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

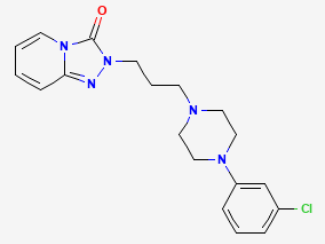
Evidence Summary

Trazodone increases sleep time and quality in people with insomnia. Cognitive effects of trazodone may depend on the presence of other conditions. Trazodone is associated with some serious adverse events.

Neuroprotective Benefit: The effects of trazodone on cognitive function have varied across studies. Cognitive effects may depend, in part, on the presence of other conditions such as sleep disturbances and depression.

Aging and related health concerns: Trazodone is approved for the treatment of depression. Numerous clinical trials have also shown that trazodone significantly increases total sleep time, slow-wave sleep, and sleep quality in people with insomnia.

Safety: Trazodone has a black box warning for suicidal thoughts. Common adverse events include drowsiness, dizziness, swelling, and gastrointestinal issues. Trazodone has been associated with a risk of QT prolongation, priapism, and liver enzyme elevations.

Availability: Rx	**Dose**: Initial adult dose for depression is 150 mg orally per day in divided doses, then increased by 50 mg per day every 3-4 days. Much lower doses are used off-label for insomnia and other conditions.	**Chemical formula:** $C_{19}H_{22}ClN_5O$ **MW**: 371.9  Source: Pubchem
Half-life: 5-13 hours	**BBB**: penetrant	
Clinical trials: A meta-analysis evaluating the effects of trazodone in people with sleep disturbance included 44 randomized controlled trials with 3,935 participants.	**Observational studies**: Numerous observational studies have included thousands of participants prescribed trazodone.	

What is it?

Trazodone is an antidepressant that belongs to a class of drugs called serotonin receptor antagonists and reuptake inhibitors (SARIs). Trazodone inhibits the reuptake of serotonin (by inhibiting serotonin 5-HT1a, 5-HT1c, and 5-HT2 receptors and the serotonin transporters) and blocks histamine and alpha-1-adrenergic receptors (Drugbank.com).

Trazodone is approved for the treatment of major depressive disorder. At lower doses (25 to 150 mg) than those used for depression, trazodone can exert hypnotic actions. It has been used off-label for insomnia, anxiety, substance abuse, and to treat symptoms of Alzheimer's disease (e.g., insomnia, agitation), frontotemporal dementia, schizophrenia, eating disorders, post-traumatic stress disorder, and fibromyalgia (Drugbank.com; Gonçalo et al., 2021).

Neuroprotective Benefit: The effects of trazodone on cognitive function have varied across studies. Cognitive effects may depend, in part, on the presence of other conditions such as sleep disturbances and depression.

Types of evidence:

- 5 meta-analyses or systematic reviews
- 3 clinical trials in Alzheimer's disease
- 1 clinical trial in Parkinson's disease
- 1 expert consensus publication on pharmacotherapy for neurological diseases
- 4 observational studies
- Numerous laboratory studies

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

In a systematic review of 16 studies including a total of 8,646 participants, trazodone treatment (25-400 mg/day) for at least 1 week resulted in 7 studies showing no effect of trazodone on cognition, 5 showing a beneficial effect by improving or reducing cognitive decline, and 4 resulted in impaired cognitive function (Gonçalo et al., 2021). Eleven of the studies were clinical trials and others were observational studies. The participants of the 16 studies were either healthy individuals or those with the following conditions: arteriosclerotic cerebral small vessel disease, insomnia, HIV/AIDS, dementia, Alzheimer's disease, frontotemporal dementia, and depression. There was no dose-dependent effect of trazodone on cognition, as studies with both low and high doses showed better, worse, or unchanged cognitive function. Aside from cognitive function, 4 of the studies showed that trazodone treatment improved sleep quality and sleep parameters (including sleep efficiency, N3 sleep ratio, sleep continuity, daytime functioning, etc.). Five studies reported a decline or relief in symptoms of depression or anxiety. The authors note that the potential effects of trazodone on cognitive function could be driven by the effects of trazodone on improvement in sleep disturbances and depressive symptoms. It is not clear if there are direct effects of trazodone on cognition. The association between trazodone and cognitive harm observed in some of the studies could be due to the acute sedative effects seen in the initial phases of treatment, or suboptimal time of administration (trazodone taken in the morning could affect daytime functioning). Trazodone effects on cognitive function may also depend on the duration of treatment.

