Curr Treat Options Neurol (2018) 20: 6
DOI 10.1007/s11940-018-0491-8

Dementia (J Pillai, Section Editor)

Clinical Management of Episodic Memory Changes in Dementia

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Published online: 28 February 2018

This article is part of the Topical Collection on *Dementia*

Keywords Dementia · Alzheimer's disease · Treatment · Non-pharmacological · Physical activities · Mediterranean diet

Abstract

Purpose of review The purpose of this review was to discuss therapeutic options available for the treatment of memory difficulties in dementia.
Recent findings Because of the lack of progress in the availability of new medications, there has been an increased interest in focusing on non-pharmacological means to management cognitive symptoms related to dementia.
Summary The clinical management of memory loss should focus both on pharmacological and non-pharmacological approaches. Treatment with medications should usually begin with a cholinesterase inhibitor and then followed by addition of memantine if there is a decline. In addition to medication management, emphasis should be placed on the importance of maintaining a healthy lifestyle that encompasses physical activities, cognitive stimulation, and a healthy diet.

Introduction

Dementia refers to a decline in one or more cognitive domains (i.e., learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition) that is significant enough to interfere with functional independence; however, the decline is not due to delirium or other mental disorders [1]. Alzheimer's disease (AD) is the most common cause of dementia, with an estimated 5.5 million Americans living with the disease in 2017. There is an immense cost (an estimated $259 billion to American society in 2017) associated with caring for people with dementia [2].

Learning and memory is the most commonly affected cognitive domain in Alzheimer disease. Episodic memory, the ability to recall personal experiences framed in our own context, is frequently the first memory system to be affected in AD [3]. Therefore,

management of episodic memory changes is likely to result in the most impact in treating symptoms associated with AD and limiting healthcare cost.

Memory symptoms can be addressed pharmacologically, non-pharmacologically, or a combination of the two. However, besides new formulations of existing ingredients, no new medications have been approved by the US Food and Drug Administration (FDA) since 2003 for the treatment of cognitive symptoms in AD. Therefore, an emphasis should be placed on non-pharmacological means to prevent and manage memory loss.

Pharmacological interventions

Two classes of medication are currently approved by the US FDA for the treatment of cognitive symptoms in AD: (1) cholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, and (2) memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist.

Cholinesterase inhibitors

There are currently three cholinesterase inhibitors available for the treatment of AD: donepezil, galantamine, and rivastigmine (Table 1). Tacrine, which was the first cholinesterase inhibitor approved by the FDA, was withdrawn from the US market in 2012 due to concern of its hepatotoxicity.

The rationale of cholinesterase inhibitor use is based on the degeneration of cholinergic neurons of nucleus basalis of Meynert in the basal forebrain that is observed in AD, which leads to a cholinergic deficient state [4, 5]. Cholinesterase inhibitors increase available acetylcholine by reversibly binding to and inactivating acetylcholinesterase, which is a post-synaptic enzyme that breaks down acetylcholine. Galantamine and rivastigmine could have additional mechanisms that enhance cholinergic transmission. Galantamine has been proposed to work as an allosteric potentiating ligand of neuronal nicotinic receptors for acetylcholine while rivastigmine inhibits butyrylcholinesterase, which is a non-specific cholinesterase [6].

The efficacy of the three cholinesterase inhibitors has been demonstrated by multiple randomized, double-blind placebo-controlled trials (RCTs) to show modest benefit in improving cognition, activities of daily living (ADLs), global change, and possibly behavior when compared with placebo [7, 8]. Although a small percentage of subjects have an immediate improvement in cognition, most patients show temporary stabilization. The effect of cholinesterase inhibitors could persist for several years with possible delay to nursing home placement suggested by observational and open-label extension studies [9–11]. However, randomized studies did not demonstrate benefit in time to nursing home placement on a long-term basis [12, 13].

