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.

Donepezil

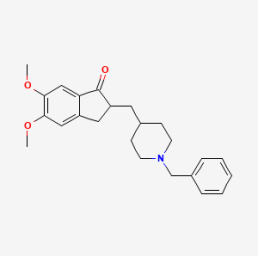
Evidence Summary

Many studies have found benefits of donepezil in dementia, though these benefits are often modest. Efficacy in MCI is unclear. GI symptoms, muscle cramps, and abnormal dreams are common side effects.

Neuroprotective Benefit: Donepezil is approved for use for dementia; it has modest but significant symptomatic benefit, particularly in the first year of use. It is used off-label for MCI and other dementias. Its efficacy in MCI is unclear.

Aging and related health concerns: Observational studies have suggested potential benefits of donepezil for cardiovascular disease in dementia patients. There are other potential indications under investigation, but much of the work is preclinical.

Safety: GI symptoms are a common side effect. Muscle cramps, fatigue, insomnia, abnormal dreams, and loss of interest in eating are also commonly reported. Cardiac monitoring may be appropriate for some patients.

Availability: By prescription	**Dose**: Oral formulations are available as 5, 10, and 23 mg pills; transdermal patches are available in 5 and 10 mg strengths. For mild to moderate dementia, dosing typically begins at 5 mg and can be increased to 10 mg. For moderate to severe dementia, dosing starts at 10 mg, and can be increased to 23 mg	**Chemical formula:** $C_{24}H_{29}NO_3$ **MW**: 379.5 g/mol  Source: PubChem
Half-life: Approximately 3 days	**BBB**: Penetrant	
Clinical trials: The largest meta-analysis of RCTs testing donepezil identified included over 8,000 patients	**Observational studies**: The largest observational study identified included over 13,500 patients who took donepezil.	

What is it?

Donepezil (Aricept®) is a centrally acting reversible acetylcholinesterase inhibitor that is FDA approved for treatment of Alzheimer's disease. It is often used off-label for dementia with Lewy Bodies (DLB), traumatic brain injury (TBI), vascular dementia, and dementia associated with Parkinson's disease (NCBI StatPearls). Below is a table of the currently approved drug types and classes for treatment of AD. Only anti-amyloid drugs are considered to be disease-modifying; the other medications treat symptoms alone. It should be noted that these drugs are specifically approved for treatment of dementia, not mild cognitive impairment (MCI).

Class	Approved Drugs
Anti-amyloid drugs	Lecaemab, aducanumab
Acetylcholinesterase inhibitors	**Donepezil**, rivastigmine, galantamine
Glutamate modulators	Memantine
Acetylcholinesterase inhibitor + glutamate modulator	Donepezil and memantine combination therapy

Orexin receptor antagonist	Suvorexant
Atypical antipsychotic	Brexpiprazole

In the canonical understanding of neurotransmission, a neurotransmitter is released from the pre-synaptic neuron into the synaptic cleft. The neurotransmitter then binds to a receptor on the post-synaptic neuron, causing some kind of response. The neurotransmitter is then degraded, taken back up by the pre-synaptic neuron, or otherwise removed from the synaptic cleft to stop its action. Acetylcholine is a neurotransmitter, and acetylcholinesterase is an enzyme that degrades acetylcholine. Acetylcholinesterase inhibitors block the action of acetylcholinesterase, thereby increasing the amount of acetylcholine in the synaptic cleft and cholinergic signaling overall. Cholinergic neurons are lost in AD, and acetylcholinesterase inhibitor treatment is thought to counteract some loss of cholinergic signaling and thereby mitigate some of the cognitive symptoms. Cholinesterase inhibitors are therefore commonly prescribed to AD patients (reviewed by Ferreira-Vieira et al., 2016 and Birks & Harvey, 2018, among others).

A note about terminology: acetylcholinesterase inhibitors are one kind of cholinesterase inhibitor; butyrylcholinesterase inhibitors are the other kind. Donepezil selectively inhibits acetylcholinesterase, but rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. When papers look at the overall drug class of donepezil, rivastigmine, and/or galantamine, authors often use the term cholinesterase inhibitors. In this report, use of 'donepezil', 'acetylcholinesterase inhibitor', and 'cholinesterase inhibitor' will mirror the citing publication to reflect the drug(s) that were examined and will not be used interchangeably.

Neuroprotective Benefit: Donepezil is approved for use for dementia; it has modest but significant symptomatic benefit, particularly in the first year of use. It is used off-label for MCI and other dementias. Its efficacy in MCI is unclear.

Types of evidence:

- 7 Cochrane systematic reviews and/or meta-analyses
- 12 meta-analyses and/or systematic reviews
- 2 comparative effectiveness research studies
- 1 pooled analysis of RCTs
- 1 professional practice guideline

- 3 clinical trials and 3 secondary analyses of clinical trials
- 3 observational studies
- 1 review
- 3 laboratory studies

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

Donepezil is not approved for use in MCI, though studies have explored whether it can prevent progression to dementia, prevent decline, or improve cognitive function. The American Academy of Neurology's current guidelines on MCI state that: "Studies of cholinesterase inhibitors showed no benefit on cognitive outcomes or reduction in progression from MCI to dementia, although some studies could not exclude an important effect. In addition to lacking efficacy, side effects of cholinesterase inhibitors are common, including gastrointestinal symptoms and cardiac concerns" (Petersen et al., 2018). Other guidance documents from other groups and regions similarly do not recommend cholinesterase inhibitors in MCI (Chen et al., 2021).

