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.

Memantine

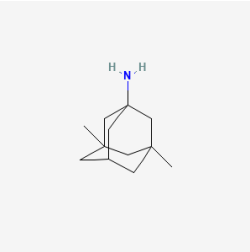
Evidence Summary

Many studies report modest benefits of memantine in moderate to severe dementia. Memantine is typically well tolerated; dizziness and headache are two commonly reported side effects.

Neuroprotective Benefit: Memantine is approved for use in moderate to severe AD; it has small but significant benefits, especially when used in combination. It is used off-label for other dementias. Its efficacy, if any, in mild AD and MCI is not clear.

Aging and related health concerns: Memantine has been explored for use in a variety of conditions, including stroke, depression, and to mitigate cognitive impairment during cranial irradiation. The latter indication is one common off-label use of memantine.

Safety: Memantine is typically well-tolerated, with little to no increase in adverse events compared to placebo treatment. Common side effects include dizziness and headache.

Availability: By prescription	**Dose**: Dosing with the immediate release formulation typically starts at 5 mg by mouth once daily and is titrated up to 10 mg by mouth twice per day. Dosing with the extended-release formulation starts at 7 mg orally once a day, and titrates up to 28 mg orally once per day.	**Chemical formula:** $C_{12}H_{21}N$ **MW**: 179.30 g/mol  Source: PubChem
Half-life: 60 to 80 hours	**BBB**: Penetrant	
Clinical trials: The largest meta-analysis identified included approximately 9,800 patients.	**Observational studies**: Two observational studies of 2000 – 2500 patients were identified.	

What is it?

Memantine (Namenda®) is an N-methyl-d-aspartate (NMDA) receptor antagonist that is one of the drugs approved for use in patients with moderate to severe AD. It should be noted that these drugs are approved for treatment of specific stages of dementia, not mild cognitive impairment (MCI).

Class	Approved Drugs
Anti-amyloid drugs	Lecaemab, aducanumab
Acetylcholinesterase inhibitors	Donepezil, rivastigmine, galantamine
Glutamatergic transmission modulators	**Memantine**
Acetylcholinesterase inhibitor + glutamate modulator	Donepezil and memantine combination therapy
Orexin receptor antagonist	Suvorexant
Atypical antipsychotic	Brexpiprazole

NMDA receptors are a family of ionotropic glutamate receptors that are critical for proper central nervous system function. As an essential player in glutamatergic neurotransmission, NMDA receptors

are necessary for the synaptic plasticity and long-term potentiation that underlie learning and memory. These functions are mediated by NMDA receptors opening to the inflow of ions such as Ca^{2+} at the appropriate time and in the appropriate place in response to the appropriate signals; the inflow of ions then leads to a cellular response. Abnormal NDMA receptor activity is thought to play a role in various neurological diseases, including depression, schizophrenia, neurodevelopmental disorders, and neurodegenerative diseases through mechanisms like excitotoxicity (Dong et al., 2009; Hardingham & Bading, 2010; Hansen et al., 2020).

Memantine is an uncompetitive open-channel NMDA receptor antagonist. As such, it is thought to help reduce aberrant NMDA receptor signaling such as excitotoxicity without disrupting necessary and physiological glutamatergic signaling through NMDA receptors (Tari et al., 2024).

While memantine has been primarily studied for its role in neurodegenerative diseases, memantine has also been explored for effects in other contexts where NMDA receptor modulation may be beneficial. It is prescribed off-label for MCI, mild AD, vascular dementia, chronic pain, psychiatric disorders, and for patients with brain metastases who are receiving particular kinds of radiation treatment (NCBI StatPearls; Gondi et al., 2022).

Neuroprotective Benefit: Memantine is approved for use in moderate to severe AD; it has small but significant benefits, especially when used in combination. It is used off-label for other dementias. Its efficacy, if any, in mild AD and MCI is not clear.

Types of evidence:

- 2 Cochrane reviews
- 7 meta-analyses, systematic reviews, or comparative effectiveness studies
- 1 review of randomized controlled trials
- 5 randomized controlled trials
- 5 open-label studies
- 3 observational studies
- 7 reviews

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

Memantine is not approved for use in mild cognitive impairment. Few trials have explored the utility of memantine in MCI. This may be in part because memantine is only approved for use in moderate to severe AD, as studies have not reliably shown a benefit of memantine in mild AD (Schneider et al., 2011).

