Alzheimer's Drug Discovery Foundation

04/12/16
For Scientific Audiences

Benzodiazepine Evidence Summary

Did you know? Hypnotic benzodiazepines have been used as truth serums.

What is it? Benzodiazepines (e.g. Klonopin, Valium, Xanax, etc.), and the mechanistically related z-drugs (e.g. Ambien) are commonly prescribed for conditions such as insomnia, anxiety, and depression. They were discovered accidently in the 1950s by a Roche chemist in New Jersey who had a compound (Librium) left over from a previous experiment. He found it had unexpected sedative and anticonvulsant properties in animals, and benzodiazepines quickly became popular as a safer alternative to barbiturates. However, benzodiazepines have grown controversial due to their addictive potential, their potential association with cognitive decline, and their over-prescription, especially in elderly populations. In fact, they are included on the American Geriatrics Society's 2015 list of Potentially Inappropriate Medicines for Older Adults [1] because elderly people are more sensitive to effects of benzodiazepines and elderly patients on benzodiazepines might have a greater chance for falls or other adverse effects.

Benzodiazepines function primarily by binding to $GABA_A$ receptors, and they increase the activity of endogenous GABA (the brain's inhibitory neurotransmitter). This decreases the activity of the brain which is why they are commonly prescribed for their sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties. They can be roughly separated into three categories (short-acting, intermediate-acting, and long-acting) based on their half-life in the body. The z-drugs have a different chemical scaffold, but they bind to the same place on $GABA_A$ receptors and function in the same manner (though they have a half-life similar to short-acting benzodiazepines). Therefore, in this report (as in much of the literature) they will largely be grouped together unless otherwise stated.

Can decreasing benzodiazepine use provide neuroprotective benefits? *Short-term benzodiazepine use is probably not associated with long-term cognitive decline. Long-term benzodiazepine use might raise the risk of Alzheimer's disease/dementia, but the data is controversial.*

Human research to suggest decreasing benzodiazepine use can reduce the risk of dementia/Alzheimer's disease?

Types of evidence:

- One meta-analysis and one systematic review
- No randomized clinical trials (for long-term effects)
- Two recent observational studies

A 2015 meta-analysis [2] suggested benzodiazepine use is associated with an increased risk of dementia (risk ratio 1.49, 95% confidence interval [CI] 1.30-1.72). That risk of dementia increased by 22% for every additional defined daily dose of benzodiazepine per year (1.22; CI 1.18-1.25). Another systematic review from 2015 [3] also concluded that benzodiazepine use is associated with an increased risk of dementia (strengths of association ranged from 1.24-2.30), but that the increased risk was not associated if the cumulative use was less than three months. Though these two studies aggregate much of the published data, they cannot separate the nuances present in the published literature.

Results from human observational studies on the association of benzodiazepine use and Alzheimer's disease/dementia are incredibly varied. Some find no significant association [4, 5]. One study found a beneficial association on the diagnosis of dementia [6] and one on Alzheimer's disease [7]. Some found

a detrimental association on diagnosis of Alzheimer's disease/dementia [8-10]. Some found associations with certain classes or dosing schedules of benzodiazepines and Alzheimer's disease/dementia [3, 7, 11-14].

In addition, some evidence exists that long-acting benzodiazepines might have a greater association with cognitive decline than short-acting benzodiazepines, but the data is very poor [13, 14].

Clearly there is no consensus on whether an association exists between benzodiazepine use and Alzheimer's disease/dementia. Each report suggests methodological issues that confound other studies. The messy difference in study designs, data collection, and study populations makes definitive comparisons between the above studies very difficult. In addition, no study separates out the more than a dozen benzodiazepines on the market, and it is not possible to conclude whether certain benzodiazepines contribute to dementia and others do not.