A Cochrane systematic review from 2006 identified three double-blinded, randomized trials testing donepezil vs. placebo for patients with MCI. Only two of the trials reported cognitive outcomes and they were not able to pool results in a meta-analysis. One trial reported improved cognitive function at 24 weeks of treatment as measured by ADAS-Cog in patients who took 10 mg donepezil daily compared to placebo (mean difference (MD)=1.90; 95% CI 0.51 to 3.29, p=0.007) but did not find significant differences in four other assessments of cognitive function. The second trial found that compared to patients taking placebo, significantly fewer patients taking donepezil progressed to dementia in the first year of treatment (16/253 donepezil, 38/259 placebo; OR=0.39; 95% CI 0.21 to 0.72, p=0.003), but that there was no significant difference in progression to dementia after 3 years of treatment (63/253, donepezil 73/259 placebo; OR=0.84; 95% CI 0.57 to 1.25, p=0.4). The authors conclusions were that the benefits of donepezil treatment were modest; that donepezil did not delay onset of AD: and that adverse events were not insignificant. The adverse events are discussed in more detail in the 'Safety' section (Birks & Flicker, 2006).

A 2022 systematic review and meta-analysis also looked at whether donepezil improves cognitive function in patients with MCI. The study included 2,847 patients from 12 RCTs and 5 non-randomized concurrent controlled trials. The authors report that compared to control treatment (placebo or

conventional treatment), donepezil treatment was associated with significant improvement in cognitive function as measured by MMSE (standard mean difference (SMD)=0.85; 95%CI: 0.40 to 1.31) and MoCA (SMD: 1.88, 95%CI: 0.32–3.45). There were trends towards improvement in cognitive function as measured by ADAS-Cog in the donepezil group as compared to the control group that did not reach significance. There was similarly a trend towards a reduced frequency of progression to dementia in MCI patients receiving donepezil as compared to those receiving control treatment, but this trend did not reach significance (RR=0.78; 95% CI 0.60 to 1.02). The authors report significant heterogeneity between studies on all measures of cognitive function, and overall low-quality evidence. They also found that the MMSE score was significant only when the trial participants were from Asia; the difference was not significant in North American subjects. Further high-quality RCTs are needed to better clarify the effects of donepezil in MCI patients (Zhang et al., 2022).

These studies are complicated by the challenges in diagnosing MCI and the heterogeneity of MCI. Some groups have hypothesized that 'false-positive' MCI cases might mask benefits of trials (Edmonds et al., 2015). For instance, one of the studies included in both meta-analyses described above enrolled 769 patients with amnestic MCI and randomized them to take placebo, Vitamin E, or donepezil (10 mg daily) for 3 years. This study found that while there was slower progression to AD in the donepezil group after 1 year, there was no difference between groups at 3 years (Petersen et al., 2005). In 2017, another group published a re-analysis of the data. Using actuarial psychometric approaches on cognitive function data collected in the original study from 756 participants, the authors classified the original participants as either single domain amnestic MCI (235), multi-domain amnestic MCI (295), or 'false positive' MCI cases (226); these 'false-positive' MCI participants were significantly younger, better educated, had significantly better scores on diagnostic and neuropsychological measures, and had fewer conversions to AD than the other two groups. When they removed the 'false-positive' MCI cases from the dataset and re-assessed the efficacy of donepezil to placebo and vitamin E group, they found that the rate of progression was significantly lower in the donepezil group at 3 years (52/174 donepezil; 143/356 placebo/vitamin E group; HR=0.71; 95% CI 0.52 to 0.98; p=0.04). This study has a number of limitations, including lack of long term follow-up data and lack of AD biomarker information (Edmonds et al., 2018). Nonetheless, it highlights some of the challenges in running trials in MCI patients.

There are also other factors that might influence the effects of donepezil in MCI patients. It has been suggested that MCI patients with particular MRI imaging subtypes known as hippocampal-sparing or minimal atrophy subtype may respond better to donepezil that those with typical or limbic-predominant patterns of atrophy (Diaz-Galvan et al., 2023). Other studies have looked at butyrylcholinesterase

(BChE), another enzyme that can modulate cholinergic metabolism. Gene variants in the population like one called BChE-K can result in a reduced enzyme activity. Studies have examined the interaction between cholinesterase inhibitors and these genetic variants. Studies have found opposing results even from the same data set, with one study finding that people with the BChE-K allele – especially those who also had an APOE4 allele – declined faster on donepezil (Sokolow et al., 2017), while another paper found that BChE-K and APOE4 carriers had greater cognitive benefits with donepezil (De Beaumont et al., 2016).

Further studies are required to clarify whether donepezil has no or only a modest benefit for MCI, or whether donepezil has benefit only for particular subgroups of patients.