The most common adverse reactions of cholinesterase inhibitors are related to increased cholinergic effect on the parasympathetic nervous system such as nausea, vomiting, and diarrhea for the gastrointestinal system and bradycardia and dizziness for the cardiovascular system. These side effects could be reduced by slowing down the dose titration, by giving the medication with food, or by reducing the dosage to previously tolerated dose.

Table 1. Administration, pharmacokinetics, and common adverse reactions of cholinesterase inhibitors

	Donepezil	Galantamine	Rivastigmine	
Dosage and titration	Start at 5 mg daily and increase to 10 mg after 4–6 weeks. The dosage could then be increased to 23 mg daily for severe AD after at least 3 months	Start at 4 mg twice daily (or 8 mg daily for ER formulation) and increase by 4 mg twice daily (or 8 mg ER daily) every 4 weeks at the minimum to maximum dosage of 12 mg twice daily (or 24 mg ER daily)	Oral formulation Start at 1.5 mg twice daily and increase by 1.5 mg twice daily every 2 weeks at the minimum to a maximum dosage of 6 mg twice daily	Transdermal system Start at 4.6 mg daily and increase to 9.5 mg after a minimum of 4 weeks. The dosage could then be increased to 13.3 mg for severe AD after at least 4 weeks
Conversion between formulations	Not applicable	Conversion from immediate release to extended-release formulation occurs on the same total daily dosage (e.g. 8 mg twice daily to 16 mg ER daily)	A total daily dose of < 6 mg of oral rivastigmine can be switched to the 4.6 mg/24 h rivastigmine patch, and a total daily dose of 6 mg to 12 mg of oral rivastigmine can be switched to the 9.5 mg/24 h patch	
Elimination half-life	70 h	7 h	1.5 h	3 h (peripheral); 8 h in CNS; 24 h for patch formulation
Absorption	Could be given with or without food	Give with food	Give with food	Highest when applied to upper back, chest, or upper arm
Most common adverse reactions	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia	Nausea, vomiting, diarrhea, anorexia, and weight decrease	Nausea, vomiting, anorexia, dyspepsia, and asthenia	Nausea, vomiting, diarrhea, depression, headache, anxiety, application site reaction

Studies comparing the three cholinesterase inhibitors and meta-analyses have generally demonstrated similar levels of efficacy and side effect profile among the three medications [7, 8, 14]. If therapy with one agent is ineffective or there is loss of efficacy or intolerable side effects, it is reasonable to switch to an alternative agent. It is recommended that a minimum of 6 months should be allowed after reaching optimal dosage of the initial therapy before contemplating a switch in medication. A prolonged washout period is not necessary unless the initial agent resulted in significant adverse reactions. The new medication should be started at the lowest dosage and titrated up as tolerated [15, 16].

Controversy exists on how long treatment with cholinesterase inhibitors should be continued. Because there is evidence indicating possible worsening of cognition and higher risk of nursing home placement in the short-term basis with discontinuation of treatment, it is judicious to continue treatment as long as the patient is tolerating the medication without significant adverse reactions [13, 17]. On the other hand, when the patient is at the advanced stage of dementia with minimal verbal communication ability and complete dependence of ADL's, it is unlikely that cholinesterase inhibitors would contribute positively to cognition and should be discontinued. A patient's performance on mini-mental state examination (MMSE) could provide a quick estimation on the degree of dementia: mild dementia with MMSE 19–26, moderate dementia with MMSE 10–18, and severe dementia with MMSE < 10.

Donepezil

Donepezil is available in tablets in three strengths (5, 10, and 23 mg) and in orally disintegrating tablets (ODT) in two strengths (5 and 10 mg). It is approved by the FDA for treatment of mild, moderate, and severe AD dementia.

Galantamine

Galantamine is available in immediate-release tablets in three strengths (4, 8, and 12 mg) and as extended-release capsules in three strengths (8, 16, and 24 mg). It is also available as a 4 mg/mL oral solution. It is approved for the treatment of mild to moderate AD dementia.