Although the evidence for the association between long-term benzodiazepine use and Alzheimer's disease/dementia is inconclusive, benzodiazepines have well-known acute cognitive effects. In a recent systematic review of 68 studies, Tannenbaum et al [15] found that benzodiazepines were associated with both amnesiac and non-amnesiac cognitive impairment. A dose-response association existed, and elderly adults over the age of 60 were more sensitive to lower doses of benzodiazepines (such as 0.5mg lorazepam). Benzodiazepines primarily affected memory storage but also impacted attention, reaction time, and other psychomotor functions.

Human research to suggest decreasing benzodiazepines use can reduce risk in patients with Alzheimer's disease/dementia

- *One systematic review*

A systematic review from Defrancesco et al [16], based on five observational studies, concluded that benzodiazepine use is associated with a faster rate of cognitive decline in Alzheimer's patients. These results should be interpreted with caution though. There is a high degree of polypharmacy in elderly patients with Alzheimer's disease (and in some of the individual studies), and it is not always clear whether benzodiazepines themselves increased the rate of cognitive decline.

Laboratory and clinical research suggesting a mechanism of action for how decreasing benzodiazepine use might reduce risk of cognitive decline

- Perhaps it is not the drug at all
  The conditions for which people are prescribed benzodiazepines – insomnia, anxiety, and depression – may associate with a long-term risk of dementia and can occur in the prodromal phase of the disease. Therefore, perhaps benzodiazepines themselves are not causing cognitive decline.

- General reduction in cognitive reserve
  Lifestyles with enriched cognitive activity are associated with delayed onset of dementia, possibly through an increase in cognitive reserve that can help the brain function despite underlying neurodegenerative disease and even slow the rate of damage through ongoing synaptic plasticity [17]. In turn, benzodiazepines can cause sedation and acute cognitive deficits (e.g. [15, 18]) that might decrease the levels of cognitive reserve when used chronically.

- Benzodiazepine binding to the 18 kDa Translocator Protein (TSPO – formerly, Peripheral Benzodiazepine Receptor)
  TSPO is located on the outer-mitochondrial membrane of steroid-producing cells. Different benzodiazepines bind to the TSPO with different affinities. It is thought to be involved in mitochondrial steroid transport, mitochondrial pore formation during apoptosis, and neurosteroid synthesis (though some of these functions remain controversial) [19-21]. Its expression is also upregulated in neuro-inflammed glia and in cancer cells [22].

- Down-regulation of benzodiazepine receptors with chronic use
  Although results are not unequivocal, animal studies suggests that chronic benzodiazepine use may be associated with a decrease in benzodiazepine binding sites in the brain [23]. This association is greater with higher benzodiazepine use and more continuous administration. This decrease in benzodiazepine binding sites could be associated with a decrease in $GABA_A$ receptors which could have a negative impact on the brain.

- Increased GABA released from astrocytes around amyloid beta plaques
  A recent study in a mouse model of Alzheimer's disease has suggested that astrocytes located near amyloid beta plaques release increased levels of GABA [24]. Patients with amyloid plaques but no dementia might see increased levels of cognitive decline or an increased effect from benzodiazepine use.

APOE4 interactions:

No studies examined use of benzodiazepines and an association with dementia/Alzheimer's disease in APOE4 patients. However, two studies suggest that APOE4 carriers may be more vulnerable to the acute cognitive deficits caused by benzodiazepines. Stonnington et al [25] found that five hours after a 2mg dose of lorazepam, APOE4 carriers scored worse in tests of visuospatial working memory and long-term verbal memory than APOE 2/3 carriers. Pomara et al [26] found a delayed recovery in long-term memory for APOE4 carriers given a 1mg dose of lorazepam.

Can decreasing benzodiazepine use slow aging or delay death? *No studies have specifically examined benzodiazepine use and the rate of aging, per se. However, there is mixed evidence suggesting benzodiazepine use might be associated with a greater mortality risk.*

Types of evidence:
- One meta-analysis pooling ten studies looking at benzodiazepine use and mortality risk
- Additional human observational studies on benzodiazepine use and death and frailty

Although the AGS does not recommend benzodiazepines for the elderly, they are still widely prescribed along with other medications, and polypharmacy is a concern for accelerated aging and death. Jamsen et al [27] examined the effects of increasing drug burden (including benzodiazepines) and the transition through frailty stages. There was an increased risk in transitioning from a robust state to death with each unit increase in the drug burden index (2.75; CI 1.60-4.75).