Five studies were identified that assessed memantine or a combination therapy of memantine and another drug in patients with MCI, but all have caveats that make it difficult to assess their findings.

- Algin et al., 2017 details a 48-week prospective open-label study that enrolled 45 patients with MCI along with 30 healthy controls; of the MCI patients, 25 took memantine and 20 did not. It does not appear that patients were randomized. The authors did find that patients receiving memantine have improved semantic memory compared to baseline, whereas the patients not receiving memantine and the healthy controls had no change or a decrease in performance. The open-label and un-randomized nature of the trial make it difficult to interpret these findings.
- Wroolie et al., 2009 was a prospective open-label study of memantine treatment in 22 postmenopausal women, each of whom had at least one risk factor for AD. Half of the participants were APOE4 carriers. Participants received memantine for 6 months and were invited back 6 months after dosing end for another assessment, and there was a baseline, end of dosing, and 6 month follow up cognitive testing. While there were trends towards improvement in certain cognitive domains such as executive function, there were significant declines in some assessments that are associated with verbal learning and memory; these deficits improved upon medication withdrawal. Of the 22 subjects who completed the dosing, three refused to discontinue memantine and therefore could not participate in the follow up visit, which adds additional complexity to assessing results from a small trial. As participants were cognitively normal, it can also be challenging to detect changes.
- Pelton et al., 2016 discusses the results of a 48-week open-label combination trial of memantine and escitalopram in 35 adults with depression and cognitive impairment. Compared to baseline, there was an improvement in measures of depression in the patient and in performance in certain cognitive assessments. The authors also stated that there was less-than-expected conversion to dementia over the course of the trial compared to conversion rates seen in other trials. The open-label, uncontrolled design, as well as the combination approach, make it difficult to assess which drug, if either, had efficacy.
- Peters et al., 2012 reported on the results of an RCT in 232 patients with MCI, testing either the acetylcholinesterase inhibitor galantamine, galantamine plus memantine, or placebo and

assessed the impact of the medication on cognitive function. This study was halted due to safety concerns of galantamine that had arisen in other trials, and their preliminary results did not show an overall benefit of combination treatment. They did observe a potential benefit in a subgroup of MCI patients with amnestic MCI, but their data must be seen as preliminary given the halting of the trial.

- Levin et al., 2010 describes a 6-month open-label study in 40 patients with MCI, half of whom received memantine and half of whom received piracetam. Assessment with the Clinical Global Impression (CGI) scale indicated that significantly more patients in the memantine group improved and fewer declined than in the piracetam group. There were significant increases in cognitive function in both groups halfway through the trial, but these improvements only persisted to the end of the trial in the memantine group. Patients receiving memantine also had improvements in measures of depression, quality of life, and subjective cognitive complaints. The open-label design and lack of placebo make it challenging to determine efficacy.

Human research to suggest benefits to patients with dementia:
Memantine is approved for use of moderate to severe AD in the US. A 2019 Cochrane review by McShane et al., 2019, assessed the efficacy and safety of memantine in patients with dementia, and also looked at whether combination therapy of memantine and cholinesterase inhibitors had any additional benefits over treatment with cholinesterase inhibitors alone. The study included 44 RCTs comprising almost 10,000 patients, and they examined outcomes at a six to seven month timepoint. Their findings, by dementia subtype and severity, if relevant, were:

- **Moderate to severe AD**: When comparing memantine treated patients to placebo treated patients, there is high-quality evidence of small but significant clinical benefit in terms of clinical global rating, cognitive function, measures of daily functioning, and behavior and mood. There is some uncertainty regarding memantine's effects on agitation; the statistical analysis indicated that people receiving memantine have a lower incidence of agitation, but studies looking only at patients with agitation found no benefit of memantine compared to placebo. These patients may or may not have been on cholinesterase inhibitors; the authors combined results from trials of monotherapies and combination therapies. These data were from up to 14 studies and approximately 3,700 patients.
- **Mild AD**: Post-hoc subgroup analyses from four studies of approximately 600 patients suggest that there is probably no difference between patients treated with memantine compared to placebo in terms of cognitive function, daily functioning, or behavior and mood. Data also hinted at no benefit in terms of clinical global rating.

- **Mild to moderate vascular dementia**: Results from two studies of approximately 750 patients suggest that there is probably a small clinical benefit of memantine compared to placebo in terms of cognitive function, and that there may be a small clinical benefit for behavior and mood. There is probably no difference in clinical global rating and there may not be a difference in daily functioning.

