JAMH Session 17 August 2023 GV Health ECHO Hub

Benzodiazepines

Do They Cause Cognitive Impairment?

Ravi Bhat

The Varieties Of Cognitive Impairment

- Cognitive impairment
- Subjective Cognitive Decline (SCD)
- Cognitive Impairment Not Dementia (CIND)
- Mild Cognitive Impairment (MCI)
- Dementia

Cognitive Impairment

- The World Health Organisation's International Classification of Functioning, Disability and Health (ICF) is a framework for describing and organising information on functioning and disability. It talks of environmental that affect (i.e., either as facilitators or barriers) *functioning at different levels*:
 - At the level of the body (body functions and structures)
 - At the level of the individual (activities)
 - As a member of society (participation)
- Impairments are problems in body function or structure such as significant deviation or loss.
- Cognitive impairment refers to problems people have with cognitive functions such as thinking, reasoning, memory, or attention.

<u>https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health</u> For an excellent summary see: https://www.cdc.gov/nchs/data/icd/icfoverview_finalforwho10sept.pdf

Roy, E. (2013). Cognitive Impairment. In: Gellman, M.D., Turner, J.R. (eds) Encyclopedia of Behavioral Medicine. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-1005-9_1118

Subjective Cognitive Decline

- The Subjective Cognitive Decline Initiative (SCD-I) has proposed research criteria for pre-MCI SCD:
 - The presence of both 1 and 2, below, are required to meet the criteria:
 - 1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
 - 2. Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD.

Lautenschlager NL, Cox K, Hill KD, Pond D, Ellis KA, Dow B, Hosking D, Chong T, You E, Curran E, Cyarto E, Southam J, Anstey KJ. Physical Activity Guidelines for Older Australians with Mild Cognitive Impairment or Subjective Cognitive Decline. Melbourne: Dementia Collaborative Research Centres, 2018. ISBN: 978 0 7340 5416 6. Available at <u>http://www.dementia.unsw.edu.au/</u> and <u>https://medicine.unimelb.edu.au/</u> <u>data/assets/pdf_file/0008/2672846/PAG.pdf</u>

CIND and MCI

- CIND: refers to referring to cases in which there is an objectively defined cognitive impairment but insufficient evidence to warrant a dementia diagnosis.
- MCI: consensus statement of the International Working Group identifies core features as being:
 - No dementia
 - Subjective and/or objective evidence of cognitive decline beyond that expected for age and education level.
 - Objective impairment with scores on cognitive testing typically 1-1.5 standard deviations below the mean for age and education matched peers.
 - Functioning in Activities of Daily Living (ADLs) is preserved.
 - Functioning in more complex activities is preserved or only minimally impaired.

Tuokko H, Frerichs RJ. Cognitive impairment with no dementia (CIND): longitudinal studies, the findings, and the issues. Clin Neuropsychol. 2000 Nov;14(4):504-25. doi: 10.1076/clin.14.4.504.7200. PMID: 11262720.

https://medicine.unimelb.edu.au/__data/assets/pdf_file/0008/2672846/PAG.pdf

Dementia

- Global cognitive impairment with associated functional decline or more simply...
- Dementia is a general term for loss of memory, language, problemsolving and other thinking abilities that are severe enough to interfere with daily life.

Understanding Causation

• "Hill's criteria"

- 1. Strength of association
- 2. Consistency (association observed across multiple studies)
- 3. Specificity (exposure \rightarrow outcome)
- 4. Temporality (contrast reverse causation/protopathic bias)
- 5. Biological gradient (or dose-response)
- 6. Plausibility
- 7. Coherence
- 8. Experiment
- 9. Analogy

Benzodiazepines & Cognitive Impairment

- Benzodiazepines cause cognitive impairments.
- Benzodiazepines are associated with CIND and MCI.
- Benzodiazepines may be associated with dementia, but it is far from clear.
- And z-drugs cause cognitive impairments.