An analysis of 6,798 people with normal cognition at baseline from the National Alzheimer's Coordinating Center Uniform Data Set reported that the hazard of mild cognitive impairment was

significantly associated with sleep disturbance (HR=1.36; 95% CI, 1.11 to1.67)(Burke et al., 2018). The significant association persisted after adjusting for demographics, APOE4 carrier status, and Alzheimer's disease medication (HR=1.39; 95% CI, 1.131.72). Among users of trazodone, there was no significant association between sleep disturbance and the development of mild cognitive impairment (HR=1.31; 95% CI, 0.54 to 3.19). (Similar findings were seen in people who used zolpidem).

In a retrospective study of 25 long-term users of trazodone and 25 propensity-matched trazodone non-users, trazodone non-users had a 2.6-fold faster decline in cognitive function, measured by Mini-Mental State Examination (MMSE) compared to trazodone users (0.27 vs 0.70 points per year, p=0.023)(La et al., 2019). The study's participants included people with normal cognition, mild cognitive impairment, or Alzheimer's disease, who were followed for an average of 4.12 years. A slower rate of MMSE decline was seen in people who had sleep problems at the baseline visit (p=0.006) and in people who had changes in sleep from baseline (p=0.006), but not in people who had an absence of sleep complaints at baseline. In people who had changes in sleep, a significant association with slower rate of MMSE decline was seen in people who had improvement in sleep on the follow-up visit (p=0.0006) but not in people who had stable (p=0.326) or worsening of sleep (p=0.176). It is not clear whether the relationship between trazodone and cognitive function is causal or completely driven by improved sleep or antidepressant effects. Secondary outcomes on processing speed, disability scores, and visual recall also worsened faster in trazodone non-users than trazodone users, though none of the results were significant after correcting for multiple comparisons.

In a double-blind crossover study of 19 healthy men, acute or continuous (for 8 days) low dose of trazodone (25 mg/night) did not affect driving performance (measured by road tracking, car following, and harsh braking tasks) or cognitive function (measured by the Wisconsin Card Sorting Test, Continuous Performance Test, and N-back Test) (Sasada et al., 2013).

Human research to suggest benefits to patients with dementia:

All-cause dementia:
In a 2023 network meta-analysis of 12 studies enrolling a total of 1,146 participants with dementia and agitation evaluated the efficacy and safety of antidepressant drugs (Chen et al., 2023). Treatment with citalopram was associated with significant benefits in agitation compared to the placebo group, without a significant difference in safety. No significant effects on agitation were seen with trazodone, sertraline, mirtazapine, and fluoxetine compared with placebo. Citalopram had the highest probability of benefit, followed by sertraline, mirtazapine, placebo, trazodone, and fluoxetine. Treatment with trazodone was

associated with a higher risk of total adverse events compared with placebo (OR=4.58; 95% CI, 1.12 to 18.69).

In an observational study that included 2,199 people with dementia from 3 naturalistic cohorts in the UK (of whom 406 were taking trazodone for at least 6 weeks), there was no significant difference in adjusted cognitive decline in people with all-cause or non-vascular dementia taking trazodone, citalopram, or mirtazapine (Sommerlad et al., 2021). The mean follow-up was 2.2 years. However, when data from the 3 cohorts were combined, there was a greater mean cognitive (MMSE) decline in people with all-cause dementia taking trazodone compared to those taking citalopram (p=0.03). Results were similar in analyses restricted to people with mild dementia. Results were consistent after adjustment for severity of neuropsychiatric symptoms.

Alzheimer's dementia:
In a systematic review of 16 studies including a total of 8,646 participants, trazodone treatment (25-400 mg/day) for at least 1 week resulted in 7 studies showing no effect of trazodone on cognition, 5 showing a beneficial effect by improving or reducing cognitive decline, and 4 resulted in impaired cognitive function (Gonçalo et al., 2021). Three studies reported beneficial effects of trazodone in the treatment of behavioral disturbances in dementia (Lawlor et al., 1994; Lebert et al., 2004) and modestly reduced agitation in patients with Alzheimer's disease (Teri et al., 2000).

In a 2024 meta-analysis of 14 randomized controlled trials that tested various drugs in people with Alzheimer's disease and sleep issues, eszopiclone positively affected sleep efficiency as did orexin antagonists (e.g., suvorexant, lemborexant) (Bedward et al., 2024). Melatonin was the most commonly studied intervention for sleep disturbances among people with Alzheimer's disease, with somewhat limited efficacy. Only two studies evaluated trazodone (described below; Camargos et al., 2014; Grippe et al., 2015); thus, more randomized controlled trials are needed to reach a verdict.