There was more limited evidence for the following dementias:

- **Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB)**: There may be a small clinical benefit for memantine treatment over placebo in terms of clinical global rating, based on four studies of 319 patients.
- **Frontotemporal dementia (FTD)**: There is a suggestion of small clinical benefit in terms of clinical global function in two studies of approximately 120 patients.
- **AIDS-related dementia complex**: One study of 140 patients suggested that there might be an improvement in cognitive function in patients receiving memantine compared to placebo.

For both PDD/LBD and FTD, there was a hint of potential benefit in terms of behavior and mood. However, the confidence intervals were large, and consistent with both no effect and benefit.

Several other comparative effectiveness studies, systematic reviews, and meta-analyses have assessed the effects of memantine compared to placebo and/or to cholinesterase inhibitors for treatment of AD. Many of these studies find that combination therapy of memantine and donepezil and/or donepezil alone has the strongest effect on outcomes such as cognition and daily functioning compared to placebo (Guo et al., 2020; Cui et al., 2019; Glinz et al., 2019; Dou et al., 2018), though some studies do report a benefit of memantine monotherapy over placebo in patients with moderate-to-severe AD (Veroniki et al., 2022; Chen et al., 2024). It should be noted that some studies find only a 'very small' effect or do not find a 'clinically significant' benefit of memantine over placebo treatment for patients with AD (Blanco-Silvente et al., 2018; Blanco-Silvente et al., 2019).

Observational studies have found stabilization or improvement in the cognitive function and daily functioning of patients as compared to baseline (Calabrese et al., 2007; Stamouli et al., 2011).

Other systematic reviews and/or meta-analyses have also assessed the efficacy of memantine in other dementias. A network meta-analysis compared cholinesterase inhibitors, memantine, and placebo for treatment of vascular cognitive impairment. The authors report that several monotherapies, including

memantine monotherapy, were superior to placebo for cognitive outcomes, though they found memantine to be the 'better comprehensive choice' based on efficacy and acceptability (Shi et al., 2022). Meng et al., 2019 assessed memantine and cholinesterase inhibitors for treatment of PDD and LBD. They found that memantine use had benefits for certain cognitive domains like attention, processing speed, and executive function compared to placebo, though memantine was not seen to statistically improve other outcomes like overall efficacy, motor symptoms, or clinical global impression of change.

Memantine has also been explored for the treatment of amyotrophic lateral sclerosis (ALS), but clinical trials have not found efficacy (Ng et al., 2017; Bhai et al., 2023).

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

Brain NMDA receptors are a class of ionotropic glutamate that play important roles in synaptic plasticity and long-term potentiation, and therefore in learning and memory. Most NMDA receptors require multiple signals to open to ion flow, a phenomenon known as coincidence detection; in the case of NMDA receptors, this involves channel binding of glutamate and a co-agonist, typically glycine or serine. Additionally, most NMDA receptors are blocked by Mg^{2+} ions at neuronal membrane resting potential. Only upon membrane depolarization is the blockade lifted and can the co-agonist binding allow the channel to open to Ca2+ ions. The frequency and length of Ca^{2+} inflow can lead to long-term potentiation or long-term depression through many downstream signaling effects (Hansen et al., 2020).

Too much glutamatergic signaling can result in excitotoxity, which is cell damage or death caused by excessive influx of ions such as Ca2+ resulting from too much excitatory signaling. NMDA receptors are thought to be particularly involved in this phenomenon (Dong et al., 2009). Memantine is a low-affinity, uncompetitive NMDA receptor antagonist that binds to already open channels. As such, memantine is thought to contribute to modulating or blockading aberrant, excessive NMDA receptor activity and its downstream consequences while sparing physiological signaling. It is also thought that memantine, particularly at the right dose, might preferentially blockade extrasynaptic NMDA receptors as compared to synaptic NMDA receptors. Extrasynaptic NMDA receptor activity is thought to be more associated with neuronal injury or death, whereas synaptic NMDA receptors activity is more associated with promotion of neuronal health. This differential action of memantine between extrasynaptic and synaptic NMDA receptors, along with its low affinity for the receptor that results in displacement for

physiological signaling, may underlie some of its efficacy (Hardingham & Bading, 2010; Shafiei-Irannejad et al., 2021; Tari et al., 2024).

