



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.

Trazodone

Evidence Summary

Trazodone is widely used for both depressed patients with insomnia and off-label for primary insomnia. However, there is a lack of controlled trials to suggest it is beneficial for primary insomnia or Alzheimer's disease.

Neuroprotective Benefit: No evidence suggests that trazodone can prevent dementia or improve cognition in Alzheimer's patients; however, it may promote sleep in Alzheimer's patients.

Aging and related health concerns: There is some evidence for increased mortality risk in elderly and case studies that it may exacerbate underlying cardiac rhythm abnormalities. But controlled studies in healthy patients is lacking.

Safety: Some side effects are associated with trazodone, but it is suggested to have a better safety profile for elderly than other sedating drugs.



What is it?

Trazodone is an anti-depressant that both blocks the serotonin receptor 2A (5HT_{2A}) and inhibits serotonin reuptake. Its sedating effects may be due to α -adrenergic and histamine blockade (however, it seems to lack anti-cholinergic activity – a potential risk factor for dementia seen with other histamine blockers) ([Schroek et al, 2016](#)). It is commonly used for depressed patients with insomnia but is also used off-label for primary insomnia. In addition, it is used off-label for insomnia in Alzheimer's patients (e.g. nearly 20% of trazodone prescriptions in Spain are for Alzheimer's patients, [Macias Stain-Gerons et al, 2016](#)). However, there is currently little research on its benefits for Alzheimer's patients with insomnia. Since it is a generic drug and there are other newer sleep medicines available, it is unlikely to be extensively studied in clinical trials in the future.

Trazodone is a dirty drug. Its primary mechanism of action is inhibition of the serotonin transporter (SERT) and antagonism of the serotonin type 2A (5-HT_{2A}) receptor. However, it is also antagonistic to the α 1- and α 2-adrenergic receptors and histamine H₁ receptors (albeit with minimal anti-cholinergic effects). In Huntington's mouse models, it was reported to improve mitochondrial respiration ([Halliday et al, 2016](#)).

Neuroprotective Benefit: No evidence suggests that trazodone can prevent dementia or improve cognition in Alzheimer's patients; however, it may promote sleep in Alzheimer's patients.

Types of evidence:

- 1 meta-analysis of 1 RCT in Alzheimer's patients
- 3 clinical trials of acute cognitive effects
- 1 retrospective study in Alzheimer's patients
- 1 RCT for insomnia in Alzheimer's patients
- 1 laboratory study in an FTD and prion mouse model

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Although evidence links decreased sleep quality and depression to cognitive decline or Alzheimer's disease, there is no evidence that long-term or short-term treatment of trazodone prevents dementia.

Concerns were raised that trazodone may affect cognition function. However, these studies are confounded by small numbers (7-19 patients), timing of trazodone treatment (e.g. daytime treatment), [Rush et al, 1997](#), or small effect sizes ([Roth et al, 2011](#)). One study reported no differences in cognition, but this too studied few patients ([Sasada et al, 2013](#)).



Trazodone has sedating effects, so it is not surprising that it is associated with decreased cognitive function if taken during the day. Its half-life may be prolonged in elderly patients (up to 16 hours), so it may have cognitive effects the following day in this population ([Schroek et al, 2016](#)).

Human research to suggest benefits to patients with dementia:

No evidence suggests that trazodone can improve cognition in Alzheimer's patients. However, a retrospective study of patients with dementia taking trazodone reported sleep improvement in 65% of patients ([Camargos et al, 2010](#)), and one RCT in 30 patients with probable Alzheimer's disease and sleep disturbances reported treated patients slept an average of 42.5 minutes more per night with 50mg per day of trazodone over two weeks. Patients also had significant improvements in a measure of circadian rhythm but no change in cognitive function ([Caramargos et al, 2014](#); [Grippe et al, 2015](#); [McCleery et al, 2016](#)). Further large-scale studies will have to confirm these results, though.