In a double-blind randomized controlled trial of 30 community-dwelling people with Alzheimer's disease and sleep disturbances, trazodone treatment (50 mg once daily at 10pm) for 2 weeks increased sleep time by 42.5 minutes per night, with nighttime percent sleep increased by 8.5%, according to actigraphic data (Camargos et al., 2014). Trazodone did not induce significant daytime sleepiness or naps. Other measures of sleep, including 'time spent awake after sleep onset' and 'number of awakenings' were not significantly different compared to placebo. Trazodone treatment did not show any effects on cognition, measured by the MMSE, forward/backward digit span task, letter-number sequencing, arithmetic, digit symbol-coding, and symbol search. The Paired Associate Learning Tests of the Wechsler Memory Scale

could not be performed due to dementia severity. Trazodone treatment also did not significantly affect functionality (measured by the Katz index of Independence in Activities of Daily Living).

In a clinical trial of 30 Alzheimer's disease patients, trazodone treatment (50 mg, orally) for 2 weeks significantly improved circadian rhythm compared to placebo, measured by the relative rhythm amplitude utilizing actigraphs from Actiwatch (Respironics brand, Mini-Mitter Co., Bend, OR)(Grippe et al., 2015). The relative rhythm amplitude after trazodone treatment was consistent with a more stable daytime behavioral pattern. However, 7 out of 8 variables tested regarding rhythmicity were not statistically different after the use of trazodone compared to placebo.

In a 2023 meta-analysis of 10 randomized controlled trials in people with Alzheimer's disease psychosis, treatment with negative allosteric modulators of 5-HT2A receptor (e.g., mirtazapine, trazodone, pimavanserin, idalopirdine, donepezil, masupirdine, and RG3487) for 2-26 weeks resulted in significantly improved Neuropsychiatric Inventory total score, the Katz Independence in Activities of Daily Living score, and the MMSE score compared to placebo (Chen et al., 2023). Only one study of trazodone (Camargos et al., 2014) was included in this meta-analysis.

In a retrospective study of 25 long-term users of trazodone and 25 propensity-matched trazodone non-users, trazodone non-users had a 2.6-fold faster decline in cognitive function, measured by MMSE compared to trazodone users (0.27 vs 0.70 points per year, p=0.023)(La et al., 2019). The study's participants included people with normal cognition, mild cognitive impairment, or Alzheimer's disease. Trazodone effects on MMSE remained significant within participants with probable Alzheimer's disease, with a 2.4-fold faster decline in non-users compared to trazodone users (p=0.038). Alzheimer's patients in the study were followed for an average of 3.75 years.

In an open-label pilot clinical trial of 13 patients with Alzheimer's disease, trazodone treatment (25 mg, 3 times daily, orally) for 10 weeks decreased irritability, anxiety, restlessness, and affective disturbance, but did not affect cognitive function measured by the MMSE (Lebert et al., 1994). Because the study was not placebo-controlled, the true effect of trazodone could not be evaluated.

Frontotemporal dementia:
In a network meta-analysis of 7 randomized controlled trials testing pharmacotherapies for frontotemporal dementia, high-dose oxytocin was associated with the greatest improvement in patients' neuropsychiatric symptoms compared to placebo (p=0.035)(Huang et al., 2023). Trazodone did not significantly change Neuropsychiatric Inventory scores compared to placebo (p=0.246) and was

associated with significantly higher rates of adverse events based on one trial (OR=9.53; 95% CI, 1.85 to 49.20, p=0.007). No pharmacological intervention significantly benefited cognitive function.

An expert consensus from the European Reference Network for Rare Neurological Diseases (ERN-RND) examined drug management options for behavioral disturbances in patients with frontotemporal dementia (Wittebrood et al., 2024). The network convened 21 experts across Europe and recommended antipsychotics (primarily quetiapine) for behaviors posing safety risks to both patients and caregivers (including aggression, self-injury, and self-harm) and nightly unrest. SSRIs (e.g., sertraline) were recommended for perseverative somatic complaints, rigidity of thought, hyperphagia, loss of empathy, and for impulsivity. Trazodone was the top recommended choice for motor unrest and a top 5 choice for 9 other behavioral symptoms.

In a double-blind randomized placebo-controlled crossover study of 26 patients with frontotemporal dementia, trazodone treatment improved Neuropsychiatric Inventory total score but did not significantly improve cognitive function measured by MMSE (Lebert et al., 2004).