Acute Effects of Benzodiazepines on Cognition

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	13.0	28.6	66.7	84.2	92.9	75.0
Total number of tests	23	28	15	38	14	12

TABLE 1. Psychomotor performance after acute administration of alprazolam

Data are from references 10,17,22–25,54,60,72–74,78,89,92,105,114,116,120,133,137,147, 155,160, 167,187–189,206,211,228,230,233,240,250,261,263,273–274,283. Tests included reaction time tests, tapping, cancellation, tracking, DSST, symbol copying, CFFT, card sorting, vigilance, stroop, and balance tests. A detailed summary of study results can be obtained upon request from the authors.

TABLE 2. Memory functioning after acute administration of alprazolam

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	11.8	36.4	53.3	75.0	85.7	100.0
Total number of tests	17	22	15	24	7	2

Data from references 14,22,23,52,60,92,105,114,116,120,137,155,167,187,206,228,230,233,260, 263,273–274. Tests included immediate and delayed recall, recognition, digit span, arithmetics, Sternberg memory scanning, and story recall. A detailed summary of study results can be obtained upon request from the authors.

Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. CNS Drug Rev. 2004 Spring;10(1):45-76. doi: 10.1111/j.1527-3458.2004.tb00003.x. PMID: 14978513; PMCID: PMC6741717.

Effects of Long-term Use on Cognition

Table 7. Summary of Hedges' *g* values calculated in the current study for current users, previous users who have recently withdrawn, and previous users measured at follow up

Cognitive domain	Current users	Recent withdrawal	At follow up
Working Memory	-0.78 √	-0.47 🗸	-0.71 <mark>V</mark>
Processing Speed	-0.76 <mark>V</mark>	-0.61 🗸	−1.24 <mark>V</mark>
Divided Attention	-0.67 V	-0.72 🗸	-0.72 🗸
Visuoconstruction	-0.25 V	-0.63 🗸	-1.11 🗸
Sustained Attention	-0.22	-0.63 V	-0.34
Recent Memory	-0.18 V	-1.19 🗸	-1.40 ∨
Immediate Memory	-0.15	N/A	N/A
Expressive Language	-0.12 V	N/A	N/A
Executive Function	-0.10	-0.28	N/A
Perceptual Motor	-0.10	-1.35 🗸	N/A
Receptive Language	0.21 V	N/A	N/A
Visual Perception	N/A	-1.05 ∨	N/A

Adapted from: Crowe SF, Stranks EK. The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. Arch Clin Neuropsychol. 2018 Nov 1;33(7):901-911. doi: 10.1093/arclin/acx120. PMID: 29244060.

A little bit more...

- False recognition refers to the phenomenon of mistakenly claiming that one has been exposed previously to a novel item.
 - triazolam produced significant dose-related reductions in false recognition rates to non-studied words associatively related to studied words, suggesting that false recognition relies on normal memory mechanisms impaired in benzodiazepine-induced amnesia
- Long-term benzodiazepine use in older adults was associated with poorer neuropsychological test performance, especially in Immediate Memory and Attention.

Mintzer MZ, Griffiths RR. Acute effects of triazolam on false recognition. Mem Cognit. 2000 Dec;28(8):1357-65. doi: 10.3758/bf03211836. PMID: 11219963. Dyer AH, Laird E, Hoey L, Hughes CF, McNulty H, Ward M, Strain JJ, Molloy AM, Cunningham C, McCarroll K. Long-term anticholinergic, benzodiazepine and Z-drug use in community-dwelling older adults: What is the impact on cognitive and neuropsychological performance? Int J Geriatr Psychiatry. 2021 Nov;36(11):1767-1777. doi: 10.1002/gps.5598. Epub 2021 Jul 10. PMID: 34227695.

But...

 Co-administration of benzodiazepines with antidepressants in patients with depression and anxiety symptoms did not result in more cognitive impairment than those on antidepressants alone.

Duan Y, Wei J, Geng W, Jiang J, Zhao X, Li T, Jiang Y, Shi L, Cao J, Zhu G, Zhang K, Yu X. The effect of short-term use of benzodiazepines on cognitive function of major depressive disorder patients being treated with antidepressants. J Affect Disord. 2019 Sep 1;256:1-7. doi: 10.1016/j.jad.2019.05.059. Epub 2019 May 28. PMID: 31154087.

