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.

Rivastigmine

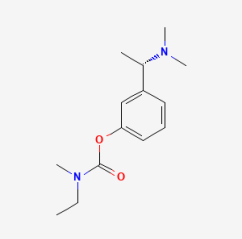
Evidence Summary

Many studies have found benefits of rivastigmine in dementia, though the benefits are modest. There are several common side effects, predominantly GI symptoms. Transdermal dosing may reduce side effects.

Neuroprotective Benefit: Rivastigmine is approved for use in dementia; it has a small but statistically significant benefit for patients.

Aging and related health concerns: Preliminary clinical work suggests that treatment with rivastigmine could help mitigate postoperative delirium in older adults, but larger studies are required to fully assess this possible use.

Safety: GI symptoms are common. Transdermal dosing may be better tolerated than oral dosing. Some observational data suggests that patients taking rivastigmine may have higher mortality than those on other ChEIs; more research in this area is needed.

Availability: By prescription	**Dose**: Oral dose: Initial dose 1.5 mg orally twice a day; titrated up to a maximum of 6 mg twice a day Transdermal patch: Initial dose 4.6 mg patch, switched once daily; titrated up to a maximum of 13.3 mg patch switched once daily.	**Chemical formula:** $C_{14}H_{22}N_2O_2$ **MW**: 250.34 g/mol  Source: PubChem
Half-life: 1.5 hours	**BBB**: Penetrant	
Clinical trials: The largest meta-analysis of RCTs testing rivastigmine included 3,450 patients.	**Observational studies**: The largest observational study identified included approximately 6,100 patients who received rivastigmine.	

What is it?

Rivastigmine is a cholinesterase inhibitor (ChEI) that is approved for treatment of mild to moderate Alzheimer's disease, as well as mild to moderate dementia associated with Parkinson's disease.

Class	Approved Drugs for AD
Anti-amyloid drugs	Lecanemab, donanemab, aducanumab
Cholinesterase inhibitors	Donepezil, **rivastigmine**, galantamine
Glutamate modulators	Memantine
Acetylcholinesterase inhibitor + glutamate modulator	Donepezil and memantine combination therapy
Orexin receptor antagonist	Suvorexant
Atypical antipsychotic	Brexpiprazole

Cholinergic system deficits are a common feature in AD. Cholinesterases such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are enzymes that break down choline-based compounds such as the neurotransmitter acetylcholine at the synapse. ChEIs can increase levels of acetylcholine and thereby enhance cholinergic signaling. There are three approved ChEIs. Unlike donepezil, which is

selective for AChE, and galantamine, which inhibits AChE and modulates nicotinic cholinergic receptors, rivastigmine inhibits both AChE and BChE. (reviewed by Marucci et al., 2021 and Ferreira-Vieira et al., 2016, among others).

Neuroprotective Benefit: Rivastigmine is approved for use in dementia; it has a small but statistically significant benefit for patients.

Types of evidence:

- 5 Cochrane systematic reviews and/or meta-analyses
- 12 meta-analyses and/or systematic reviews, including comparative effectiveness studies
- 4 studies that pooled multiple randomized controlled trials
- 1 professional practice guideline
- 5clinical trials
- 2 observational studies
- 6 reviews
- 2 laboratory studies

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

Rivastigmine is not approved for use in mild cognitive impairment (MCI). 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).

One RCT enrolled 1018 patients with MCI and randomized them to either rivastigmine or placebo. Over the 3-to-4-year duration of the study, there was no significant difference in the incidence of progression to dementia between groups (17.3% on rivastigmine vs. 21.4% on placebo; HR=0.85; 95% CI 0.64-1.12, p=0.225). There was no significant difference in cognitive score between groups.

A small trial of 28 patients with MCI in Parkinson's disease (PD) tested transdermal rivastigmine vs. placebo for 24 weeks. No difference between the groups was observed in terms of clinical global impression of change, the study's primary outcome measure. There were trends towards benefit for cognition, disease rating, and anxiety, as well as significant improvement on a performance-based measure of cognitive ability, which was a secondary outcome measure. This is in line with a Cochrane review of ChEI treatments for dementia with Lewy bodies (LBD), Parkinson's disease dementia (PDD), and cognitive impairment in PD; the Cochrane review concluded that there was no then-current evidence to support the use of ChEIs in cognitive impairment without PD (Rolinski et al., 2012).

Human research to suggest benefits to patients with dementia:

Rivastigmine is approved for use in mild and moderate Alzheimer's disease (AD) and mild and moderate dementia associated with Parkinson's disease (PD).

