European Addiction Research

Brief Report

Eur Addict Res 2022;28:377–381
DOI: 10.1159/000525988

Received: February 15, 2022
Accepted: June 30, 2022
Published online: August 30, 2022

Cognitive Functioning in Long-Term Benzodiazepine Users

Shirley P.G. Zetsen[a, b] Arnt F.A. Schellekens[c, d, e] Erik P. Paling[c, f]
Cornelis C. Kan[c, g] Roy P.C. Kessels[d, h, i, j]

[a]School of Psychology, Radboud University, Nijmegen, The Netherlands; [b]Dimence Mental Health, Deventer, The Netherlands; [c]Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands; [d]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands; [e]Nijmegen Institute for Scientist Practitioners in Addiction, Nijmegen, The Netherlands; [f]Brijder Addiction Care, Alphen Aan den Rijn, The Netherlands; [g]MoleMann, Mental Health, Leeuwarden, The Netherlands; [h]Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands; [i]Tactus Addiction Care, Deventer, The Netherlands; [j]Department of Medical Psychology, Radboud University Medical Center, Nijmegen, The Netherlands

Keywords
Neuropsychological assessment · Benzodiazepine use · Cognition · Substance use disorder

Abstract
Background: Benzodiazepines are widely used in the treatment of anxiety disorders and sleep disturbances, but negative cognitive side effects have been reported after long-term use. Studies on the cognitive effects of long-term benzodiazepine use to date have typically included small samples and limited cognitive assessments. ***Objectives:*** This study examined cognitive performance on four cognitive domains in long-term benzodiazepine users, compared to normative data. Furthermore, it was examined whether sex, age, benzodiazepine dose, and state and trait anxiety moderated cognitive functioning in long-term benzodiazepine users. ***Methods:*** Neuropsychological tests targeting different cognitive domains were administered to 92 patients with long-term benzodiazepine use who were accepted for enrolment into a benzodiazepine discontinuation programme in an academic hospital. Test scores were compared to a large normative data sample. ***Results:*** Of the long-term benzodiazepine users, 20.7% could be classified as cognitively impaired across all domains, with the largest effects found in the domains processing speed and sustained attention, and an overall worse performance in women, an effect which appears to be moderated by state anxiety. No effects of age or benzodiazepine dose were found. ***Conclusions:*** These results extend those of earlier studies on benzodiazepine effects on specific cognitive domains. This study implies an overall detrimental cognitive effect in long-term benzodiazepine users rather than specific effects. Therefore, long-term benzodiazepine use should be avoided, and once present, tailored interventions aimed at tapering benzodiazepines are warranted.

Introduction

Benzodiazepines are the most frequently used drugs worldwide and are primarily used for their anxiolytic and sedative properties. For instance, in 2015–2016, 12.6% of adults in the USA reported having used benzodiazepines in the past year [1]. Despite the benefits of benzodiazepines on the short term, using benzodiazepines for longer periods may lead to significant negative side effects. These include the risk of dependency and adverse effects such as cognitive impairment.

Correspondence to:
Roy P.C. Kessels, roy.kessels@donders.ru.nl

Meta-analyses showed impaired performances in all cognitive domains in long-term benzodiazepine users. The largest effect sizes were found in sensory processing, psychomotor speed, episodic memory, executive function, and visuospatial abilities; smaller effect sizes have been reported in verbal reasoning, working memory, and motor control [2, 3]. However, sample sizes of included studies are small (with a reported mean sample size of 33.5 [2] and 29.4 [3], respectively), and studies in larger samples were either limited to older adults with a mean age of 79.6 (n = 331 benzodiazepine users in [4]) or included cognitive assessments limited to one domain (n = 113 in [5]).

The aim of the current study was to further our understanding of impaired cognitive functioning in patients with long-term benzodiazepine use. A relatively large sample size, an above-average number of measured cognitive domains, a high mean dose of diazepam equivalence, and the application of high-quality normative data characterize our study. We expect cognitive impairments to be present across all domains. In addition, we hypothesize a dose-response relationship as tolerance to sedative effects during chronic benzodiazepine use may lead to an increase in the amount or frequency of dose, which, in turn, may further exacerbate the cognitive side effects.