Rivastigmine

Rivastigmine is available in capsules in four strengths (1.5, 3, 4.5, and 6 mg), as a 24 h transdermal system ("patch") in three strengths (4.6, 9.5, and 13.3 mg), and it is available as a 2 mg/mL oral solution. It is approved for the treatment of mild, moderate, and severe AD dementia. It also has additional indication for mild to moderate Parkinson's disease dementia.

In addition to their official indications, cholinesterase inhibitors have been used on an off-label basis in other types of dementias including vascular dementia and dementia with Lewy Bodies due to the cholinergic deficient state seen in these conditions and support from small clinical trials. However, cholinesterase inhibitors should not be used in frontotemporal dementia.

Memantine

Memantine is a low to moderate affinity, non-competitive NMDA receptor antagonist that binds preferentially to the NMDA receptor-operated cation

channels and blocks excessive NDMA receptor activity. As a result of this action, it is theorized to decrease excitotoxicity, which is the pathological process in which neurons are damaged or killed via persistent activation of NMDA receptors leading to influx of calcium ions that triggers a cascade of events such as lipid peroxidation, nucleic acid damage, and mitochondrial disruption, which result in cell death [18, 19].

Memantine is approved by the FDA for the treatment of moderate-to-severe AD dementia. Its efficacy has been demonstrated through RCTs with beneficial effects seen in cognition, ADL's, and behaviors in patients with AD [20, 21]. It has also been used on an off-label basis in other types of dementias including vascular dementia, dementia with Lewy Bodies, and Parkinson's disease dementia based on support from small clinical trials.

Memantine is available in tablet in two strengths (5 and 10 mg), in extended-release capsule formulation in four strengths (7, 14, 21, and 28 mg), and it is available as a 2 mg/mL oral solution (Table 2).

The principal adverse reactions of memantine are dizziness, headaches, and somnolence.

Combination therapy

Combination therapy of cholinesterase inhibitors and memantine has been advocated due to their different and potentially complementary mechanisms of action. Randomized controlled trials and meta-analysis have demonstrated benefits of combination therapy in cognition, ADL's, behavior, and global change in patients with moderate-to-severe AD dementia. Safety profile and tolerability are generally good [22–24, 25•]. Memantine is usually added to cholinesterase inhibitor after the patient has been on treatment with a cholinesterase inhibitor for at least 6 months with a stable dosing regimen for at least 3 months. Combination therapy is usually initiated due to decline of a patient's status while on monotherapy.

Table 2. Administration, pharmacokinetics, and common adverse reactions of memantine

	Tablet and oral solution	Extended-release capsule formulation*
Dosage and titration	Start at 5 mg once daily and increase by 5 mg daily every week at the minimum to maximum dosage of 10 mg twice daily. (5 mg daily to 5 mg twice daily to 5 and 10 mg separately, and 10 mg twice daily)	Start at 7 mg XR once daily and increase by 7 mg daily every week at the minimum to maximum dosage of 28 mg XR daily
Conversion between formulations	Patients taking 10 mg twice daily of memantine tablet could be converted to 28 mg XR formation once daily after the last tablet dose	
Elimination half-life	60–80 h	
Absorption	Could be given with or without food	
Most common adverse reactions	Dizziness, confusion, headache, and constipation	Headache, diarrhea, and dizziness

*A capsule with combination of memantine XR and donepezil 10 mg (brand name Namzaric) is also available for patients stabilized on donepezil 10 mg daily to add on memantine XR

In December 2014, the US FDA approved a once daily, fixed-dose combination of extended-release formulation memantine and donepezil for patients with moderate-to-severe AD. It should be used as a conversion from donepezil monotherapy or immediate-release memantine plus donepezil combination therapy.

Non-pharmacological interventions

There has been an increased interest in focusing on non-pharmacological means such as physical activities, cognitive interventions, and healthy diets as therapeutic options for the treatment of AD because currently available pharmacotherapies only offer modest improvement of memory symptoms.