Human research to suggest benefits to patients with dementia:

Donepezil is one of the few FDA-approved treatments for patients with AD. Many trials, systematic reviews, and meta-analyses have assessed the efficacy of donepezil in patients with dementia.

A Cochrane systematic review and meta-analysis analyzed double-blinded randomized controlled trials of donepezil compared to placebo, or two different doses of donepezil, that lasted for at least 12 weeks. The authors included 30 studies comprising 8,257 patients. The authors found moderate quality evidence that donepezil significantly improves cognitive function as compared to placebo after 26 weeks as measured by ADAS-Cog (mean difference [MD]= -2.67; 95% CI -3.31 to -2.02), MMSE (MD=1.05; 95% CI 0.73 to 1.37), and the Severe Impairment Battery (SIB) (MD=5.92; 95% CI 4.53 to 7.31). They also found significant improvement in patients taking donepezil in measures of daily living (ADCS-ADL) (MD=1.03; 95% CI 0.21 to 1.85) and that patients taking donepezil were more likely to show improvement on the clinician-rated global impression of change scale (OR=1.92; 95% CI 1.54 to 2.39). They did not find benefits of donepezil compared to placebo on behavioral symptoms or quality of life. When the authors compared the effects of different doses of donepezil, they found that 23 mg daily dosing did not have significantly more benefit than 10 mg daily, and that 5 mg daily was associated with slightly worse cognitive function on ADAS-Cog but not other measures, and was also associated with fewer adverse events (Birks & Harvey, 2018).

A number of comparative effectiveness studies, systematic reviews, and meta-analyses have assessed the effects of donepezil on cognitive function as compared to placebo and also to memantine and the other cholinesterase inhibitors. These studies generally have reported that donepezil or donepezil +

memantine combination therapy has the strongest or among the strongest associations with improved cognitive function among the medication options for mild, moderate, and severe dementia (Dou et al., 2018; Guo et al., 2020; Veroniki et al., 2022), though other studies do not find that cholinesterase inhibitors produce clinically significant symptomatic improvement of dementia (Blanco-Silvente et al., 2019).

An observational study followed patients with AD from the Swedish Dementia Registry and compared those who started taking cholinesterase inhibitors within 3 months of dementia diagnosis to those who did not take cholinesterase inhibitors at any point over the up-to-10-year follow-up period. The database had 31,054 patients who fit their eligibility criteria. Patients in the database who were not prescribed cholinesterase inhibitors tended to be older, had lower MMSE scores, and had more co-morbid conditions. The researchers used propensity matching to select cholinesterase inhibitor users and non-users who were more similar to one another in terms of age, sex, baseline cognitive function, medication use and co-morbid conditions in order to control for some of these confounding factors. This matching process resulted in a group of cholinesterase treated patients (n=11,652) and untreated patients (n=5,826) that were not significantly different in terms of age, other medications, or co-morbid conditions. When comparing these matched groups, the authors found that those who had been prescribed cholinesterase inhibitors had mitigated cognitive decline; the effect was modest, but did persist; cholinesterase inhibitor treatment was associated with higher MMSE scores at each visit (0.13 MMSE points per year; 95% CI 0.06 to 0.20). Cholinesterase inhibitor treatment was associated with lower risk of death compared to non-use (HR=0.73; 95% CI 0.69 to 0.77). Another cholinesterase inhibitor, galantamine, was associated independently with lower risk of severe dementia as compared to no use of cholinesterase inhibitors (HR=0.69; 95% CI 0.47 to 1.00); this may be because this cholinesterase inhibitor is also an allosteric nicotinic modulator. There were no significant differences when comparing the cholinesterase inhibitors to one another. There are limitations to the study, such as their study design to treat a patient as 'treated' with a cholinesterase inhibitor if they had received a prescription within 3 months of diagnosis, regardless of whether the patient continued taking the medication (Xu et al., 2021).

Donepezil has also been explored for non-AD dementias, including vascular dementia, Lewy body dementia (LBD), Huntington's disease (HD) and Parkinson's disease dementia (PDD) (Li et al, 2015).

A 2021 Cochrane network meta-analysis assessed the use of cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in RCTs of patients with vascular dementia or vascular cognitive impairment.

There were a total of 4,373 patients in the trials. The authors found that of the three drugs and different doses assessed that 10 mg donepezil performed statistically significantly better than placebo and had the greatest effect on cognition, though it was not clear if this was a clinically meaningful benefit. This dose of donepezil was also associated with an increased frequency of adverse events (Battle et al., 2021). Similar results were reported by a 2022 network meta-analysis of all three cholinesterase inhibitors and memantine compared to one another and placebo, with the authors reporting that 10 mg donepezil had the most significant benefits but was also significantly associated with increase in adverse events (Shi et al., 2022). These results are in line with a Cochrane meta-analysis of donepezil compared to placebo in 1,219 patients with mild to moderate cognitive decline due to vascular dementia, which found that patients taking donepezil performed significantly better on cognitive assessments than those receiving placebo, and that the benefits were most marked in the group receiving 10 mg donepezil. The 10 mg donepezil group also had significantly higher frequencies of some adverse events (Malouf & Birks, 2004).