Parkinson's disease:
In a double-blind randomized trial of 93 patients with Parkinson's disease and sleep disorders, trazodone treatment (50 mg/day) for 4 weeks significantly improved Pittsburgh Sleep Quality Index scores compared to baseline (as did 3 mg/day of melatonin and 1 mg/day of clonazepam)(Hadi et al., 2022). With regards to mean changes from baseline on the rapid eye movement (REM) sleep behavior disorder (RBD) screening questionnaire (RBDSQ), melatonin treatment was associated with a greater improvement compared to trazodone treatment (p=0.011) and clonazepam (p=0.004). Trazodone treatment was associated with a greater decrease in the Epworth Sleepiness Scale (ESS) compared to clonazepam (p=0.010). Melatonin showed a better safety profile than trazodone and clonazepam.

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

In addition to trazodone's effects on the serotonin, adrenergic, and histamine systems, preclinical studies have reported that trazodone also inhibits the eIF2α-P branch of the unfolded protein response, which is overactivated in brains of patients with Alzheimer's disease (Halliday et al., 2017). In mouse models of neurodegenerative diseases, overactivation of PERK/eIF2α-P signaling causes sustained attenuation of protein synthesis, leading to memory impairment and neuronal loss.

APOE4 interactions:

It is not known whether there are interactions between the effects of trazodone and APOE status. An analysis of 6,798 people with normal cognition at baseline from the National Alzheimer's Coordinating Center Uniform Data Set reported that the hazard of mild cognitive impairment was significantly associated with sleep disturbance (Burke et al., 2018). APOE4 carriers had a significantly higher hazard of mild cognitive impairment, but the association with mild cognitive impairment was not significant when APOE4 carriers used trazodone (or zolpidem).

Aging and related health concerns: Trazodone is approved for the treatment of depression. Numerous clinical trials have also shown that trazodone significantly increases total sleep time, slow-wave sleep, and sleep quality in people with insomnia.

Types of evidence:

- 3 meta-analyses or systematic reviews
- 2 clinical trials in diabetic neuropathy

Depression: APPROVED FOR TREATING DEPRESSION

Trazodone is approved for the treatment of major depressive disorder. Clinical studies have shown that the efficacy of trazodone on depression, when administered at ≥ 150 mg/day, is comparable to that of tricyclic antidepressants, SSRIs, and SNRIs (reviewed in Fagiolini et al., 2023). However, trazodone is an older drug and is not listed as one of the first-line pharmacotherapies (e.g., SSRIs, SNRIs, serotonin modulators, tricyclics, and others) for depression (Simon et al., 2024).

Insomnia: INCREASES TOTAL SLEEP TIME, SLEEP QUALITY, AND SLOW-WAVE SLEEP

Trazodone has been widely prescribed for off-label use to treat insomnia and other sleep issues.

In a 2024 meta-analysis of 44 randomized controlled trials including a total of 3,935 participants with sleep disturbance, trazodone treatment (mean dose of 179.49 mg/day) for a minimum of 5 days did not significantly affect subjective total sleep time but improved sleep quality compared to placebo ($p<0.01$)(Kokkali et al., 2024). Trazodone treatment also improved secondary outcomes, including the number of nocturnal awakenings ($p<0.01$), nocturnal time awake after sleep onset (weighted mean

difference [WMD]=-13.47 min, p<0.01), objective total sleep time by polysomnography (WMD=27.98 min, p=0.02), and sleep efficiency (p=0.02). No significant effects of trazodone were seen on sleep onset latency, daytime impairment, dropouts owing to any reason, insomnia as a treatment-emergent adverse event. The meta-analysis included participants with various conditions, including depression, substance misuse, erectile dysfunction, sleep disturbances, dementia, anxiety, pain, schizophrenia, tremor, tinnitus, rheumatoid arthritis, obsessive-compulsive disorder, esophageal contraction abnormalities, bulimia nervosa, and cerebral small vessel disease. Trazodone may be more suitable for people primarily experiencing sleep maintenance insomnia rather than those with sleep onset insomnia.