In a meta-analysis of ten studies, Parsaik et al [28] concluded that benzodiazepine use was associated with a greater risk of mortality over non-use (1.60; CI 1.03-2.49) and the use of z-drugs was associated with a non-significant trend for increased risk of mortality (1.73; CI 0.95-3.16). In this meta-analysis, however, five of the ten studies pooled studies examined populations with pre-existing conditions (schizophrenia, dialysis, pneumonia, COPD, and hemodialysis). Of the remaining five, only two studies found an association between benzodiazepine use and mortality [29, 30]. Parsaik et al concluded that the increased mortality risk from the meta-analysis was due largely to suicide, cancer, and cardiovascular disease.

Recently, Lan et al [31] analyzed 1.3 million people (average age in 40s) registered in Taiwan's National Health Insurance database over ten years. Benzodiazepine use was associated with a greater chance of incident mortality (1.81 CI 1.78-1.85), but zolpidem (Ambien) use was associated with a decrease risk of incident mortality (0.73 CI 0.71-0.75). Interestingly, the study showed an inverse relationship between duration of zolpidem use and mortality (<30 days 0.78[CI 0.76-0.81]; >365 days 0.57[0.52-0.62]).

One caveat to consider – zolpidem (taken by ~70% of the population that takes hypnotics in Taiwan, average dose 10mg) can be prescribed for sleeping troubles without a diagnosis of insomnia. If benzodiazepines are only prescribed for more serious conditions, and if increased sleep is associated with better health, this prescribing bias could explain why zolpidem but not benzodiazepines had an apparent association with decreased mortality.

Although, Lan et al did not find an association between zolpidem use and all-cause mortality, they did find an association with increased cancer risk (1.65 CI 1.57-1.74). Likewise, Kripke et al [32] found an association between 132 doses/year of hypnotics (1.35 CI 1.18-1.55) and zolpidem (1.28 CI 1.03-1.59) and cancer. Iqbal et al [33] examined the association between individual benzodiazepines and cancer. Alprazolam, Bromazepam, Clonazepam, Fludiazepam, Flunitrazepam, Lorazepam, Lormetazepam, Oxazolam, Zopiclone, and Zolpidem were associated with cancer risk. Chlordiazepoxide, Diazepam, Medazepam, Nitrazepam, and Oxazepam were not associated with cancer risk. The field is still very controversial. However, one could speculate that since TSPO expression is increased in cancer cells and benzodiazepines bind with different affinities, different benzodiazepines might be associated with cancer risk.

Is it safe to decrease the use of benzodiazepines? *Decreasing benzodiazepine use is not associated with serious adverse effects as long as the original reason for their use (e.g. an indication of anxiety or insomnia) can be adequately treated in other ways.*

Types of evidence:

- One systematic review investigating tapering off benzodiazepines

Benzodiazepines grew in popularity because of their relative safety compared to barbiturates – benzodiazepines potentiate the effects of endogenous GABA binding to the $GABA_A$ receptor whereas as high levels barbiturates can themselves activate the $GABA_A$ receptor. However, though benzodiazepines are relatively safe when used on their own, they do have the potential to be habit forming. In addition, their use in elderly patients might lead to falls and they can potentially interact with other drugs, including other sedative drugs (such as alcohol and barbiturates – see http://www.drugs.com/drug-class/benzodiazepines.html for more information); therefore, their safety

profile must be carefully assessed. Note, however, that benzodiazepine use is not recommended at all for those over the age of 65. The American Geriatrics Society has listed them for years as Potentially Inappropriate Medication because even short-term use in the elderly can put individuals at risk for cognitive impairment, delirium, falls, fractures, and motor vehicle crashes [1].