Meta-analyses, including a Cochrane systematic review, have reported that cholinesterase inhibitors, including donepezil (10 mg daily), appears to have cognitive benefits for PDD and LBD (Rolinski et al., 2012; Mori et al., 2024).

Most research on donepezil or cholinesterase inhibitors focuses on performance on cognitive assessments, though there are some studies on potential other benefits to dementia patients. For instance, a 2023 systematic review and meta-analysis compromising 25,399 patients found that treatment with cholinesterase inhibitors was associated with reduced risk of falls (RR=0.84; 95% CI 0.73 to 0.96, p=0.009) (Ahuja et al., 2023). An observational study also found that after adjusting for confounders, critically ill dementia patients in the ICU who were receiving donepezil had a reduced incidence of delirium compared to those not receiving donepezil, and this was associated with other outcomes such as reduced length of ICU stay and 90-day mortality (Lieberman et al., 2023).

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

Acetylcholine is an important neurotransmitter for optimal brain function. Cholinergic signaling is thought to contribute to many neurological functions such as learning, memory, attention, response to stress, sleep, and wakefulness. Dysfunction of cholinergic signaling is highly implicated in AD, as AD patients show degeneration of cholinergic neurons and loss of acetylcholine. Under physiological conditions, acetylcholine and other neurotransmitters are released by one neuron into the synaptic cleft to provoke a response in other neuron(s), and then the neurotransmitters are appropriately removed

from the synaptic cleft to stop the action of that neurotransmitter. Enzymes like acetylcholinesterase can degrade the neurotransmitters in the cleft to stop their action and then recycle the constituent parts for reuse. In disease states with cholinergic neuron degeneration where levels of acetylcholine are low, acetylcholinesterase inhibitors like donepezil can help increase cholinergic signaling and thereby partially restore some cholinergic function (reviewed by Ferreira-Vieira et al., 2016, among others).

While modulation of cholinergic function is the primary mechanism of action of donepezil, there are other potential ways by which donepezil can improve or stabilize cognitive function. It is thought that donepezil might modulate different receptors more directly, such as nicotinic receptors and NMDA receptors (Shen et al., 2010). Based on preclinical and blood samples taken from patients with AD treated with donepezil, donepezil is also thought to have anti-inflammatory actions such as reducing peripheral cytokines and modulating neuroinflammatory responses of microglia and astrocytes (Reale et al., 2004; Kim et al., 2021).

APOE4 interactions:

It is not yet fully clear as to whether APOE4 status interacts with treatment response to donepezil; there have been widely varying reports in the field. A 2022 systematic review examined various predictors of response to acetylcholinesterase inhibitors in dementia. They included 32 studies that examined treatment response in relation to APOE4 status; the authors largely do not reach a conclusion, but state that most studies 'did not find an effect of APOE status on cognitive response' (Pozzi et al., 2022).

A 2018 meta-analysis assessed RCTs, case-control studies, and cohort studies of AD patients that looked at the associations between APOE4 carrier status and treatment response to acetylcholinesterase inhibitors; 38 studies met their inclusion criteria. Of these 38 studies, 5 trials reported that APOE4 carriers had better responses to acetylcholinesterase inhibitor treatment than non-carriers; 4 studies reported that APOE4 non-carriers had better responses than APOE4 carriers; and 29 studies reported no differences in treatment response between genotypes. Thirty of the studies were eligible for meta-analysis. The authors reported that there were no significant differences in response to treatment based on APOE status (standardized mean difference (SMD)=0.022; 95% CI 0.089 to 0.133, p=0.702, I2 = 55.3%) (Cheng et al., 2018).

The above meta-analysis included studies of all three acetylcholinesterase inhibitors, but some studies of donepezil alone have come to similar conclusions. For instance, a pooled analysis of 3 RCTs that

assessed efficacy of 12 weeks of treatment with donepezil compared to placebo, comprising a total of 335 patients, found that both APOE4 carriers and non-carriers treated with donepezil had significant improvement in cognitive function as measured by ADAS-Cog from baseline (-2.95 and -4.09, respectively; p=0.23) (Waring et al., 2015).

The systematic review by Cheng et al., 2018 does state that there is a trend towards better cognitive response to acetylcholinesterase inhibitors in APOE4 carriers when looking at long-term follow up of more than 9 months. The authors also caveat that they were unable to explore whether APOE status interacts with treatment response in MCI. There are hints in the literature that MCI patients who are APOE4 carriers may experience more benefit from acetylcholinesterase inhibitors including donepezil as compared to non-carriers (Peterson et al., 2005), but the studies did not have enough statistical power to draw any firm conclusions. It may also be that certain subgroups of APOE4 carriers will respond differently than others to donepezil, depending on other genetic variations. For instance, some groups have found that having genetic variation in both APOE4 and another gene that codes for butyrylcholinesterase can affect response to donepezil, though there is some controversy as to carrying both genetic polymorphisms predicts poorer or better response to donepezil than carrying just one or neither (Sokolow et al., 2017, De Beaumont et al., 2016).

Aging and related health concerns: Observational studies have suggested potential benefits of donepezil for cardiovascular disease in dementia patients. There are other potential indications under investigation, but much of the work is preclinical.

