Cognitive reserve and age predict cognitive recovery after mild to severe traumatic brain injury. Journal of neurotrauma. 2019 Oct 1;36(19):2753-61. https://doi.org/10.1089/neu.2019.6430

FINANCING

None.

CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

Conceptualization: Prabavathy S, Salahuddin, Takveer Singh, Nyalam Ramu, Srimant Pattnaik, Lovish Dhingra.

Data curation: Prabavathy S, Salahuddin, Takveer Singh, Nyalam Ramu, Srimant Pattnaik, Lovish Dhingra.

Formal analysis: Prabavathy S, Salahuddin, Takveer Singh, Nyalam Ramu, Srimant Pattnaik, Lovish Dhingra.

Drafting - original draft: Prabavathy S, Salahuddin, Takveer Singh, Nyalam Ramu, Srimant Pattnaik, Lovish Dhingra.

Writing - proofreading and editing: Prabavathy S, Salahuddin, Takveer Singh, Nyalam Ramu, Srimant Pattnaik, Lovish Dhingra.