Materials and Methods

We used data from a larger study on the efficacy of a protocolled benzodiazepine discontinuation programme [6]. Participants were patients at the department of Psychiatry at the Radboud University Medical Center in Nijmegen, the Netherlands, who had used benzodiazepines for at least 3 months. Patients using benzodiazepines for a period of 3 months or longer were contacted through their psychiatrist and informed about disadvantages of prolonged use of benzodiazepines and the possibility to participate in a protocolled discontinuation programme. Patients using non-benzodiazepines (Z-drugs) were also eligible.

All data were collected as part of routine clinical assessments after participants were accepted into the discontinuation programme but had not yet began with their taper and were stored in an in-house clinical database in a pseudonymous manner, compliant with the EU Data Protection Directive 95/46/EC, and written informed consent was obtained from all patients. Data extraction from that database for this study was done in compliance with the EU General Data Protection Regulation 2016/679, resulting in a fully anonymous database for further analysis.

Sociodemographic information of the patients and data on benzodiazepine dosage and use were collected through conducting file reviews, telephone survey, and consultation of the medicine prescriptions at the general practitioner or pharmacy. Prior to the telephone survey, all participants received a letter with information on the study and a declaration of consent concerning insight in medicine prescriptions.

Table 1. Background variables of the total sample and the scores on the Bendep SRQ and STAI (mean, standard deviation [SD] unless otherwise noted)

	Mean	SD
Age	48.4	13.2
Sex (m:w)[1]	41:51	
Education level[2]	4	1–7
NART IQ	97.3	16.1
Benzodiazepine dose[3]	43.4	55.3
Benzodiazepines,[4] *n*	1	1–5
Type of benzodiazepine,[5] *n*		
Short acting	55	
Short/intermediate acting	4	
Intermediate acting	2	
Long acting	8	
Mixture	21	
Unknown	2	
Bendep SRQ[6]		
Problematic use	3.72	1.29
Preoccupation	3.92	1.23
Lack of compliance	1.79	1.71
Withdrawal	3.75	1.31
STAI		
State anxiety	45.9	13.0
Trait anxiety	57.0	12.0

[1] Number of men (m) and women (w). [2] Mode (range); assessed using 7 categories according to the Dutch educational system (1 = less than primary school, 7 = academic degree); NART IQ, estimated verbal intelligence quotient assessed using the National Adult Reading Test. [3] Expressed as diazepam equivalent (mg). [4] Median (range). [5] Based on the classification of the European Monitoring Centre for Drugs and Drug Addiction (www.emcdda.europa.eu/publications/drug-profiles/benzodiazepines_en). Bendep SRQ, benzodiazepine dependence self-report questionnaire; STAI, state-trait anxiety inventory. [6] Compared to the reference group of outpatient benzodiazepine users reported in [7], our sample scored significantly higher on all Bendep SPQ subscales (all p values <0.001).

Severity of benzodiazepine dependence was measured with the Benzodiazepine Dependence Self-Report Questionnaire (Bendep SRQ) [7]. State and trait anxiety were measured with Spielberger's State-Trait Anxiety Inventory (STAI) [8]. In addition, a set of widely-used and validated neuropsychological tests were administered. Premorbid intelligence was estimated using the Dutch version of the National Adult Reading Test (NART). Psychomotor speed was measured with the Trial Making Test (TMT) part A (total time), the Stroop Colour-Word Test (parts I and II, completion time), and the Substitution subtest from the Wechsler Adult Intelligence Scale (number of items correct). In order to measure episodic memory, the Rey Auditory Verbal Learning Test (AVLT) was administered (immediate and delayed recall). Executive function was measured with the Stroop Colour-Word Test part III (completion time, measuring response inhibition) and the TMT