Types of evidence:

- 1 Cochrane systematic review
- 2 clinical trials
- 3 observational studies
- 3 laboratory studies

Donepezil has been primarily studied in the context of dementia but has also been investigated for cognitive benefits outside of dementia. For instance, donepezil has been explored as a mitigation strategy for cognitive deficits stemming from cranial irradiation, brain tumors, and/or chemotherapy overall (Lawrence et al., 2016; Kirkman et al., 2022; Rapp et al., 2023).

While research focus has largely been on cognitive function, cholinergic drugs may have a variety of effects in the body. There are preclinical and clinical studies assessing whether donepezil or cholinesterase inhibitors in general can impact health outside of neurodegeneration, such as wound healing, bone loss, and chemotherapy-induced peripheral neuropathy (Sato et al., 2015; Kawashiri et al., 2019; Lin et al., 2024).

Cardiovascular Disease, Stroke, and Mortality: POTENTIAL BENEFIT

An observational study of 44,288 individuals in the Swedish Dementia Registry selected a matched subset of people taking cholinesterase inhibitors (n=11,572) and compared to people who were not taking cholinesterase inhibitors (n=11,572). The authors found that taking a cholinesterase inhibitor is associated with a lower incidence of all-cause mortality (HR=0.76; 95% CI 0.72 to 0.80) and stroke (HR=0.8; 95% CI 0.75 to 0.95) when compared to non-users, though the association with stroke was not significant after adjusting for all-cause mortality as a competing risk (Tan et al., 2018). Another study in Taiwan also found a lower incidence of ischemic stroke in patients with mild to moderate dementia (n=5,182) who were taking cholinesterase inhibitors compared to a group of propensity matched patients with the same diagnosis who were not taking cholinesterase inhibitors (n=5,182) (aHR=0.508; 95% CI 0.434 to 0.594, p<0.001); none of the patients had a history of stroke. However, this group did not find differences in mortality rates (Lin et al., 2016). Both of these studies found dose effects, with higher doses of cholinesterase inhibitors being associated with at least a trend towards lower frequency of ischemic stroke and/or death.

The group behind Tan et al., 2018 also used the Swedish Dementia Registry to evaluate whether there was an association between cholinesterase inhibitors and myocardial infarction and/or death in 7,083 patients with AD. After adjusting for confounders such age, gender, MMSE score, living condition, history of cardiovascular disease, and use of medications like antidepressants, antihypertensives, and antidiabetics, they found that compared to patients who had never been prescribed cholinesterase inhibitors, patients who received at least one cholinesterase inhibitor prescription had a lower frequency of myocardial infarction (HR=0.62; 95% CI 0.40 to 0.95), death (HR=0.64; 95% CI: 0.54 to 0.76), and death from cardiovascular causes (HR=0.74; 95% CI 0.57 to 0.97). They also observed a dose response, with higher doses of cholinesterase inhibitors being more significantly associated with lower frequency of myocardial infarction and death (Nordström et al., 2013).

It is hypothesized that the effects of cholinesterase inhibitors on stroke and cardiovascular diseases are mediated through the protective effects on endothelial cells and anti-inflammatory properties of cholinesterase inhibitors, such as by decreasing peripheral cytokine production. It is also possible that the cholinergic modulation affects vagal tone (Nordström et al., 2013; Lin et al., 2016; Tan et al., 2018).

As the above are observational studies, it is also impossible to establish a cause-and-effect relationship. Further work is needed to assess whether these results reflect unrelated confounders or a true biological effect of cholinesterase inhibitors. It is also not clear whether any of the cholinesterase inhibitors are superior to the others for these effects.

Safety: GI symptoms are a common side effect. Muscle cramps, fatigue, insomnia, abnormal dreams, and loss of interest in eating are also commonly reported. Cardiac monitoring may be appropriate for some patients.

Types of evidence:

- 4 meta-analyses and/or systematic reviews
- 2 professional resource documents such as FDA prescribing information or StatPearls
- 3 reviews

The safety profile of donepezil is relatively well understood. Gastrointestinal symptoms including nausea, vomiting, and diarrhea are the most commonly reported adverse events. Loss of interest in eating, sometimes leading to weight loss, insomnia, abnormal dreams / nightmares, muscle cramps, and fatigue are also commonly reported, especially with higher doses. Many of these side effects are mild, transient, and resolve even while the patient stays on the medication (StatPearls). Some studies suggest that transdermal formulations of donepezil may be associated with a lower frequency of GI symptoms than oral formulations (Tariot et al., 2022).

A Cochrane review performed a systematic review and meta-analysis of at least 12-week long double-blinded randomized controlled trials of donepezil in patients with dementia. They included a total of 30 studies and 8,257 patients, though not every study was included in every analysis. The authors found that there were significantly more adverse events in donepezil treated patients as compared to placebo treated patients, and in patients treated with higher doses of donepezil compared to those treated with lower doses of donepezil. Adverse events included GI symptoms such as nausea, vomiting, and diarrhea,

and were mostly mild and transient – though some were moderately severe. Other reported adverse events that were significantly more common in donepezil than placebo were anorexia, dizziness, fatigue, hallucinations, insomnia, muscle cramping, peripheral edema, tremor, vertigo, and weight loss. The meta-analysis found no difference between donepezil and placebo, or donepezil dosing groups, in terms of serious adverse events at 12, 24, or 26 weeks. One study of 286 patients did report a significantly higher rate of serious adverse events in patients taking 10 mg donepezil at 52 weeks compared to those taking placebo (OR=1.99; 95% CI 1.11 to 3.59, p=0.02). There was no difference in number of deaths at any time point, between donepezil and placebo or at different doses of donepezil (Birks & Harvey, 2018).