Success rates for tapering off benzodiazepines are relatively high. Paquin et al [34] reported in a systematic review of 28 studies that the mean success rate for patients becoming drug-free after a range of 3-160 months was 60% (range 25%-85%). Furthermore, the success rates were similar for all modalities (taper alone, taper plus cognitive behavioral therapy, and taper plus medication substation) and were independent of dose and duration of use. There were some minor withdrawal symptoms but no severe safety withdrawal symptoms reported in any of the studies.

Although benzodiazepine use may be harmful, there are situations where their use is warranted. Conditions such as anxiety and insomnia may themselves increase the risk of dementia, so dropping benzodiazepine use at the expense of these conditions may not be beneficial.

Research Underway and Research needs:

No clinical trials currently listed in clinicaltrials.gov or clinicaltrialsregister.eu. Interestingly, one project listed in the NIH Reporter (project 5R01AG035361-06) is investigating whether $GABA_A$ receptor inverse agonsits are able to enhance cognitive performance in primates and an Alzheimer's mouse model (https://projectreporter.nih.gov/project_info_description.cfm?aid=8681288&icde=28860416).

More research is needed to investigate whether certain benzodiazepines are more assocaited with Alzheimer's disease/demenia. Iqbal et al's [33] study finding that certain benzodiazepines might be associated with cancer argues for additional studies mining large pharmacoepidemiological databases to separate out individual benzodiazepines.

Additionally, since many of the conditions for which benzodiazepines are prescribed might contribute to Alzheimer's disease/dementia, research should compare whether individuals with anxiety or insomnia are better or worse off with benzodiazepines versus other treatment options.

If certain benzodiazepines are association with a greater risk for Alzheimer's disease/dementia, additional research needs to find out why. Recent work at Stanford suggests that increased slow wave activity during sleep is associated with improved cognitive function in elderly. It is unclear how certain benzodiazepines might affect slow wave actvitiy in sleep. Additionally, not much is know how different benzodiazepines affect the TSPO. Since the TSPO is upregulated in glia cells in Alzheimer's disease and in cancer cells, future research should focus on how benzodiazepines might affect these cells.

1. By the American Geriatrics Society Beers Criteria Update Expert, P., *American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.* J Am Geriatr Soc, 2015. **63**(11): p. 2227-46.
2. Zhong, G., et al., *Association between Benzodiazepine Use and Dementia: A Meta-Analysis.* PLoS One, 2015. **10**(5): p. e0127836.