A Cochrane review included thirteen RCTs of rivastigmine that lasted at least 12 weeks in patients with AD. Their main analysis compared the safety and efficacy of rivastigmine (oral dose of 6 to 12 mg a day or 9.5 mg a day via transdermal patch) to placebo. After 26 weeks of treatment, patients had better cognitive scores as measures by ADAS-Cog (mean difference [MD): -1.79; 95% CI -2.21 to -1.37) and MMSE (MD: 0.74; 95% CI 0.52 to 0.97), along with improvements in activities of daily living (SMD: 0.20; 95% CI 0.13 to 0.27). Patients treated with rivastigmine also had a lower incidence of being assessed as 'no change' or 'deterioration' on the clinician rated global impression of changes as compared to placebo (OR=0.68; 95% CI 0.58 to 0.80). They did not identify any differences in behavioral symptoms between groups. Overall, the authors concluded that rivastigmine 'appeared to be beneficial' for those with mild to moderate AD, though the effects were small and of 'uncertain clinical importance'. The authors looked at the effects of different doses and formulations on cognitive function compared to placebo and/or each other. Compared to placebo, they found evidence of efficacy for high dose oral (6 to 12 mg daily) rivastigmine at all time points, but efficacy for low dose (1 to 4 mg daily) only at later timepoints. Compared to placebo, they found efficacy for higher doses of the transdermal patches (9.5 and 17.4 mg per day) but not for lower doses (4.6 mg per day). When comparing high dose oral formulation to 9.5 mg transdermal patches, they found no difference in effect on cognitive function, though this data was from only one trial (Birks et al., 2015).

Another Cochrane review assessed the efficacy of rivastigmine in patients with vascular cognitive impairment. The review included three RCTs. The authors were not able to pool the data, as one trial

was in patients with cognitive impairment but no dementia, and while the two other studies were both of patients with dementia, differences between the studies precluded pooled analysis. The largest study of the three included 710 patients with vascular dementia and compared a mean dose of 9.4 mg per day of oral rivastigmine to placebo over the course of 24 weeks; in this trial, statistically significant benefits of rivastigmine on cognitive function were observed as measured by MMSE and also by the Vascular Dementia Assessment Scale (VaDAS). A smaller study of a lower dose of rivastigmine (3 mg twice daily) in 40 patients did not find any significant differences in terms of cognition or function compared to placebo. The third study tested the effects of 4.5 mg twice daily rivastigmine compared to placebo in patients who had cognitive impairment but no dementia following ischemic stroke. The study enrolled 50 patients and lasted 24 weeks; the authors did not report any significant differences in cognition or function. Overall, the authors concluded that there is some evidence of benefit of rivastigmine in patients with vascular dementia, but that this conclusion is based on limited data (Birks et al., 2013).

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 low-certainty evidence that there was an effect of rivastigmine on cognition, but these studies included doses of 3 to 12 mg daily and were the smallest trials (Battle et al., 2021).

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, though one study found that rivastigmine 9.5 mg transdermal patches were the most efficacious at improving daily functioning (Dou et al., 2018) and another study found that transdermal rivastigmine and donepezil ranked best for mild-to-moderate impairment (Veroniki et al., 2022). It should be noted that other studies do not find that ChEIs produce clinically significant symptomatic improvement of dementia (Blanco-Silvente et al., 2019). More work is needed to more robustly assess the efficacy and safety of transdermal rivastigmine compared to the other ChEIs and formulations.

An observational study followed patients with AD from the Swedish Dementia Registry and compared those who started taking ChEIs within 3 months of dementia diagnosis to those who did not take ChEIs 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 ChEIs tended to be older, had lower MMSE scores, and had more co-morbid conditions. The researchers used propensity matching to select ChEI 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 ChEI 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 ChEIs had mitigated cognitive decline; the effect was modest, but did persist; ChEI treatment was associated with higher MMSE scores at each visit (0.13 MMSE points per year; 95% CI 0.06 to 0.20). ChEI treatment was associated with lower risk of death compared to non-use (HR=0.73; 95% CI 0.69 to 0.77). There were no significant differences when comparing the ChEI to one another. There are limitations to the study, such as their study design to treat a patient as 'treated' with a ChEI if they had received a prescription within 3 months of diagnosis, regardless of whether the patient continued taking the medication (Xu et al., 2021).

Meta-analyses, including a Cochrane systematic review, have reported that ChEIs, including rivastigmine, appears to have cognitive benefits for PDD and LBD. Rivastigmine also had significant benefits for behavioral disturbances in these patient populations (Rolinski et al., 2012; Wang et al., 2015).