In a 2022 meta-analysis of 11 randomized controlled trials including a total of 466 participants with insomnia, trazodone treatment significantly increased total sleep time (mean difference [MD]=39.88 min, p=0.002) and non-rapid eye movement stage 3 (N3; standardized MD [SMD]=1.61, p=0.0006) compared to placebo (Zheng et al., 2022). The N3 stage is the deepest stage of sleep and is characterized by slow-wave sleep. Trazodone treatment significantly decreased the latency to onset of persistent sleep (MD=- 19.30 min, p=0.04), non-rapid eye movement stage 1 (N1, p=0.02), the number of awakenings (SMD=- 0.67, p<0.00001), and waking time after persistent sleep onset (SMD=- 0.42, p=0.04), with no effects on non-rapid eye movement stage 2 (N2), rapid eye movement sleep, rapid eye movement latency, or apnea-hypopnea index. High-dose trazodone (≥ 100 mg/day) was more effective than control for decreasing N2 (p=0.009) and increasing N3 (p=0.0002). Both short-term (1-2 weeks) and long-term trazodone treatment (≥ 1 month) decreased latency to onset of persistent sleep (p<0.0001) and increased N3 (p=0.005).

In a 2022 network meta-analysis of 170 trials in insomnia investigating the comparative effectiveness of sleep medications, eszopiclone and lemborexant had a favorable profile, but eszopiclone might cause substantial adverse events (De Crescenzo et al., 2022). Many licensed drugs (including benzodiazepines, daridorexant, suvorexant, and trazodone) can be effective in the acute treatment of insomnia but are associated with poor tolerability, or information about long-term effects is not available. Melatonin and ramelteon did not show overall material benefits. No long-term data were available for trazodone.

Peripheral neuropathy: POTENTIAL BENEFIT IN REDUCING PAIN

Up to half of diabetic patients with neuropathy suffer from chronic pain that significantly impacts quality of life. Gabapentin is widely used for painful diabetic neuropathy but it has dose-limiting effects.

In a phase 2 double-blind randomized controlled trial of 141 patients with painful diabetic neuropathy, treatment with very low doses of trazodone (10 mg or 20 mg, 3 times daily) for 8 weeks with gabapentin as background therapy (slow titration from 100 mg, 3 times daily, to 400 mg, 3 times daily) did not significantly improve the primary outcome (Brief Pain Inventory Short Form item 5) compared to the placebo group (Lipone et al., 2020). The pain score was reduced from 5.7 ± 1.01 (baseline) to 2.6 ± 1.68 (after 8 weeks) in the 30 mg daily trazodone group; from 5.6 ± 1.05 to 3.0 ± 1.86 in the 60 mg daily trazodone group, and from 5.7 ± 1.14 to 3.2 ± 1.80 in the placebo group. The mean changes were -3.1, -2.6, and -2.5 in the 30 mg trazodone, 60 mg trazodone, and placebo groups, respectively. The 30 mg daily trazodone treatment resulted in a numerically better pain score compared to the placebo group, but the difference was not statistically significant (p=0.1179). Significant differences were observed for other time points, however. At 4 weeks, 30 mg trazodone group showed a significantly better pain score than placebo (p=0.0182). The percentage of patients that achieved a ≥ 50% reduction in pain was 62.8% in the 30 mg daily trazodone group, 54% in the 60 mg daily trazodone group, and 45.8% in the placebo group. While not the primary endpoint, a statistically significant improvement was observed in 'Brief Pain Inventory Short Form item 6 (how much pain you have right now)' for the 30 mg daily trazodone group compared to placebo (p=0.0314) after 8 weeks of treatment. Significant differences compared to placebo were also seen after 4 weeks (p=0.041) and after 7 weeks (p=0.0155). All treatment arms showed similar effects on secondary outcomes including the Neuropathic Pain Symptom Inventory, Hamilton Anxiety Rating Scale, and Patient Global Impression of Change.

In a larger double-blind randomized controlled dose-finding study in 240 patients with painful diabetic neuropathy, a combination of trazodone/gabapentin (2.5/25 mg t.i.d, 5/50 mg t.i.d., 10/100 t.i.d.), gabapentin alone, and placebo were administered for 8 weeks (Tesfaye et al., 2024). Changes in the average daily pain score based on the 11-point Numeric Rating Score (NRS) from baseline were -2.52 ± 2.31 in trazodone/gabapentin 2.5/25 mg group, -2.24 ± 1.96 in trazodone/gabapentin 5/50 mg group, -2.46 ± 2.12 in trazodone/gabapentin 10/100 mg group, -1.92 ± 2.21 in gabapentin alone group, and -2.02 ± 1.95 in the placebo group. None of the fixed-dose combinations of trazodone/gabapentin significantly affected pain scores compared to placebo after 8 weeks of treatment. However, patients receiving the lowest dose of trazodone/gabapentin (2.5/25 mg t.i.d.) showed a statistically significant difference compared to placebo after 6 weeks of treatment (p=0.0116). Based on these findings, the lowest dose of trazodone/gabapentin fixed-dose combination (2.5/25 mg t.i.d.) may be the best candidate for further clinical development for painful diabetic neuropathy.