3. Billioti de Gage, S., A. Pariente, and B. Begaud, *Is there really a link between benzodiazepine use and the risk of dementia?* Expert Opin Drug Saf, 2015. **14**(5): p. 733-47.
4. Lagnaoui, R., et al., *The risk of cognitive impairment in older community-dwelling women after benzodiazepine use.* Age Ageing, 2009. **38**(2): p. 226-8.
5. Gray, S.L., et al., *Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study.* BMJ, 2016. **352**: p. i90.
6. Fastbom, J., Y. Forsell, and B. Winblad, *Benzodiazepines may have protective effects against Alzheimer disease.* Alzheimer Dis Assoc Disord, 1998. **12**(1): p. 14-7.
7. Imfeld, P., et al., *Benzodiazepine Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case-Control Analysis.* Drug Saf, 2015. **38**(10): p. 909-19.
8. Lagnaoui, R., et al., *Benzodiazepine use and risk of dementia: a nested case-control study.* J Clin Epidemiol, 2002. **55**(3): p. 314-8.
9. Gallacher, J., et al., *Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS).* J Epidemiol Community Health, 2012. **66**(10): p. 869-73.
10. Billioti de Gage, S., et al., *Benzodiazepine use and risk of dementia: prospective population based study.* BMJ, 2012. **345**: p. e6231.
11. Wu, C.S., et al., *The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data.* Am J Geriatr Psychiatry, 2009. **17**(7): p. 614-20.
12. Wu, C.S., et al., *Effect of benzodiazepine discontinuation on dementia risk.* Am J Geriatr Psychiatry, 2011. **19**(2): p. 151-9.
13. Billioti de Gage, S., et al., *Benzodiazepine use and risk of Alzheimer's disease: case-control study.* BMJ, 2014. **349**: p. g5205.
14. Shash, D., et al., *Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study.* Alzheimers Dement, 2015.
15. Tannenbaum, C., et al., *A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs.* Drugs Aging, 2012. **29**(8): p. 639-58.
16. Defrancesco, M., et al., *Use of Benzodiazepines in Alzheimer's Disease: A Systematic Review of Literature.* Int J Neuropsychopharmacol, 2015. **18**(10).
17. Stern, Y., *Cognitive reserve in ageing and Alzheimer's disease.* Lancet Neurol, 2012. **11**(11): p. 1006-12.
18. Stranks, E.K. and S.F. Crowe, *The acute cognitive effects of zopiclone, zolpidem, zaleplon, and eszopiclone: a systematic review and meta-analysis.* J Clin Exp Neuropsychol, 2014. **36**(7): p. 691-700.
19. Kalk, N.J., et al., *Are prescribed benzodiazepines likely to affect the availability of the 18 kDa translocator protein (TSPO) in PET studies?* Synapse, 2013. **67**(12): p. 909-12.
20. Miao, Y.L., et al., *Midazolam ameliorates the behavior deficits of a rat posttraumatic stress disorder model through dual 18 kDa translocator protein and central benzodiazepine receptor and neurosteroidogenesis.* PLoS One, 2014. **9**(7): p. e101450.
21. Ramirez, K., A. Niraula, and J.F. Sheridan, *GABAergic modulation with classical benzodiazepines prevent stress-induced neuro-immune dysregulation and behavioral alterations.* Brain Behav Immun, 2016. **51**: p. 154-68.
22. Selvaraj, V. and D.M. Stocco, *The changing landscape in translocator protein (TSPO) function.* Trends Endocrinol Metab, 2015. **26**(7): p. 341-8.

23. Hutchinson, M.A., P.F. Smith, and C.L. Darlington, *The behavioural and neuronal effects of the chronic administration of benzodiazepine anxiolytic and hypnotic drugs.* Prog Neurobiol, 1996. **49**(1): p. 73-97.
24. Jo, S., et al., *GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease.* Nat Med, 2014. **20**(8): p. 886-96.
25. Stonnington, C.M., et al., *Double-blind crossover study of the cognitive effects of lorazepam in healthy apolipoprotein E (APOE)-epsilon4 carriers.* J Clin Psychiatry, 2009. **70**(10): p. 1379-84.
26. Pomara, N., et al., *Apolipoprotein E epsilon4 allele and lorazepam effects on memory in high-functioning older adults.* Arch Gen Psychiatry, 2005. **62**(2): p. 209-16.
27. Jamsen, K.M., et al., *Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study.* J Am Geriatr Soc, 2016. **64**(1): p. 89-95.
28. Parsaik, A.K., et al., *Mortality associated with anxiolytic and hypnotic drugs-A systematic review and meta-analysis.* Aust N Z J Psychiatry, 2015.
29. Kripke, D.F., *Mortality Risk of Hypnotics: Strengths and Limits of Evidence.* Drug Saf, 2016. **39**(2): p. 93-107.
30. Weich, S., et al., *Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study.* BMJ, 2014. **348**: p. g1996.
31. Lan, T.Y., et al., *The Use of Hypnotics and Mortality - A Population-Based Retrospective Cohort Study.* PLoS One, 2015. **10**(12): p. e0145271.
32. Kripke, D.F., R.D. Langer, and L.E. Kline, *Hypnotics' association with mortality or cancer: a matched cohort study.* BMJ Open, 2012. **2**(1): p. e000850.
33. Iqbal, U., et al., *Is long-term use of benzodiazepine a risk for cancer?* Medicine (Baltimore), 2015. **94**(6): p. e483.
34. Paquin, A.M., K. Zimmerman, and J.L. Rudolph, *Risk versus risk: a review of benzodiazepine reduction in older adults.* Expert Opin Drug Saf, 2014. **13**(7): p. 919-34.

-