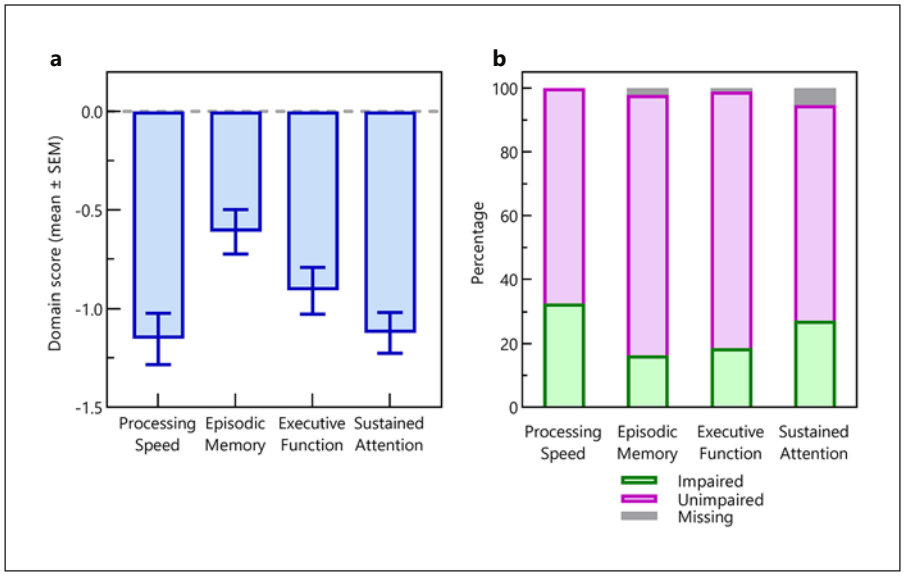

Fig. 1. a Mean standardized age- and education-adjusted domain scores (± standard error of the mean) for processing speed, episodic memory, executive function, and sustained attention, with the dashed line representing the normative mean; lower than average scores reflect a worse cognitive performance. **b** Percentage of cognitively impaired and unimpaired individuals for each cognitive domain (classified as having a performance more than 1.5 standard deviation below the age-, sex-, and/or education-adjusted normative mean). The grey shaded areas indicate the percentage of missing values.

part B (completion time, assessing mental flexibility). Sustained attention was measured with the Bourdon-Wiersma dot cancellation task (total time and number of misses) (see [9] for a more detailed description of these tests).

The neuropsychological observed test results of each participant were compared with extensive regression-based Dutch normative data (www.andinorms.nl [10]) that allow for fine-grained age, education, and/or sex-adjustment at an individual level to compute the individual's expected score. The difference between the observed and expected score results in an individual *z*-score, which indicates the extent of the cognitive impairment (compared to the control mean of 0). *Z*-scores were averaged for tests within the same cognitive domain as well as into an overall cognition compound score, which were statistically analysed using one-sample *t* tests (reference value: normative mean = 0). In case of missing data, available tests were used to calculate domain scores, and Little's MCAR test was performed to examine whether missing data were completely random. Furthermore, the percentage of "impaired" *z*-scores (more than 1.5 SD below the age/education-adjusted normative mean) was calculated for each cognitive domain score, as well as for the cognitive compound score. Next, a blockwise multiple linear regression analysis (enter method) was performed with sex, age, and dose of benzodiazepine as predictors in block 1, STAI state and trait anxiety in block 2, and the cognitive compound score as an outcome measure. All analyses were performed using the Statistical Package for the Social Sciences (SPSS 27, IBM), and α was set at 0.05 throughout.

Results

In total, 92 patients (41 men, 51 women; ages between 25 and 78) who took part in the benzodiazepine discontinuation programme completed a neuropsychological assessment. Patients were on average 48.4 years old (SD = 13.2) and used on average 43.4 mg diazepam equivalent benzodiazepine doses (SD = 55.3). See Table 1 for demographics of the patients and their Bendep SRQ and STAI scores and [6] for a more extensive description of the sample's psychopathology (in short, most participants met the DSM-IV-TR criteria for anxiety disorders (n = 47), mood disorders (n = 37), or sleep disorders (n = 11). In addition, 22 participants also misused other psychoactive substances (n = 8 alcohol, n = 7 cannabis, n = 1 cocaine, n = 2 methadone). Figure 1 shows the cognitive domain scores for each domain and the number of impaired individuals per domain. Little's MCAR test showed that the missing data (between 0 and 5.4% for the individual domains) were missing at random ($\chi^2(4) = 2.144$, $p = 0.709$).