A small open label study suggested that trazodone may improve behavioral symptoms, such as agitation, in Alzheimer's patients ([Lebert et al, 1994](#)), but further RCTs in patients with Alzheimer's disease and frontal temporal dementia suggest that it is no better than placebo or behavioral management techniques ([Teri et al, 2000](#); [Martinon-Torres et al, 2004](#)).

However, 6-week cross-over trial compared trazodone (150-300mg/day) to placebo in patients with frontotemporal dementia. There were decreases in agitation, irritability, and depression in trazodone treated groups but no change in cognition ([Nardell et al, 2014](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The primary mechanism of action by which trazodone was thought to benefit Alzheimer's patients is through its anxiolytic, anti-depressant, and sedating effects. There is insufficient evidence of trazodone's benefits for primary insomnia. One RCT with 306 patients (age 21-65; 100 on 50mg trazodone) reported a benefit in subjective sleep duration and quality over the first week but not the second ([Mendelson, 2005](#)). Two small RCTs (28 patients combined) suggested that trazodone increased percentage or time spent in slow wave sleep in young and middle aged individuals ([Roth et al, 2011](#); [Suzuki et al, 2002](#)). But there is no evidence that this will prevent cognitive decline.

Trazodone improved outcomes in prion and FTD mouse models. Specifically, in prion mouse models, trazodone reduced neuron loss in the hippocampus and improved memory. It also increased lifespan (max ~11%). However, mice still lost weight (requiring sacrifice), and trazodone did not decrease prion aggregation ([Halliday et al, 2017](#)).

In an FTD mouse model, trazodone prevented some neuron loss in the hippocampus, reduced ptau, and rescued memory deficits to control levels. Activation of the unfolded protein response (UPR) is reported to increase the phosphorylation of tau through GSK β . The authors speculate that trazodone prevented



ptau due to inhibition of the UPR. Interestingly, the other drug used in the study also inhibited the UPR through the same mechanism but did not prevent ptau ([Halliday et al, 2017](#)).

The authors note that the doses used (40mg/kg) were clinically relevant doses (equivalent to 194mg/day in humans). However, these are doses for depression. Doses used for insomnia are generally much lower (25-100mg/day).

APOE4 interactions:

Not reported

Aging and related health concerns: There is some evidence for increased mortality risk in elderly and case studies suggest that it may exacerbate underlying cardiac rhythm abnormalities. But controlled studies in healthy patients is lacking.

Types of evidence:

- 3 observational studies on cardiac health
- A few case studies on cardiac effects in patients with underlying cardiac rhythm abnormalities
- A meta-analysis of observational studies on risk of falls
- An observational study on risk of mortality
- One open-label study on diabetic neuropathy
- Multiple studies for insomnia

Details:

No reports on lifespan/healthspan. Some case studies reported that orthostatic hypotension is more frequent with trazodone than other anti-depressants, and it may exacerbate underlying cardiac rhythm abnormalities ([Teply et al, 2016](#)). However, in observational studies there is no evidence that trazodone increases risk of cardiac mortality, chronic heart failure, or coronary artery disease more than other anti-depressants ([Camacho et al, 2016](#); [Leonard et al, 2011](#); [Acharya et al, 2013](#)). Although trazodone has not been extensively studied for its effects on heart disease compared to placebo or in patients with primary insomnia, it is widely used and there is not strong evidence for negative effects on the heart. One open-label, uncontrolled study reported benefits in patients with diabetic neuropathy ([Wilson, 1999](#)).

One observational study suggested that compared to other anti-depressants trazodone had the greatest risk for all-cause mortality. This may be driven, however, by an increased risk of attempted suicide/self-harm and risk of falls in elderly ([Coupland et al, 2011](#); [Ruxton et al, 2015](#)). However, low-dose trazodone is suggested to have a better safety profile than other sedating drugs ([Schroeck et al, 2016](#)).