Safety: Trazodone has a black box warning for suicidal thoughts. Common adverse events include drowsiness, dizziness, swelling, and gastrointestinal issues. Trazodone has been associated with a risk of QT prolongation, priapism, and liver enzyme elevations.

Types of evidence:

- 6 meta-analyses or systematic reviews
- 1 publication from the FDA Adverse Event Reporting System
- 4 clinical trials
- 2 observational studies
- 1 case study of trazodone exposure during pregnancy/lactation

Trazodone has a black box warning which states: "antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients" and "Desyrel is not approved for use in pediatric patients" (Desyrel prescribing information).

Common side effects of trazodone include drowsiness, dizziness, tiredness, swelling, weight loss, blurred vision, diarrhea, constipation, and stuffy nose (Drugs.com).

Trazodone has been associated with a risk of developing priapism, a painful and persistent incidence of penile tissue erection that can cause permanent neurological damage if left untreated (PubChem). Surgical or pharmacological intervention may be required. The mechanism by which trazodone induces priapism is not fully understood but may involve α-adrenergic blockade of the corpora cavernosa of the penis (reviewed in Yu et al., 2025). People who are at high risk of developing priapism include those with sickle cell anemia, leukemia, autonomic nervous system dysfunction, hypercoagulability, and those taking an SSRI.

Trazodone has been associated with transient, asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent acute liver injury (LiverTox, 2020).

In the FDA Adverse Event Reporting System, the adverse event data of trazodone were extracted from 2004 to 2024 and a total of 5,199 adverse event reports were found (Yu et al., 2025). A total of 179 significant adverse event signals were found, with suicide, formulation toxicity, abnormal penile erection, insomnia, and cardiac and respiratory arrest reported. The three most frequently reported adverse event categories were 'psychiatric disorders', 'general disorders and administration site conditions', and 'nervous system disorders'. These findings are consistent with the adverse events listed

in the drug inserts. The most commonly reported Preferred Terms included 'completed suicide' (n=610), 'toxicity to various agents' (n=412), and 'priapism' (n=332). Priapism and erectile dysfunction were prevalent in 40-50-year-olds, and 'completed suicide' and 'cardio-respiratory arrest' occurred most frequently in 50-60-year-olds.

Trazodone may have some cardiotoxic potential, with potential risk of prolongation of the QT interval, torsade de pointe, and cardiac arrest (Yu et al., 2025). Precise mechanisms are unclear, but high doses of trazodone may inhibit cardiac HERG potassium channels, leading to prolonged repolarization of cardiomyocytes, increasing the risk of cardiac arrhythmias (Zitron E et al., 2004). People with cardiac disease who take trazodone may need to have their heart rate and electrocardiogram monitored.

Data from clinical trials: In a systematic review of 16 studies including a total of 8,646 participants, trazodone treatment (25-400 mg/day) for at least 1 week was tolerated well and adverse events were mild and not a major cause of participant drop-out (Gonçalo et al., 2021). Examples of adverse events included worsening insomnia, akathisia (restlessness), nausea, loss of appetite, dizziness, and headache.

In insomnia patients: In a 2024 meta-analysis of 44 randomized controlled trials including a total of 3,935 participants with sleep disturbance, trazodone treatment (mean dose of 179.49 mg/day) for a minimum of 5 days led to more dropouts due to adverse events (RR=2.30, p<0.01), any sleep-related adverse effects (RR=3.67; p=0.04), more adverse events in general (RR=1.18; p=0.02), and more sleep-related adverse events (RR=4.31; p<0.01)(Kokkali et al., 2024). Trazodone caused more somnolence compared with placebo (RR=2.48; p<0.01).

In a 2022 meta-analysis of 11 randomized controlled trials including a total of 466 particiapnts with insomnia, trazodone treatment led to a significantly greater frequency of daytime drowsiness (OR=2.53, p=0.02) and decreased appetite (OR=2.81, p=0.02) compared to the control group (Zheng et al., 2022). Trazodone did not significantly increase the frequency of headache (OR=1.01, p=0.99) or dizziness (OR=2.10, p=0.05). There was no significant difference between trazodone treatment and control groups in discontinuation for all causes (OR=0.63, p=0.15).