Cholinesterase inhibitors have been associated with increased risk of syncope compared to placebo, including in a systematic review and meta-analysis that included 53 RCTs comprising 25,399 patients with dementia, Parkinson's disease, MCI, or traumatic brain injury (RR=1.50; 95% CI 1.02 to 2.21, p=0.04); there was no associated between cholinesterase inhibitors and accidental injury or fractures (Ahuja et al. 2023).

There are other rare side effects reported for donepezil. These include cardiac adverse events like bradycardia, QT-prolongation, and changes in heart rate, and may be more common in patients already at risk for these conditions (Young et al., 2021; Varadharajan et al. 2023). Higher doses of donepezil (20 – 23 mg per day) may be associated with a higher incidence of cardiac events than a standard dose of donepezil (10 mg per day) (Wang et al., 2022). There are mixed reports on whether cholinesterase inhibitors can mitigate or exacerbate psychological health in AD and PD patients, with some meta-analyses finding that patients receiving cholinesterase inhibitors were more likely to report depression, and other meta-analyses finding that cholinesterase inhibitors might reduce frequency of hallucinations and delusions (Bittner et al., 2023; d'Angremont et al., 2023)

Donepezil has been tested for, but is not approved for, use in MCI. The safety profile of donepezil in MCI is similar to that in dementia patients. A 2006 Cochrane systematic review of donepezil in MCI by Birks & Flicker, 2006 included three double-blinded, randomized, placebo-controlled studies comprising 782 patients, though safety information was only available from one study. The safety information from that study is included below:

Event	Frequency	OR; 95% CI, p
Withdrawal due to adverse event	43/133 donepezil, 23/137 placebo	OR=2.37; 95% CI 1.33 to 4.22, p=0.003
Any adverse events	116/133 donepezil, 100/137 placebo	OR=2.52; 95% CI 1.34 to 4.76, p=0.004
Diarrhea	36/133 donepezil, 10/137 placebo	OR=4.71; 95% CI 2.23 to 9.97, p<0.0001
Nausea	20/133 donepezil, 9/137 placebo	OR=2.52; 95% CI 1.10 to 5.75, p=0.03
Vomiting	12/133 donepezil, 0/137 placebo	POR=8.30; 95% CI 2.61 to 26.37, p=0.0003
Leg Cramps	12/133 donepezil, 2/137 placebo	POR=4.63; 95% CI 1.58 to 13.55, p=0.005
Abnormal Dreams	30/133 donepezil, 5/137 placebo	POR=5.31; 95% CI 2.61 to 10.79, p<0.00001

A 2022 systematic review and meta-analysis that included 12 RCTs and 5 non-randomized concurrent controlled trials compared use of donepezil to control treatment (placebo or conventional treatment) in MCI patients and also assessed the frequency and type of adverse events. (Zhang et al., 2022).

Event	Frequency	RR; 95% CI
Total adverse events	769/920 donepezil, 509/915 control	RR=1.64; 95% CI 1.13 to 2.38
Nausea / vomiting	116/837 donepezil, 39/843 control	RR=3.01; 95% CI 2.12 to 4.27
Diarrhea	172/837 donepezil, 53/843 control	RR=3.29; 95% CI 2.46 to 4.40
Musculoskeletal and connective tissue disorder	130/837 donepezil, 20/843 control	RR=6.43; 95% CI 4.08 to 10.14
Insomnia / fatigue	85/837 donepezil, 35/843 control	RR=2.45; 95% CI 1.68 to 3.58
Headache / dizziness	42/452 donepezil, 20/447 control	RR=2.08; 95% CI 1.25 to 3.46

Abnormal dreams	83/837 donepezil, 22/843 control	RR=3.81; 95% CI 2.41 to 6.02

In three meta-analyses of cholinesterase inhibitors or donepezil alone in vascular dementia, reported adverse events included anorexia, nausea, vomiting, diarrhea, dizziness, headache, insomnia, leg cramps., abnormal dreams, and/or hypertension, and donepezil 10 mg daily but not 5 mg daily was overall associated with increase in frequency in adverse events. These studies did not find a significant difference in the frequency of serious adverse events or death (Malouf & Birks, 2004; Battle et al., 2021; Shi et al., 2022).

As reported in a Cochrane systematic review, some studies suggest that discontinuing cholinesterase inhibitors can lead to worse cognitive and functional status. More research is needed in this area (reviewed by Parsons et al., 2021).

Drug interactions:

Donepezil is known to interact with 475 drugs; 11 are major, 337 are moderate, and 127 are minor (Drugs.com). Donepezil, along with other cholinomimetic agents, can potentially: cause QT interval prolongation, bradycardia, and/or heart blocks; increase gastric acid secretion and therefore increase risk of ulcer or other GI bleeding; trigger seizures; and/or cause bronchoconstriction, and so should be used with caution with other medications that can increase the risk of the same phenomena (Drugs.com, NCBI StatPearls).

Donepezil should be used with particular caution in patients with bradycardia, bronchospasms, coronary artery disease, parkinsonianism, peptic ulcer disease, seizures, and/or are at risk for rhabdomyolysis; donepezil has the potential to seriously exacerbate these conditions. Donepezil should also be used with caution and monitoring in patients with hyperthyroidism (Drugs.com; NCBI StatPearls).

Research underway:

There are 16 ongoing studies exploring the efficacy of donepezil and are registered on clinicaltrials.gov. As donepezil is an FDA approved treatment for cognitive symptoms associated with AD, donepezil is used as a control treatment or background treatment in other studies. Of the 16 studies that are directly testing donepezil, some are exploring novel uses for the drug – for instance, its effects on bone

remodeling, peripheral neuropathy, wound repair, for alcohol use disorder, for speech recognition in cochlear implant users, or for urinary retention after extensive total hysterectomy in patients with cervical cancer. Sixteen of the studies focus on AD, another neurodegenerative disease, or cognitive function.

NCT05709301 is a randomized double-blinded controlled multi-center study evaluating the safety, tolerability, and efficacy of donepezil for mild cognitive impairment in Parkinson's disease (PD). The researchers plan to enroll 120 patients with MCI in PD. Patients will be randomized to either 10 mg oral donepezil or matching placebo for 1 year. The primary outcomes are global cognition and cognitive functional performance as measured by the PD Cognitive Rating Scale (PD-CRS) and PD Cognitive Functional Rating Scale (PD-CFRS). Secondary outcome measures include several other assessments of different cognitive domains such as memory, attention, executive function, and language, neuropsychiatric symptoms like depression, apathy, and hallucinations, and measures of quality of life and subjective clinical change.

NCT02255799 is an ongoing study investigating donepezil in the treatment of traumatic brain injury (TBI). The study plans to enroll 160 individuals who have had a TBI at least 6 months before starting the study and have persistent, functionally significant memory impairment from the TBI. Participants will be randomized to either placebo or donepezil treatment. Those in the donepezil group will receive 5 mg oral donepezil for 2 weeks and then 10 mg oral donepezil for the remaining 8 weeks of the trial. The primary outcome of the study is any differences between groups in terms of persistent verbal memory impairment as measured by the Hopkins Verbal Learning Test – Revised Total Trials 1-3 at week 10. Other outcome measures include other assessments of cognitive function, neuropsychiatric symptoms, daily functioning, caregiver burden, and frequency of adverse events.

NCT04661280 is an ongoing study in France. Donepezil is no longer reimbursed by the French healthcare system. This trial plans to enroll 240 individuals with mild or moderate dementia and randomize them to either current standard of care treatment, which consists of cognitive, psychiatric, functional, and social care centered on the patient and their environment carried out by AD specialist teams, or similar management plus donepezil. Patients randomized to the drug treatment group will take 5 mg oral donepezil daily for one month and then increase to 10 mg oral donepezil once per day for 5 months. The primary outcome measure of the trial is difference in change in cognitive function as measured by MMSE. Secondary outcome measures include other assessments of cognition, quality of life, and daily functioning.

NCT03454646 is a trial examining the impact of long-term treatment with cholinesterase inhibitors in patients with mild to moderate AD. It is thought that cholinesterase inhibitors delay decline rather than improve patients, but data on more than 6 months of treatment is lacking, as is data in earlier-stage patients. This study plans to enroll 1,205 individuals with mild to moderate AD. Patients will all be treated with a cholinesterase inhibitor (donepezil, galantamine, or rivastigmine) for 6 months. They will then be classified as either a non-responder or responder, based on whether they had a 6-point increase or more on ADAS-Cog score. Higher scores indicate more severe impairment. Responder patients will continue their treatment. Non-responders – those who had a 6-point increase or more on ADAS-Cog – would be randomized to either discontinue treatment or continue treatment for 2 years. No placebo will be given. The primary outcome measure will be loss of independent functioning and/or institutionalization or death at 2 years after randomization. Other outcome measures include overall cognition, specific aspects of daily functioning, mortality, and hospitalizations.

Some of the trials are combination trials, testing donepezil with other interventions.

NCT05114499 is an observational trial to assess the safety and efficacy of donepezil and sodium oligomannate (GV-971). The trial plans to enroll 150 people with mild to moderate AD. They will enroll patients receiving either donepezil (5 mg daily), GV-971 (450 mg twice daily), or both donepezil and GV-971 at the same doses and frequencies. It is not clear how long the study will run for, though it appears it will run for at least 36 weeks. The primary outcome measure is change in cognitive function as measured by ADAS-Cog.

NCT05383183 is investigating whether a combination treatment of donepezil with choline alfoscerate, a cholinergic precursor, is superior to donepezil monotherapy. The study plans to enroll 630 patients with mild to moderate AD. The double-blinded study will randomize patients to either placebo + donepezil or choline alfoscerate + donepezil. Donepezil will be taken as 5 or 10 mg doses once daily, and choline alfoscerate will be taken as 400 mg three times daily doses or matching placebo. Treatment will last for 48 weeks. The primary outcome will be change in cognitive function as measured by ADAS-Cog from baseline to 48 weeks. Other outcome measures include changes in cognitive and daily function over the course of the trial.