Primary Insomnia

One RCT studied the subjective efficacy of trazodone (50mg), zolpidem (10mg), or placebo for 2 weeks in 206 patients with primary insomnia. During week 1, patients taking trazodone and zolpidem reported benefits in subjective sleep latency, sleep duration, wake time after sleep onset (WASO), and sleep quality. During week 2, however, the trazodone group did not differ significantly from the placebo group ([Mendelson, 2005](#)). Another open label study in 9 'poor sleepers' reported subjective benefits with trazodone in weeks 1 and 2 but not week 3. Objective measures by polysomnography (PSG) showed that trazodone had no effect on sleep duration or latency, but WASO was reduced over 3 weeks compared to baseline. It also increased the duration of slow-wave sleep, but there was a negative rebound after withdrawal ([Montgomery et al, 1983](#)).

A retrospective study in 79 patients taking trazodone (no control group) reported that trazodone was efficacious in treating insomnia (defined as no longer meeting the criteria for insomnia) and that the highest percentage of responders were those taking the lowest doses (25mg) ([Savarese et al, 2015](#)). Another study in patients with primary insomnia reported that both cognitive behavior therapy (CBT) and CBT+trazodone (100mg over 8 weeks) improved sleep latency, sleep efficiency, and total sleep time. Only CBT+ trazodone increased slow-wave sleep duration ([Zavesicka et al, 2008](#)).

Sleep architecture

Ten additional studies (seven in depressed or dysthymic patients) made objective measures of sleep architecture with trazodone, and there was a consistent finding that it increased slow-wave sleep (though there could be a negative rebound after stopping trazodone – see above) ([Mendelson, 2005](#)).

Safety: Some side effects are associated with trazodone, but it is suggested to have a better safety profile for elderly than other sedating drugs.

Types of evidence:

- A systematic review of safety compared to other sleep medications

Details:

Side-effects of trazodone include dizziness, drowsiness, fatigue, headache, nausea and vomiting. Trazodone may lower blood pressure and has been reported to be associated with orthostatic hypotension, a side-effect of other anti-depressants ([Teply et al, 2016](#)). In addition, clinical trials suggest a high discontinuation rate at doses used for depression (25%-60%), usually due to drowsiness, dizziness, hypotension, confusion, edema, and itching. There are also rare reports of priapism (erection >4 hours) ([Mendelson, 2005](#)). Despite this, trazodone lacks anti-cholinergic activity, cardiotoxicity (other than a few case reports), and potential for abuse, and low-dose trazodone is suggested to have a better safety profile than other sleep medicines such as hypnotics and benzodiazepines ([Schroeck et al, 2016](#)). However, there are no controlled studies on the long-term safety of trazodone. Trazodone may be



associated with a higher risk of suicide than other anti-depressants ([Coupland et al, 2011](#), [Coupland et al, 2015](#), [drugs.com](#)).

Drug interactions:

Trazodone is metabolized by the CYP2D6 and CYP3A4 enzymes and may have a high potential for possible drug interactions ([Schroek et al, 2016](#)). In fact, [drugs.com](#) lists 205 major drug interactions, including MAO inhibitors. For more information, visit [drugs.com](#).

Sources and dosing:

For depression, doses of trazodone range from 150-600mg/day. Low-dose trazodone taken before bed is used for insomnia, with most studies using 25-100mg/day, though one study reported that 25mg/day was more efficacious than higher doses ([Schroek et al, 2016](#), [Savarese et al, 2015](#)).

Research underway:

A few clinical trials are underway for depression and insomnia ([clinicaltrials.gov](#)). One study is testing trazodone (10mg, 20mg, placebo) for painful diabetic neuropathy ([NCT03202979](#)). However, trazodone is 3 decades old and is available as a generic, so there is not a lot of active research going on.

Search terms:

Pubmed:

Trazodone + alzheimer, mortality, cardiovascular, orthostatic hypotension, cognition, lifespan, aging, apoe, apolipoprotein

Clinicaltrials.gov:

- Trazodone

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