Across all domains, 20.7% of the participants (n = 19) could be classified as cognitively impaired, with an overall cognitive compound score of −0.96 ($t(91) = 9.95$, $p < 0.0005$, 95% CI: [−1.16, −0.77]). Participants performed significantly worse on all domains compared to age-, education-, and/or sex-adjusted norms (all t values >5.4, p values <0.0005), with the largest effect sizes and most frequent impairments for the domains processing speed (32.6%) and sustained attention (27.2%) compared to episodic memory (18.5%) and executive function (23.9%). The multiple regression model explained a significant amount of variance of overall cognitive performance ($F(3,88) = 2.8$, $p < 0.05$, $R^2 = 0.088$). Sex was a significant predictor of cognitive performance (β = −0.226, $t(88)$ =

2.21, $p < 0.05$), with women having a 0.42 lower cognitive compound score than men ($B = -0.42$; 95% CI: [−0.798, −0.044]). Age (β = 0.043) and benzodiazepine dose (β = −0.168) did not significantly predict cognitive performance. Adding state and trait anxiety to the model resulted in a highly significant change in explained variance ($F(2,86) = 10.32$, $p < 0.001$, $R^2 = 0.265$), with state anxiety predicting cognitive performance (β = −0.419, $t(86) = 3.75$, $p < 0.001$) but not trait anxiety (β = −0.025). In this model, sex was no longer a significant predictor (β = −0.141).

Discussion

In this study, we showed that a large number of long-term benzodiazepine users have impaired performances on neuropsychological tests assessing processing speed, episodic memory, executive function, and sustained attention. Sex was a strong predictor of cognitive performance, with a worse performance in women, but this effect disappeared when state anxiety was entered into the model. We did not find any effects of age or benzodiazepine dose on cognitive performance in our sample of long-term benzodiazepine users.

These findings corroborate and extend previous studies that have examined the effects of long-term benzodiazepine use [2, 3]. Compared to previous studies, the current study sample consisted of individuals with an average education level and intelligence, which is higher than in most previous studies. However, our sample is highly representative for long-term benzodiazepine users seeking treatment in the Netherlands. Furthermore, compared to most other studies, ours had a relatively large sample size ($n = 92$). While studies in larger samples exist, they focused either only on older adults or used smaller test batteries than ours [2, 3].

Our observational cross-sectional study design does not make it possible to examine the underlying mechanisms of cognitive impairment in benzodiazepine users in detail. One possible mechanism is that samples with benzodiazepine users report high levels of anxiety and anxiety in itself can be associated with cognitive decrements [11]. This is also supported by our results showing that state – but not trait – anxiety was a significant predictor of cognitive performance. However, it should be stressed that our regression model that includes state anxiety still only explains 26.5% of the variance, indicating that anxiety alone cannot fully explain the observed cognitive impairments in our patient sample. Other factors, such as sleep disorders, mood disorders, or other psychiatric comorbidity, including misuse of other psychoactive substances, may also be relevant to take into account more systematically in future studies, which ideally should include a control group of individuals with anxiety disorders not receiving treatment with benzodiazepines. Also, although all participants used benzodiazepines for more than 3 months and met the criteria for benzodiazepine dependence, with its severity quantified using the Bendep, we do not have data on the exact duration of the benzodiazepine use. Also, analyses on the type of benzodiazepine used (e.g., short vs. longer-acting ones) would require larger samples. These are limitations, as the extent of the cognitive impairment may be moderated by the duration of use or benzodiazepine type.

To our knowledge, our result that women using long-term benzodiazepine may be more vulnerable for cognitive decline is a novel finding. As down-regulation of GABA interneurons plays an important role in the mechanism of impaired cognition, sex hormones may module the effect of GABA levels on cognitive decline [12]. However, state anxiety appeared to explain the effect of sex on cognitive performance, even though there were no significant differences in state or trait anxiety scores between men and women. Since the discipline of how sex differences may influence brain function is still in its infancy, possible moderation effects of sex on cognitive outcomes need to be examined in future studies using larger samples.

A meta-analysis showed partial recovery of cognitive function after a follow-up of up to 10 month of abstinence [3]. It remains unclear whether and, if so, when full recovery occurs after withdrawal, especially after prolonged abstinence. Furthermore, although our neuropsychological test battery covered the main cognitive domains, even more extensive assessments may provide further insights into the profile of cognitive impairment. For instance, a recent meta-analysis argued that benzodiazepines may also impair social cognition [13], a domain we did not measure in the present study. Thus, the long-term use of benzodiazepines itself is likely to underlie the observed cognitive impairments, but longitudinal studies with other patient control groups are needed to provide more conclusive evidence about mechanism and course after abstinence. Finally, the current sample was motivated to participate in a benzodiazepine discontinuation programme and may have been more aware of cognitive deficits as a negative consequence that individuals who are not motivated to discontinue use, which may have introduced selection bias.