In a 2022 network meta-analysis of 170 trials in insomnia investigating the comparative effectiveness of sleep medications, a large group of drugs (including benzodiazepines, trazodone, doxylamine, eszopiclone, lemborexant, ramelteon, suvorexant, zolpidem, and zopiclone) had a higher risk of sedation and somnolence than placebo or other active treatments (De Crescenzo et al., 2022).

In dementia patients: In a 2023 network meta-analysis of 12 studies enrolling a total of 1,146 participants with dementia and agitation evaluated the efficacy and safety of antidepressant drugs and found that the incidence of total adverse events reported for trazodone (OR=4.58, 95% CI, 1.12 to 18.69) was significantly higher than that reported for placebo (Chen et al., 2023).

In a double-blind randomized controlled trial of 30 community-dwelling people with Alzheimer's disease and sleep disturbances, trazodone treatment (50 mg once daily at 10pm) for 2 weeks did not significantly alter the frequency or severity of adverse events compared to placebo (Camargos et al., 2014). No reported adverse event was rated as moderate or severe, with mild adverse events observed in 4 subjects using trazodone and in 6 subjects using placebo. In the trazodone group, one patient had dyspepsia and diarrhea, one had coryza (inflammation of the mucous membrane in the nose), one had irritability, and another had swollen lower limbs. In the placebo group, one subject experienced itching, one had a memory worsening complaint, two had anxiety, one had dyspepsia, and one had agitation. Neither trazodone nor placebo induced significant daytime sleepiness or naps.

In a network meta-analysis of 7 randomized controlled trials testing pharmacotherapies for frontotemporal dementia, trazodone treatment led to significantly higher rates of adverse events compared to placebo (OR=9.53, p=0.007)(Huang et al., 2023). In a randomized controlled trial of 26 patients with frontotemporal dementia, trazodone treatment (150-300 mg/day) led to 42% (11 out of 26) of patients experiencing side effects including fatigue, dizziness, hypotension, and cold extremities (Lebert et al., 2004).

In a retrospective study of 37 long-term care facilities including a total of 427 participants (most of whom with dementia), the main adverse event related to trazodone treatment was falls, reported by more than 30% of participants(Coin et al., 2024). Falls were also reported before trazodone treatment, but at a lower frequency (21% among people with dementia with behavioral/psychological symptoms, 24% among people with dementia only, 19% among people with dementia and depression, 15% among people with depression only). All other adverse events were reported in under 4% of individuals.

In Parkinson's disease patients: In a double-blind randomized trial of 93 patients with Parkinson's disease and sleep disorders, trazodone treatment (50 mg/day) for 4 weeks resulted in two patients experiencing adverse events; one dizziness and one orthostatic hypotension (Hadi et al., 2022).

In neuropathic pain patients: In a phase 2 double-blind randomized controlled trial of 141 patients with painful diabetic neuropathy, treatment with very low doses of trazodone (10 mg or 20 mg, 3 times daily)

for 8 weeks with gabapentin as background therapy (slow titration from 100 mg, 3 times daily, to 400 mg, 3 times daily) did not lead to any serious adverse events (Lipone et al., 2020). The most frequent treatment-emergent adverse events involved the nervous system, QT prolongation, and gastrointestinal issues. Laboratory analysis (blood and urine), vital signs, ECG, and physical findings did not show any significant clinical effect of the study treatments.

In a larger double-blind randomized controlled dose-finding study in 240 patients with painful diabetic neuropathy, a combination of trazodone/gabapentin (2.5/25 mg t.i.d, 5/50 mg t.i.d., 10/100 t.i.d.), gabapentin alone, and placebo were administered for 8 weeks, and two serious adverse events occurred but were judged to be unrelated to study treatment (Tesfaye et al., 2024). Treatment-emergent adverse events were mainly mild-to-moderate in intensity and included nervous system events such as headache, insomnia, somnolence (4 events in the 2.5/25 mg trazodone/gabapentin group, 4 in the 5/50 mg trazodone/gabapentin group, 1 event in the 10/100 mg trazodone/gabapentin group, 2 in the placebo group, and 2 in the gabapentin alone group), gastrointestinal disorders (4 events in the 2.5/25 mg trazodone/gabapentin group, 2 in the 5/50 mg trazodone/gabapentin group, 1 event in the 10/100 mg trazodone/gabapentin group, 3 in the placebo group, and 3 in the gabapentin alone group), and QT prolongation (which were similar across placebo and active drug groups). Laboratory analysis (blood and urine), vital signs, ECG, and physical findings did not show any significant clinical effect of the study treatments.