Most research on rivastigmine or ChEIs 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 with cognitive impairment found that treatment with ChEIs was associated with reduced risk of falls (RR=0.84; 95% CI 0.73 to 0.96, p=0.009) (Ahuja et al., 2023). A Cochrane review on preventing falls in patients with PD found that ChEIs including rivastigmine may reduce the rate of falls by 50%, though this was low-certainty evidence (Allen et al., 2022). It is thought that rivastigmine (and other ChEIs) may be especially efficacious for patients experiencing hallucinations (Cummings et al., 2010; Hershey & Coleman-Jackson, 2019). Rivastigmine is also thought to provide benefit for rapid eye movement sleep behavior disorder (RBD) and apathy, reduce falls, and potentially mitigate psychotic symptoms in patients with PD without dementia (Reilly et al., 2021), and ChEIs including rivastigmine may be beneficial for psychotic symptoms in patients with AD and PD (d'Angremont et al., 2023).

Long-term follow-up data from RCTs suggests that compared to historical controls and/or model-based projections, rivastigmine treated patients have slower decline (Grossberg et al., 2004; Small et al., 2005).

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 can degrade the neurotransmitters in the cleft to stop their action and then recycle the constituent parts for reuse; for acetylcholine, cholinesterase inhibitors (ChEI) like acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are responsible for the catabolism. In disease states with cholinergic neuron degeneration where levels of acetylcholine are low, ChEI like rivastigmine can help increase cholinergic signaling and thereby partially restore some cholinergic function (reviewed by Ferreira-Vieira et al., 2016, among others).

While the three approved ChEIs are all thought to exert their neuroprotective effect through increasing the amount of acetylcholine at synapses, there are technical differences in their mechanism of action that may underlie their differential clinical effects. Rivastigmine is a pseudo-irreversible noncompetitive inhibitor and is intermediate-acting. Rivastigmine preferentially binds to the G1 isoform of AChE, which is thought to be particularly relevant in AD. Among the three approved ChEIs, rivastigmine is the most selective for BChE. Studies have suggested that AChE levels and/or activity may progressively decrease over the course of the disease in AD patients, whereas BChE levels and/or activity may increase during AD pathogenesis. Some studies have also suggested that in AD, BChE expression may be higher in AD-relevant regions like the hippocampus, whereas AChE expression is decreased. Genetic variants in the BChE-coding gene, such as the BChE-K polymorphism, are thought to affect BChE levels and/or enzyme activity; these variants have been suggested to affect risk of AD at least in certain populations, which further suggests that modulating BChE activity may be relevant for disease treatment (Ballard et al., 2002; Marucci et al., 2021;

In the brain, BChE is also primarily found on glia whereas AChE is primarily found on neurons, opening up another realm of potential mechanisms underlying differences between drugs (Janiescki et al., 2021; Marucci et al., 2021). Some preclinical studies have suggested that rivastigmine may have anti-

inflammatory effects (Liu et al., 2022), though whether this contributes to any clinical efficacy is not known.

APOE4 interactions:

Studies have reported conflicting results as to whether APOE status is associated with differential response to rivastigmine. Some studies find no interaction between APOE status and response to rivastigmine (Farlow et al., 2004, retrospective analysis of two RCTs of a total of 367 patients; Blesa et al., 2006; open-label study in 167 patients in Spain), some report that APOE4 non-carriers respond better to rivastigmine than APOE4 carriers (Chen et al., 2017; observational study of 63 patients in Taiwan), and others report that APOE4 carriers respond better to rivastigmine and memantine combination therapy compared to non-carriers (Han et al., 2012; subgroup analysis of 146 patients in an RCT). The differences in these findings may be due to small sample size, genetic differences between populations, different disease stage, a combination of these factors, or other variables.

Some larger analyses have looked at APOE status and response to ChEIs. A 2022 systematic review examined various predictors of response to ChEIs 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 ChEIs; 38 studies met their inclusion criteria. Of these 38 studies, 5 trials reported that APOE4 carriers had better responses to ChEI 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).

Aging and related health concerns: Early clinical work suggests that rivastigmine could mitigate postoperative delirium in older adults, and observational studies indicate a potential class benefit for cardiovascular disease; these findings await further studies.

Types of evidence:

- 1 Cochrane review
- 1 systematic review
- 5 clinical trials
- 3 observational studies
- 2 reviews

Rivastigmine has been studied primarily in the context of dementia. There have been some preliminary investigations for other conditions in which cognitive status can be affected, such as traumatic brain injury (Dougall et al., 2015), post-traumatic stress disorder (Maguire et al., 2024), and multiple sclerosis (Gotur et al.,2021). Many of these studies have conflicting results; larger studies are required to assess whether rivastigmine has a true biological benefit for any of these conditions.