In conclusion, this study shows that long-term benzodiazepine use is associated with cognitive impairment across the domains of processing speed, sustained attention, executive function, and episodic memory, reflecting a widespread profile of cognitive dysfunction rather than selective deficits. These findings have clinical relevance, as cognitive impairment may interfere with the psychiatric treatment, but cognitive impairments in substance use disorders often remain unnoticed. Therefore, it is relevant to prevent long-term benzodiazepine use, monitor cognitive functioning in long-term benzodiazepine users, motivate them for tapering, and follow-up on cognitive functioning after tapering.

Acknowledgments

We thank Jeanneke Sengers, Bram Slagter, and Mathilde Caspers for their assistance in the data collection and preprocessing of the data.

Statement of Ethics

All data were collected as part of routine clinical assessments between 1997 and 2001 and were stored in an in-house clinical database in a pseudonymous manner, compliant with the then-current EU Data Protection Directive 95/46/EC, and written informed consent was obtained in all patients. Data extraction from that database for this study was done in compliance with the EU General Data Protection Regulation 2016/679, resulting in a fully anonymous database for further analysis. Sociodemographic information of the patients and data on benzodiazepine dosage and use were collected through conducting file reviews, telephone survey, and consultation of the medicine prescription at the general practitioner or pharmacy. Since all assessments were noninvasive and no treatment exposure or following rules of behaviour was required for study participation, this study was exempt from formal ethics review. Prior to the telephone survey, all participants received a letter with information on the study and a declaration of consent concerning insight in medicine prescriptions.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding for the current study.

Author Contributions

Shirley P.G. Zetsen and Roy P.C. Kessels analysed the data and wrote the first draft of the manuscript. Arnt F.A. Schellekens and Erik P. Paling supervised the data analysis and revised the final manuscript. Cornelis C. Kan initiated the study, supervised the data collection, and revised the final manuscript. Roy P.C. Kessels created the figure and revised and uploaded the definitive manuscript.

Data Availability Statement

All data are available from the corresponding author upon request, as the informed consent forms completed by all participants did not ask for permission to share the data via a data repository. Further enquiries can be directed to the corresponding author.

References

1 Maust DT, Lin LA, Blow FC. Benzodiazepine use and misuse among adults in the United States. Psychiatr Serv. 2019;70(2):97–106.
2 Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs. 2004;18(1):37–48.
3 Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. Arch Clin Neuropsychol. 2018;33(7):901–11.
4 Helmes E, Østbye T. Associations between benzodiazepine use and neuropsychological test scores in older adults. Can J Aging. 2015;34(2): 207–214. https: //doi.org/10.1017/S0714980815000082.
5 Rickels K, Lucki I, Schweizer E, García-España F, Case WG. Psychomotor performance of long-term benzodiazepine users before, during, and after benzodiazepine discontinuation. J Clin Psychopharmacol. 1999;19(2):107–113. https://doi.org/10.1097/00004714-199904000-00003.
6 Kan CC, Mickers FC, Barnhoorn D. [Short- and long-term results of a systematic benzodiazepine discontinuation programme for psychiatric patients]. Tijdschr Psychiatrie. 2006;48(9):683–93.
7 Kan CC, Breteler MH, van der Ven AH, Zitman FG. Cross-validation of the benzodiazepine dependence self-report questionnaire in outpatient benzodiazepine users. Compr Psychiatry. 2001;42(5):433–9.
8 Gaudry E, Vagg P, Spielberger CD. Validation of the state-trait distinction in anxiety research. Multivariate Behav Res. 1975;10(3):331–41.
9 Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York: Oxford University Press; 2012.
10 de Vent NR, Agelink van Rentergem JA, Schmand BA, Murre JM; ANDI Consortium, Huizenga HM. Advanced neuropsychological diagnostics infrastructure (ANDI): a normative database created from control datasets. Front Psychol. 2016;7:1601.
11 Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lönnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord. 2008;106(1–2):1–27.
12 Jiménez-Balado J, Eich TS. GABAergic dysfunction, neural network hyperactivity and memory impairments in human aging and Alzheimer's disease. Semin Cell Dev Biol. 2021;116:146–59.
13 Haime Z, Watson AJ, Crellin N, Marston L, Joyce E, Moncrieff J. A systematic review of the effects of psychiatric medications on social cognition. BMC Psychiatry. 2021;21(1):597.