In pregnant/lactating women: In a cohort study of 221 trazodone-exposed and 869 SSRI-exposed pregnancies, exposure to trazodone in the first trimester was not associated with a significant difference in the risk of major congenital anomalies compared to SSRI exposure (adjusted OR=0.2, 95% CI, 0.03 to 1.77)(Dao et al., 2023). Trazodone use was not associated with a significantly increased risk of pregnancy termination and pregnancy loss compared to use of SSRIs. The cumulative incidences of live birth were 61% and 73% in the trazodone and SSRI group, respectively (25% vs 18% for pregnancy loss and 14% vs 10% for pregnancy termination). The rate of 'small for gestational age' infants did not differ between trazodone users and SSRI users.

In a 44-year-old woman with anxiety and depression who received trazodone (50 mg daily) from 28-38 gestational weeks and during lactation, along with etizolam, trazodone and its active metabolite (mCPP) crossed into the placenta and breast milk (Saito et al., 2021). A male infant weighing 2,918 g was born at 38 weeks of gestation. Oxygenation was initiated immediately after birth due to persistent respiratory disturbance, and the infant was admitted in the neonatal intensive care unit for 5 days. No pulmonary dysfunction or birth defects were detected, and no medication and circulatory support were needed

during admission. A causal relationship between trazodone/etizolam and respiratory disturbance at birth could not be ruled out. Concentrations of trazodone and mCPP in cord blood at 7.4 hours after maternal dosing were 267.6 and 22.8 ng/mL, respectively, which were comparable with maternal serum levels. The trazodone and mCPP concentrations in breast milk collected 7.2 hours after maternal dosing were 50.2 and 3.2 ng/mL, respectively. The infant developed normally, with no drug-related adverse effects at the 1-, 3-, and 6-month postpartum checkups. Further studies are needed to carefully assess the safety of trazodone in fetuses and breastfed infants.

Drug interactions: Trazodone should not be used if an MAO inhibitor (isocarboxazid, linezolid, methylene blue injection, phenelzine, tranylcypromine, and others) was taken in the past 14 days (Drugs.com). Trazodone can cause serotonin syndrome, a life-threatening condition, when it is taken alone or with other medications that affect serotonin levels. Trazodone should not be used with alcohol. Using an NSAID with trazodone may increase the risk of bruising or bleeding. Other drugs that can interact with trazodone include other antidepressants, phenytoin, St. John's wort, tramadol, diuretics, blood thinners (warfarin, coumadin, jantoven), and migraine medications (sumatriptan, imitrex, etc.). For a full list of 138 major, 505 moderate, and 15 minor drug interactions with trazodone, see Drugs.com.

Sources and dosing:

Initial adult dose for depression is 150 mg orally per day in divided doses, then increased by 50 mg per day every 3-4 days (Drugs.com). Maximum dose for outpatients is 400 mg/day and for inpatients is 600 mg/day.

Lower doses (25-100 mg, nightly) have been tested in numerous clinical trials in people with sleep disturbances (Zheng et al., 2022; Kokkali et al., 2024).

On Drugs.com, trazodone has an average rating of 6.3 out of 10 from a total of 1,410 reviews, with 53% reporting a positive experience and 31% reporting a negative experience. Reviewers included people who used trazodone for insomnia, depression, anxiety, sedation, fibromyalgia, major depressive disorder, headache, and reflex sympathetic dystrophy syndrome.

Research underway:

According to ClinicalTrials.gov, there are 17 ongoing clinical trials testing trazodone for various conditions, including insomnia, obstructive sleep apnea, delirium, depression, and neurodegenerative diseases.

The REST trial is a randomized placebo-controlled double-blind crossover study investigating the effect of trazodone on sleep, hippocampal-dependent memory, sleep time, and slow-wave sleep in people with amnestic mild cognitive impairment and sleep complaints (NCT05282550). Trazodone or placebo will be administered to 100 subjects for 4 weeks each, with a 4-week washout period in between. Primary outcomes are changes in total sleep duration, slow wave sleep, and other sleep parameters. Secondary outcomes include memory performance and hippocampal activation. This trial is estimated to be completed in June 2028.

Search terms:

Pubmed, Google: trazodone

- + meta-analysis, + cognitive, + dementia, + Alzheimer, + APOE4, + neuropathy, + lifespan, + mortality, + safety

Websites visited for trazodone:

- Clinicaltrials.gov
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca

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