Postoperative Delirium: POSSIBLE BENEFIT

It is theorized that reduction in cholinergic activity may contribute to delirium. A handful of studies have assessed whether rivastigmine treatment can reduce postoperative delirium. Some have found that older patients treated with rivastigmine had reduced postoperative cognitive impairment and reduced postoperative delirium (Massoudi et al., 2023). At least one study in older patients with cognitive impairment found that rivastigmine treatment was associated with reduction of delirium (Youn et al., 2017). However, not all studies have found evidence that rivastigmine is effective for prevention of postoperative delirium (Gamberini et al., 2009; other studies discussed in Youn et al., 2017). Future work is required to clarify whether rivastigmine has a true biological benefit and if so, at what dosing regimen, route of administration, and whether there are particular surgical populations for whom rivastigmine is particularly beneficial.

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 common. Transdermal dosing may be better tolerated than oral dosing. Some observational data suggests that patients taking rivastigmine may have higher mortality than those on other ChEIs; more research in this area is needed.

Types of evidence:

- 2 pharmacovigilance studies
- 1 clinical trial
- 1 observational study
- 1 professional resource document

Like other ChEIs, the most commonly reported adverse events while taking rivastigmine are gastrointestinal in nature. These events are often nausea and vomiting and tend to occur during dose-escalation. Slow titration may mitigate the effects; if taking an oral formulation, taking rivastigmine with food can minimize these events. The transdermal patch is thought to have a lower overall incidence of adverse events, though it may not decrease the number of events that lead to stopping the treatment. The transdermal patch is associated with higher incidence of skin adverse events such as application site reaction or dermatitis. Besides for gastrointestinal adverse events, patients receiving rivastigmine have also commonly reported sleep issues, muscle cramps, weakness, and extrapyramidal symptoms (Birks et al., 2015; Patel & Gupta, 2023).

Birks et al., 2015 details a Cochrane review of rivastigmine in patients with AD. Compared to patients receiving placebo treatment, patients receiving 6 to 12 mg daily of oral rivastigmine were significantly more likely to report nausea, vomiting, diarrhea, loss of interest in eating, headache, syncope, abdominal pain, and dizziness. Similar types of adverse events were reported in patients receiving transdermal rivastigmine; transdermal rivastigmine was also associated with increased incidence of contact dermatitis, application site reaction, and erythema. Most of these adverse events occurred during the titration phase. Overall, rivastigmine was associated with a higher instance of at least one adverse event at 26 weeks (OR=2.14; 95% CI 1.80 to 2.53). The authors also assessed the adverse events and trial withdrawals at 24 to 26 weeks by the dose and formulation:

Formulation and Dose	Withdrawals	Incidence of Adverse Events
Oral dose (1 to 4 mg / day)[1]	OR 1.01; 95% CI 0.75 to 1.34	OR=0.93; 95% CI 0.71 to 1.23
Oral dose (6 to 12 mg / day)	OR=2.19; 95% CI 1.83 to 2.63, p<0.00001	OR=2.49; 95% CI 2.05 to 3.02, p<0.00001

Transdermal Patch (4.6 mg / day)[1]	OR=1.53; 95% CI 1.01 to 2.33 p=0.05	OR=1.80; 95% CI 1.16 to 2.78, p=0.009
Transdermal Patch (9.5 mg / day)	OR=1.67; 95% CI 1.23 to 2.26, p=0.001	OR=1.39; 95% CI 1.08 to 1.80, p=0.01
Transdermal Patch (17.4 mg / day)[2]	OR=1.90; 95% CI 1.22 to 2.97, p=0.005	OR=2.28; 95% CI 1.64 to 3.16, p<0.00001

[1] These doses were not found to be efficacious at all time points

[2] This dose does not appear to be on the market

When the authors assessed the one trial looking at the oral formulation compared to the transdermal patch, they found that there were significantly fewer patients reporting at least one adverse event by 24 weeks in those receiving the transdermal patch compared to oral tablets (OR=0.59; 95% CI 0.43 to 0.82, p=0.002). However, there are no differences in incidence of withdrawals (OR=1.09; 95% CI 0.70 to 154, p=0.85).

Other studies also provide supporting evidence that the rivastigmine patch is preferable to the oral formulation. A 2017 pragmatic open-label study enrolled 196 patients with AD and randomized them to one of the three ChEIs; the patients were then followed for 18 weeks. There were no statistical differences between discontinuations between the three drugs for adverse events. Patients assigned to rivastigmine were more likely to achieve the maximum dose (6 mgs twice a day by oral tablet or the 9.5 mg per day transdermal patch) if they were on the patch; 7 of 20 participants achieved the maximum dose on the patch, while 0 of the 16 participants on oral rivastigmine reached the maximum oral dose (Campbell et al., 2017).