Modulation of glutamatergic signaling through NMDA signaling is thought to be the main mechanism of action of memantine. There are other potential mechanisms of action that may also be at play based on preclinical work. At therapeutic doses, memantine may modulate other receptors, such as the nicotinic acetylcholine receptors and/or serotonin receptors (Tari et al., 2024). It is also thought that memantine could have an anti-inflammatory role, including in the brain; NMDA receptors are found on microglia, and memantine may help prevent excessive microglial activation. Memantine may also reduce oxidative stress such as through mitigating ROS production by NMDA receptor activation (Shafiei-Irannejad et al., 2021). Some work suggests NMDA receptors may modulate levels or consequences of pathological tau and/or Aβ (Shafiei-Irannejad et al., 2021; Tari et al., 2024), and there is some preliminary clinical evidence that there were statistically significant decreases in phosphorylated tau in CSF in memantine-treated patients with AD, though it was a small, non-placebo controlled study (Gunnarsson et al., 2007). If any of these mechanisms are at play, they are not mutually exclusive with the primary glutamatergic signaling action of memantine.

APOE4 interactions:

It is not clear whether there is an interaction between APOE4 status and memantine, in part because many of the studies that have looked at APOE4 status and treatment response have examined studies of combination therapies rather than monotherapies. The two studies identified that appear to have assessed memantine monotherapy and APOE4 status were open-label and/or not placebo controlled, and one was in individuals at risk for AD but cognitively normal; both of these studies found no interaction between APOE status and memantine response (Wroolie et al., 2009; Kholin et al., 2016).

Some combination therapy trials have reported differences based on APOE4 status; for instance, one study of 206 individuals with AD, 146 of them whose APOE4 status was known, found that compared to non-carriers, APOE4 carriers had higher response rates on measures of daily living while taking the cholinesterase inhibitor rivastigmine and memantine compared to rivastigmine alone (Han et al., 2012). Other studies, though, have reported differences between carriers only in particular combinations of therapy. Belitskaya-Lévy et al., 2018 describes the results of a trial of 613 patients with mild to moderate AD who were randomized to receive either vitamin E, memantine, both, or placebo. All patients were receiving acetylcholinesterase inhibitor therapy before trial enrollment. The authors report that there

was no difference in response to memantine between APOE4 carriers and noncarriers, but APOE4 carriers declined faster than noncarriers in the vitamin E + memantine group.

Taken together, the evidence suggests there is likely no interaction between memantine and APOE status, but larger analyses are required to answer this question.

Aging and related health concerns: Memantine has been explored for use in a variety of conditions, including stroke, depression, and to mitigate cognitive impairment during cranial irradiation. The latter indication is one common off-label use of memantine.

Types of evidence:

- 1 clinical practice guideline
- 3 Cochrane reviews
- 3 meta-analyses or systematic reviews
- 1 clinical trial
- 1 observational study
- 1 book chapter
- 4 reviews

While most research on memantine has focused on its cognitive effects in dementia, it has been explored for other indications such as psychiatric conditions, cognitive function enhancement in non-dementia contexts, migraines, stroke, and pain. Memantine is currently prescribed off-label for chronic pain, psychiatric disorders, and patients with brain metastases who are receiving cranial irradiation (NCBI StatPearls).

Depression: POTENTIAL FOR BENEFIT

A systematic review and meta-analysis of 11 studies comprising 899 patients found that memantine had a small but significant effect on reducing depressive symptoms in patients with major depressive disorder. Their subgroup analysis indicated that this effect may depend on the underlying diagnosis; for instance, they found memantine had a significant effect in those with mood disorders but not those with schizophrenia (Hsu et al., 2022). Other studies have not found an effect of memantine on

depression, though they had a limited number of studies to assess (Dean et al., 2021). Further work is required to elucidate the effects of memantine in patients with depression.

Memantine is also sometimes prescribed off-label for a variety of other conditions, such as obsessive-compulsive disorder, autism spectrum disorder, and posttraumatic stress disorder, among others (Lu & Nasrallah, 2018).

Stroke: POTENTIAL FOR BENEFIT
As reviewed by Pichardo-Rojas et al., 2023, there is theoretical and preclinical evidence that suggests a potential use of memantine for stroke. Preliminary clinical evidence suggests a potential improvement in outcomes in stroke patients who receive memantine after stroke as compared to those who receive standard of care.

Pain: UNCLEAR BENEFIT

Memantine has been explored for clinical use for a variety of kinds of pain, including neuropathic pain, postoperative pain, chronic pain and fibromyalgia. The data is still largely preliminary or unclear, and require further study (Pickering & Morel, 2018; Kurian et al., 2019; Shanthanna, 20220). There is also some suggestion of benefit for migraine and/or headaches, though this evidence is also preliminary (Xu et al., 2021; Zhou et al., 2022).