CIND and MCI

- Nafti et al, 2019:
 - Compared with nonusers, current use of benzodiazepines was associated with an increased risk of CIND (hazard ratio = 1.36; 95% CI = 1.08-1.72) in the simplest model.
 - Results remained similar in the fully adjusted model (hazard ratio = 1.32; 95% CI = 1.04-1.68).
 - There was no association between benzodiazepine use and the risk of dementia or AD.
 - All these effects were similar between men and women.
- Teverovsky et al, 2023:
 - Taking BZDs was significantly associated with higher risk of developing MCI, but not of developing dementia.

Nafti M, Sirois C, Kröger E, Carmichael PH, Laurin D. Is Benzodiazepine Use Associated With the Risk of Dementia and Cognitive Impairment-Not Dementia in Older Persons? The Canadian Study of Health and Aging. Ann Pharmacother. 2020 Mar;54(3):219-225. doi: 10.1177/1060028019882037. Epub 2019 Oct 9. PMID: 31595772. Teverovsky EG, Gildengers A, Ran X, Jacobsen E, Chang CH, Ganguli M. Benzodiazepine use and risk of incident MCI and dementia in a community sample. Int Psychogeriatr. 2023 May 26:1-7. doi: 10.1017/S1041610223000455. Epub ahead of print. PMID: 37231775.

Dementia

- Islam et al, 2016: 10 studies. Odds of dementia 78% higher in those who used benzodiazepines compared with those who did not use benzodiazepines (OR 1.78; 95% CI 1.33–2.38).
 - Unclear if causal.
- Penninkilampi & Eslick, 2018: 15 studies. Ever use of benzodiazepines was associated with a significantly increased risk of dementia [odds ratio (OR) 1.39, 95% confidence interval (CI) 1.21–1.59]. With lag time ≥5 years OR 1.30, 95% CI 1.14–1.48. May be associated with an increased risk of dementia.
 - Partly due to high heterogeineity.
 - Highest lifetime cumulative use of benzodiazepines was not associated with a higher risk of dementia than any use. In fact, two large studies reported a protective effect at the highest cumulative dose against Alzheimer's disease.
- Lucchetta et al 2018: 12 studies. benzodiazepines can be a risk factor for developing dementia (odds ratio 1.38, 95% confidence interval 1.07–1.77; I 2 = 98%; 95% prediction interval 0.58–3.25; very low certainty)
 - High heterogeneity.
 - No statistically significant association found studies that controlled for protopathic bias were assessed.
- Ferreira et al 2022: this systematic review of reviews found an association between the use of benzdiazepines and the development of dementia, particularly if longer half-life agents, extended use and earlier exposure are considered.

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. Eur Geriatr Med. 2022 Feb;13(1):19-32. doi: 10.1007/s41999-021-00553-w. Epub 2021 Aug 17. PMID: 34403113.

Islam MM, Iqbal U, Walther B, Atique S, Dubey NK, Nguyen PA, Poly TN, Masud JH, Li YJ, Shabbir SA. Benzodiazepine Use and Risk of Dementia in the Elderly Population: A Systematic Review and Meta-Analysis. Neuroepidemiology. 2016;47(3-4):181-191. doi: 10.1159/000454881. Epub 2016 Dec 24. PMID: 28013304.

Penninkilampi R, Eslick GD. A Systematic Review and Meta-Analysis of the Risk of Dementia Associated with Benzodiazepine Use, After Controlling for Protopathic Bias. CNS Drugs. 2018 Jun;32(6):485-497. doi: 10.1007/s40263-018-0535-3. PMID: 29926372.

Lucchetta RC, da Mata BPM, Mastroianni PC. Association between Development of Dementia and Use of Benzodiazepines: A Systematic Review and Meta-Analysis. Pharmacotherapy. 2018 Oct;38(10):1010-1020. doi: 10.1002/phar.2170. Epub 2018 Sep 6. PMID: 30098211.