Birks et al., 2013 detailed a Cochrane review of the use of rivastigmine in vascular dementia or patients with cognitive impairment but not dementia following ischemic stroke. Two smaller studies included in the review did not find significant differences in assessments of adverse events, but the largest study that included 710 patients did find significantly higher rates of nausea, vomiting, diarrhea, and anorexia in the rivastigmine group compared to placebo. They also found significantly higher rates of withdrawals from the study (OR=2.02; 95% CI 1.38 to 2.98) and rates of withdrawal due to adverse events (OR=2.66; 95% CI 1.53 to 4.62) in the rivastigmine group compared to placebo.

There have been some reports about rare but serious adverse events of rivastigmine. For instance, one observational longitudinal study of patients with AD found that the rate of death was higher in patients who received rivastigmine than patients who received donepezil. The patients in the donepezil group

had lower comorbidity, better functional status, and reported more depressive symptoms; while the authors controlled for these factors in their analysis, it remains a potential influence on the study findings. An alternative hypothesis is that donepezil has a survival benefit that rivastigmine does not have (Kazmierski et al., 2018). Another study reported on a statistical analysis of adverse event reporting databases in Canada and the US, which found a disproportionately higher frequency of reports of death for rivastigmine compared to the other ChEIs. (Ali et al., 2015). Given that these are observational reports, it is not clear whether these data reflect a risk from rivastigmine itself, or whether there is a confounding variable at play. For instance, it is possible that sicker patients are prescribed rivastigmine; that patients with co-morbidities are not ideal candidates for rivastigmine treatment; that there is a greater potential for usage error with rivastigmine, as incorrect application of patches or not removing the patches have led to rivastigmine toxicity. Another pharmacovigilance paper detailed serious cardiovascular events from ChEI use, including rivastigmine, and suggested that cardiovascular events may have been previously underreported (Kröger et al., 2015). It should be noted that other observational studies have reported potential cardiovascular, cerebrovascular, and mortality benefits of ChEI usage (see 'Aging and Related Health Conditions' section). Overall, further research is required to assess the causal relationship between rivastigmine and these rare but serious adverse events.

Some comparative effectiveness studies or network meta-analyses have suggested that among the ChEIs, oral rivastigmine has the least favorable safety profile, had significant higher risk of adverse events than other ChEIs or placebo, or was a ChEI associated with significant trial withdrawal compared to placebo (Dou et al., 2018; Veroniki et al., 2022, Chen et al., 2024), though other network meta-analyses reported different findings (Shi et al., 2022). More work is required to compare transdermal rivastigmine to other ChEIs.

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:

Rivastigmine has 352 known drug-drug interactions. Of these known interactions, 11 are major, 327 are moderate, and 14 are minor. The major interactors are bupropion, iohexol, iomeprol, iopramidol, metrizamide, ozanimod, pacritinib, papaverine, ponesimod, siponimod, and tramadol; many of these

interactions are either due to increased risk of seizures or increased chance of changes to cardiac function. Cholinesterase inhibitors, including rivastigmine, can affect heart rate, constriction of the bronchi, and parkinsonism, may increase gastric acid secretions, and have been associated with convulsions or seizures. Therefore, they should be used with caution in patients with preexisting bradycardia or cardiac conduction abnormalities, asthma, respiratory dysfunction, chronic obstructive pulmonary disease, peptic ulcer disease, or seizure disorders (Drugs.com).

Research underway:

There are six trials registered on clinicaltrials.gov that are ongoing and investigating the use of rivastigmine. Two are for treatment of antimuscarinic delirium; two for treatment of psychiatric illness, including hallucinations and individuals with severe depression who were treated with electroconvulsive therapy; and two in patients with dementia.

NCT04226248 is a trial of 600 patients with Parkinson's disease (PD). Patients will be randomly assigned to receive either placebo or rivastigmine, both in the form of a daily transdermal patch, and will receive study medication for 1 year. The study is assessing whether treatment with cholinesterase inhibitors like rivastigmine reduces the rate of falls in patients. There are a variety of secondary outcome measures, including disease progression and measures of daily functioning and quality of life.

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.

Search terms:

Pubmed, Google: rivastigmine

- Dementia, Alzheimer's, Parkinson's, dementia with Lewy bodies, mild cognitive impairment, inflammation

Websites visited for rivastigmine

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma