*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Benzodiazepines

**Evidence Summary**

Short-term use is generally safe; chronic use has conflicting evidence on potential increased risk of Alzheimer's disease/dementia and mortality. Given benzodiazepines' potential for abuse, increased sensitivity in elderly patients, and acute cognitive impairment, long-term use is not recommended.

**Brain health risk:** 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.

**Risk for aging and related health concerns:** There is mixed evidence suggesting benzodiazepine use might be associated with a greater mortality risk.

**Safety:** Benzodiazepines might increase the risk of falls, but the data is mixed.

**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 because elderly people are more sensitive to effects of benzodiazepines, and might have a greater risk for falls.

Benzodiazepines function primarily by binding to $GABA_A$ receptors and 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. 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.

**Brain health risk:** 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 meta-analysis from Zhong et al 2015, based on five nested/case-control studies, suggested benzodiazepine use is associated with an increased risk of dementia (risk ratio 1.49, 95% confidence interval [CI] 1.30-1.72). The risk of dementia increased by 22% for every additional defined daily dose of benzodiazepine per year (1.22; CI 1.18-1.25). Additionally, a recent systematic review from Billiote de Gage et al 2015, based on ten studies, concluded benzodiazepine use is associated with an increased risk of dementia (strengths of association ranged from 1.24-2.30), but the increased risk is not associated for total use of 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, (Lagnaoui et al 2009; Gray et al 2016). One study found a beneficial association on the diagnosis of dementia (Fastbom et al 1998) and Alzheimer's disease (Imfeld et al 2015). Some found a detrimental association on diagnosis of Alzheimer's disease/dementia (Lanaoui et al 2002; Gallacher et al 2012; Billiote de Gage et al 2012; Zhong et al 2015). Some found associations with certain classes or dosing schedules of benzodiazepines and Alzheimer's disease/dementia (Wu et al 2009; Wu et al 2011; Billiote de Gage et al 2014; Billiote de Gage et al 2015; Shash et al 2015; Imfeld et al 2015).

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 poor (Billiote de Gage et al 2014; Shash et al 2015).

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 (e.g. different binding affinities exist to the 18 kDa transporter protein which may be another confounding factor).

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 (2012) 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*

*Types of evidence:*

- One systematic review

A systematic review from Defrancesco et al (2015), 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
  As mentioned previously, 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 or even slowing the rate of damage through ongoing synaptic plasticity (Stern et al 2012). In turn, benzodiazepines can cause sedation and acute cognitive deficits (e.g. Stranks and Crowe 2014, Tannenbaum et al 2012) 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). Its expression is also upregulated in neuro-inflammed glia and in cancer cells.

- Down-regulation of benzodiazepine receptors with chronic use
  Although results are not always consistent, animal studies suggests that chronic benzodiazepine use may be associated with a decrease in benzodiazepine binding sites in the brain (Hutchinson et al 1996). 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 tau phosphorylation by decreased PP2A-tau interaction in response to benzodiazepines
  Protein phosphatase 2A (PP2A) dephosphorylates tau at SP/TP sites. Using a live cell reporter system, Nykanen et al (2012) found that activation of $GABA_A$ receptors by norfluorazepam (a benzodiazepine metabolite) increased tau phosphorylation and decreased interaction of PP2A with tau. Increased tau phosphorylation might increase the rate of cognitive decline. However, this study has yet to be replicated.

- 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 (Jo et al, 2014). 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 (2009) 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 (2005) found a delayed recovery in long-term memory for APOE4 carriers given a 1mg dose of lorazepam.

**Risk for aging and related health concerns:** 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 (2016) 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 unit increase in the drug burden index (2.75; CI 1.60-4.75).

In a meta-analysis of ten studies, Parsaik et al (2015) 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 greater, but non-significant, 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 (Kripke et al 2012; Weich et al 2014). 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 (2015) 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 could explain why zolpidem decreased mortality but not benzodiazepines.

Although, Lan et al (2015) did not find an association between zolpidem use and all-cause mortality, they did find an association with cancer (1.65 CI 1.57-1.74). Likewise, Kripke et al (2012) 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 (2015) 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.

**Safety:** Benzodiazepines might increase the risk of falls, but the data is mixed.

*Types of evidence:*

- One meta-analysis of and one systematic review on association of benzodiazepines and falls
- 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.

A meta-analysis from Woolcott et al (2009) concluded, based on eleven previous studies from 1996-2007, that benzodiazepine use was associated with a great risk of falls in elderly patients (>60 years old) (1.57; CI 1.43-1.72). However, a systematic review from Park et al (2015) examined the studies done in the five years after the Woolcott study and reported that one study found an association between benzodiazepine use and falls while five studies did not. It is unclear why the results from Park et al differed from the results from Woolcott et al or whether there would be an association between elderly benzodiazepine use and falls if all studies were pooled together.

Success rates for tapering off benzodiazepines are relatively high, and it is relatively safe. Paquin et al (2014) 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 chronic 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.

**Sources and dosing:**
For more information on benzodiazepines available in the United States visit http://www.drugs.com/drug-class/benzodiazepines.html.

American Geriatrics Society recommendation on not using benzodiazepines for the elderly: http://www.choosingwisely.org/societies/american-geriatrics-society/

**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).

**Search terms:**
Pubmed:
Benzodiazepine + dementia, Alzheimer, cognitive delinve, elderly, aging, mortality, frail, atherosclerosis, cardiovascular disease (filter clinical trials, meta-analysis, systematic review)

Clinicaltrials.gov, clinicaltrialsregister.eu, NIH-reporter

- Benzodiazepines + dementia; benzodiazepines + Alzheimer

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.*