Cognitive Function Sparing during Radiation Treatment for Brain Metastases: BENEFIT
The America Society for Radiation Oncology, for instance, 'strongly recommends' memantine for patients who are receiving particular types of brain radiation treatment for brain metastases in order to mitigate the cognitive effects of treatment (Gondi et al., 2022). A Cochrane review also found supportive evidence that memantine may help mitigate or prevent cognitive deficits for patients receiving cranial irradiation for treatment of brain metastases (Kirkman et al., 2022).

Some preclinical work has explored the potential of memantine in cardiovascular and oncological contexts (reviewed by Shafiei-Irannejad et al., 2021).

Safety: Memantine is typically well-tolerated, with little to no increase in adverse events compared to placebo treatment. Common side effects include dizziness and headache.

Types of evidence:

- 3 Cochrane reviews
- 6 meta-analyses, systematic reviews, or comparative effectiveness studies
- 1 pooled analysis from randomized controlled trials
- 1 open label trial
- 3 observational studies
- 1 content analysis
- 1 professional resource document

Memantine is typically said to be well-tolerated. The most commonly reported side effects include dizziness and headache. Confusion and constipation are also common side effects. Less common side effects can include fatigue, pain, hypertension, hallucination, hypertension, and weight gain, among others (NCBI StatPearls).

A 2019 Cochrane review included 44 RCTs of memantine compared to placebo in approximately 10,000 patients with dementia. Their analysis found high-certainty evidence that there was no difference in the incidence of experiencing at least one adverse event when comparing memantine to placebo, regardless of subtype of dementia or severity (RR=1.03; 95% CI 1.00 to 1.06). There were no significant differences between memantine and placebo groups in terms of the number of participants experiencing a serious adverse event (RR=0.92; 95% CI 0.83 to 1.02). Dizziness (6.1% vs. 3.9%) and headache (5.5% vs. 4.3%) were significantly more likely to be reported in memantine patients compared to placebo, respectively. There was high-certainty evidence that there was no difference in frequency of falls between memantine and placebo groups. The authors found evidence that discontinuation rates from memantine, whether due to adverse events or other causes, may depend on disease severity. In mild AD, patients are more likely to discontinue memantine as compared to placebo (RR=1.74; 95% CI 1.08 to 2.81) but discontinuation rates are more similar in moderate to severe AD, with a trend towards less discontinuation in those taking memantine (RR=0.93; 95% CI 0.83 to 1.04) (McShane et al., 2019).

Overall, meta-analyses, systematic reviews, or comparative effectiveness studies examining the safety of cholinesterase inhibitors and/or memantine for treatment of dementia find memantine to have the best tolerability and/or acceptability among the treatment options (Dou et al., 2018; Guo et al., 2020). Observational studies report that patients typically tolerate memantine well (Calabrese et al., 2007; Stamouli et al., 2011). Uncommon events of syncope has been reported (NCBI StatPearls) and at least

one observational study has found an association between memantine use and syncope in patients with AD (Curcio et al., 2020), though a meta-analysis of randomized controlled trials did not find an effect of memantine on syncope (Kim et al., 2011).

Studies of memantine in other patient populations such as Parkinson's disease dementia, dementia with Lewy bodies, depression, and multiple sclerosis have also found memantine treatment to be tolerable and acceptable, with no significant difference in number of adverse events between placebo and memantine and no serious adverse events (He et al., 2013; Meng et al., 2019; Dean et al., 2021; Hsu et al., 2022). Other studies, though, have found increased frequency of adverse events such as dizziness, headache, and fatigue in studies of treatment of memantine for pain (Kurian et al., 2019).

A small open-label study of memantine treatment in women at risk for AD enrolled 26 patients. The most commonly reported adverse events were fatigue, constipation, hot flashes, dizziness, and diminished libido. Two participants withdrew from the study due to adverse events; they experienced hallucinations, mild delusional thoughts, intermittent diarrhea, dizziness, muscle and joint pain and/or fatigue, foggishness, and irritability. Four participants also required dose reductions. Three participants refused to stop memantine treatment at the end of the study. The lack of a placebo group makes it difficult to fully assess these findings (Wroolie et al., 2009).