NCT05564169 is a trial assessing masitinib as an adjunct therapy to cholinesterase inhibitors and/or memantine in mild to moderate AD. Masitinib is an oral tyrosine kinase inhibitor that inhibits mast cells

and microglia / macrophage activity. The randomized, blinded study plans to enroll 600 mild to moderate AD patients. Patients will be randomized to either placebo + standard of care, defined as cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) and/or memantine, or to masitinib + standard of care. Masitinib will be first dosed at 3 mg per kg per day in two oral daily doses, and then titrated up to 4.5 mg per kg per day after 4 weeks of treatment. Treatment will last for 24 weeks, at which point all patients can opt to enter an additional 24-week extension phase. The primary outcome is change from baseline to 24 weeks in cognitive function and daily function. Other outcome measures include other measures of cognitive function, clinician impression of global change, and time to severe dementia; some of these outcome measures are change from baseline to 24 weeks, and others are from baseline to 48 weeks.

NCT03810794 is a randomized 12-week study looking at the effects of donepezil treatment plus acupuncture. The study plans to enroll 180 patients with mild to moderate AD. The patients will be randomized to either 5 mg oral donepezil daily or 5 mg oral donepezil plus three 30-minute acupuncture sessions weekly for the duration of the trial. Cognitive assessments will be performed at baseline, at the end of treatment, and then 12 and 24 weeks after the end of treatment. The primary outcome measure will be cognitive function as assessed by ADAS-Cog; secondary outcome measures include other assessments of cognitive function, functioning, quality of life, and fMRI measurements of functional connectivity.

NCT05078944 is also assessing the effects of adding acupuncture to donepezil treatment. This study plans to enroll 240 individuals with mild AD. All patients will receive 5 mg of donepezil for a total of 32 weeks; 4 of those weeks will be a run-in period. Half of the patients will be assigned to active acupuncture treatment, whereas the other half will receive sham acupuncture treatment via non-penetrating blunt needles. Both groups will receive the acupuncture or sham treatment 3 times weekly for 14 weeks. The primary outcome measure is change in cognitive function as assessed by ADAS-Cog. Secondary outcome measures include changes in gut microbiota diversity, cognitive and daily function, psychiatric symptoms, and frequency of adverse events.

NCT03954613 is an ongoing open-label randomized trial of 198 patients with AD to evaluate the efficacy of cognitive exercises with and without particular drug combinations. Participants were assigned to one of 6 groups: one taking donepezil alone; one taking memantine alone; one taking both; one taking donepezil and performing cognitive exercises; one taking memantine and performing cognitive exercises; and one taking both drugs and performing cognitive exercises. All cognitive exercises are done

through the BEYNEX software platform. The trial is for 6 months, and the outcome measures are assessments of cognition, daily living, and depression.

NCT05538507 is investigating the efficacy of 'Smart Soup', a traditional Chinese medicine formulation of three different herbs, alongside either donepezil and/or memantine. The study plans to enroll 180 individuals with MCI or AD. The AD patients will be randomized to one of 4 groups and take either: donepezil, memantine, and Smart Soup; donepezil, memantine, and placebo; donepezil and Smart Soup; or donepezil and placebo. Any group taking donepezil will receive 10 mg donepezil, and any group taking memantine will receive 20 mg memantine. MCI patients will be randomized to either Smart Soup alone or placebo. The study will last for 1 year. The outcome measures include change in cognitive function, behavior, psychiatric symptoms, daily functioning, and biomarkers such as CSF Aβ, tau, p-tau, brain activity as measured by EEG and brain structure as measured by MRI.

Other studies involve donepezil but aren't directly testing efficacy.

NCT05345509 is a safety and pharmacokinetic single ascending dose study in 42 healthy volunteers comparing IVL3003, a subcutaneous injection of donepezil, to oral doses. NCT06127368 is a safety, tolerability, and pharmacokinetic study of a single dose of GB-5001, an intramuscular and subcutaneous injection of donepezil, to oral doses in 56 healthy volunteers. NCT06285240 is a small study assessing the safety of efficacy of MK-1167 to participants on stable donepezil treatment. NCT05801380 is a study exploring different factors associated with response to donepezil and memantine; the prospective observational study will follow the estimated 60 patients for up to 6 months and see if changes in gene signature, metabolome, or gut microbiome metabolome are associated with change in cognitive function / response to drug. Other studies are comparing drugs to donepezil as an active control or standard of care, including NCT05811000, NCT06313866, and NCT05641480.

Search terms:

Pubmed, Google: donepezil

- Dementia, MCI, vascular dementia, stroke, prescribing guidelines, Lewy body dementia, peripheral neuropathy

Websites visited for donepezil:

- Clinicaltrials.gov
  Drugs.com
- WebMD.com: Oral, Transdermal Patch
- PubChem
- DrugBank.ca
- Cafepharma (Aricept)