Self-report data on memantine use was also found on reddit.com, and a paper was published on this data. According to the analysis, 136 users discussed their experiences taking memantine; many were self-medicating for off-label uses such as anxiety, depression, attention-deficit hyperactivity disorder, or obsessive compulsive disorder (n=87 in total), nootropic uses (n=42), and recreationally (n=39). Many individuals were taking doses above the recommended range; the average acute dose was 156 ± 110 mg and the average chronic dose was 23 ± 24 mg. The median chronic dose was 16 mg, potentially indicating outlier effects on the average. It should be noted that the typical daily dose for AD patients is 10 mg or 28 mg for the extended-release formulation. Of the 100 chronic users, 77 self-reported at least one adverse event; the most common were dissociation (n=26), brain fog (16), anxiety (9), insomnia (6), and cognitive impairment (5). Many users reported side effects when starting memantine, but later reported a decrease in side effects. While memantine is not thought to have significant abuse potential given its long half-life, it is clear that at least some people are misusing memantine, whether recreationally or to self-medicate for health conditions or to improve cognition (Natter & Michel, 2020).

Drug interactions:

Drugs.com lists 43 medication-memantine interactions. Of these drug interactions, 2 are moderate and 41 are minor. The two moderate interactions are with trihexyphenidyl and trimethoprim; the former interaction can result in side effects of trihexyphenidyl, and the latter can increase blood levels and effects of memantine.

Combining memantine and other NMDA antagonists such as ketamine and dextromethorphan is thought to potentially increase neuropsychiatric adverse events, though some studies indicate that combinations of certain NMDA antagonists and memantine may not increase risk of adverse events. Memantine is partly excreted through urine, and urine pH of more than 8 can reduce drug clearance, which leads to drug accumulation. Drugs that increase urine pH such as sodium bicarbonate and carbonic anhydrase inhibitors – some glaucoma medications like acetazolamide are in this drug class – should be discussed with your medical professional before combining with memantine (NCBI StatPearls, Drugs.com).

Research underway:

There are 33 trials registered on clinicaltrials.gov that are assessing the efficacy of memantine. Almost all of the trials focus on memantine's effects on cognitive function in different patient populations. Many trials are assessing the cognitive effects of memantine in patients with brain cancer who are receiving radiotherapy and/or chemotherapy. Other trials are testing whether memantine has any utility in patients with psychiatric conditions such as schizophrenia, psychosis, obsessive-compulsive disorder, or autism spectrum disorder. The efficacy of memantine in traumatic brain injury (NCT06337994; NCT05531383), stroke recovery (NCT02144584), orthostatic hypotension (NCT00262470), neurotoxicity from chemotherapy, or lupus is being explored in one or two trials a piece.

Of the 33 trials, 6 are examining the effects of memantine in patients with dementia.

NCT05063851 is a randomized controlled trial assessing whether memantine may be feasible as a preventative therapy for AD and seeks to collect preparatory data for a potential Phase 3 trial. The study plans to enroll patients who are 50 to 65 years old, APOE4 positive, and have a family history of AD. They will randomize 32 participants to either placebo or memantine, and the study will last for 2 years.

The primary outcome measure is feasibility, as assessed by number of participants who are lost to follow up. Other outcome measures will include measures of cognition and other data for Phase 3 trial planning.

NCT05430867 is assessing the efficacy and safety of memantine and sodium oligomannate (GV-971). The study plans to enroll 150 individuals with moderate to severe AD. Patients will receive either memantine alone, GV-971 alone, or a combination therapy of both drugs. It is not clear how long the study will run for, though it appears that it will run for at least 48 weeks. The primary outcome measure is cognitive function from baseline to the end of the study.

NCT05564169 is a trial assessing masitinib as an adjunct therapy to memantine and/or cholinesterase inhibitors 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. 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.

NCT03703856 is a study attempting to identify biomarker predictors or memantine sensitivity. The trial plans to enroll 32 individuals with mild to moderate AD. The study will have two phases. In the first phase, participants will be randomized to receive either placebo or memantine, and the acute effects of memantine on early auditory information processing will be assessed. A set of early auditory information processing measures that appear to be memantine sensitive will be derived for each patient. In the second phase, all participants will receive open label memantine for 24 weeks. The outcome measures of this study are change in cognitive and behavioral function from baseline to the end of the trial.

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. 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.

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.

Search terms:

Pubmed, Google: memantine

- Dementia, AD, vascular dementia, stroke, pain, MCI, safety, depression

Websites visited for memantine:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma: Memantine; Namenda