Physical activities

Various mechanisms have been proposed to explain physical activity's role in brain health enhancement. Physical activities have been associated with elevated levels of brain-derived neurotrophic factor (BDNF) and nitric oxide (NO), which promotes neurogenesis, angiogenesis, and synaptogenesis. Another theory is that regular exercise improves cerebrovascular perfusion via decreases in blood pressure and oxidative stress and an increase in antioxidant activity [26]. Neuroimaging studies have also demonstrated that physical activity leads to an increase in the size and metabolic activities of hippocampus and other brain regions such as the prefrontal cortex [27–29].

A recent systematic review was published by the Cochrane Collaboration on the topic of exercise programs for people with dementia [30]. The review examined 17 RCTs with 1067 participants and concluded that there is no clear evidence of benefit from exercise on cognitive functioning. However, there is promising evidence that exercise programs may improve the ability to perform ADLs in people with dementia. It was noted that the included trials were highly heterogeneous in the dementia subtype and severity and the type, duration, and frequency of the exercises.

Another recent systemic review was performed that focused specifically on AD dementia [31]. It identified six RCTs with exercise intervention for at least 4 week duration and concluded that there is preliminary evidence on the beneficial effects of exercise on cognition for people with AD. Meta-analysis was carried out on four out of the six trials with objective cognitive outcomes assessment, which revealed a positive effect on global cognitive function. Again there was heterogeneity regarding the type, duration, and frequency of exercises.

National Institute on Aging's Go4Life campaign (https://go4life.nia.nih.gov/), which promotes physical activity as an important part of healthy aging, recommends participating in physical activities at least 3 days a week with at least 150 min (2 ½ h) of moderate endurance activity a week. Endurance type of physical activities should be supplemented by strength (2 or more days per week for 30-min sessions each), balance (2 or more days a week), and flexibility/stretching type of exercises.

Cognitive interventions

Three approaches in cognitive intervention have been described in AD: (1) Cognitive stimulation: Engagement in a range of activities and discussions, usually taken place in a group setting, that aim to enhance general cognitive and social functioning; (2) Cognitive training: Involvement in repeated guided practice on a set of standardized tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving; and (3) Cognitive rehabilitation: Implementation of individualized approach on personally relevant compensatory strategies to improve daily functioning [32].

Proposed mechanisms of cognitive enhancement include (1) increase of cognitive reserve, which is defined as the brain's ability to perform cognitive tasks adequately despite neuropathological damage, and (2) increase of central nervous system plasticity via regular activation of various brain networks from cognitive interventions [33].

A Cochrane meta-analysis identified 11 RCTs with cognitive training and one RCT with cognitive rehabilitation as active treatment for mild to moderate AD and vascular dementia [32]. The authors concluded that no significant benefit was derived from cognitive training, but the sole cognitive rehabilitation trial showed promise. Another Cochrane review analyzed 15 RCTs that utilized cognitive stimulation in people with dementia [34]. The meta-analysis demonstrated evidence that cognitive stimulation had beneficial effect on cognition in people with mild to moderate dementia over and above any medication effects. However, the authors had concerns regarding quality variability, small sample sizes, and lack of randomization method transparency in the trials.

Another recent meta-analysis investigating cognitive interventions in dementia reaffirmed that cognitive stimulation improves scores on cognitive measures of mini-mental state examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) although clinical significance of ADAS-Cog change is weak [35]. In addition, the analysis highlighted the difficulty of blinding of patients and use of appropriate placebo controls in cognitive intervention trials. There are also studies that demonstrated benefits with combined physical activity and cognitive intervention [36, 37, 38•].

Practically to implement cognitive interventions, patients and caregiver should be made aware of adult day programs ("Adult Day Care") in the community that offer activities designed for physical and mental stimulation. Referrals could be made to occupational therapy for cognitive training and speech language pathology for cognitive rehabilitation.

Healthy diets

Adherence to a Mediterranean-style diet (MeDi), which focuses on substantial intake of plant based foods (vegetables including legumes, fruits, whole grains, nuts, olive oil) and fish with a lower consumption of dairy, red meat, and sugars, has been shown in various studies to be associated with improved cognitive function [39, 40•]. Following a MeDi has also been associated with less brain atrophy, with an effect similar to 5 years of aging [41].

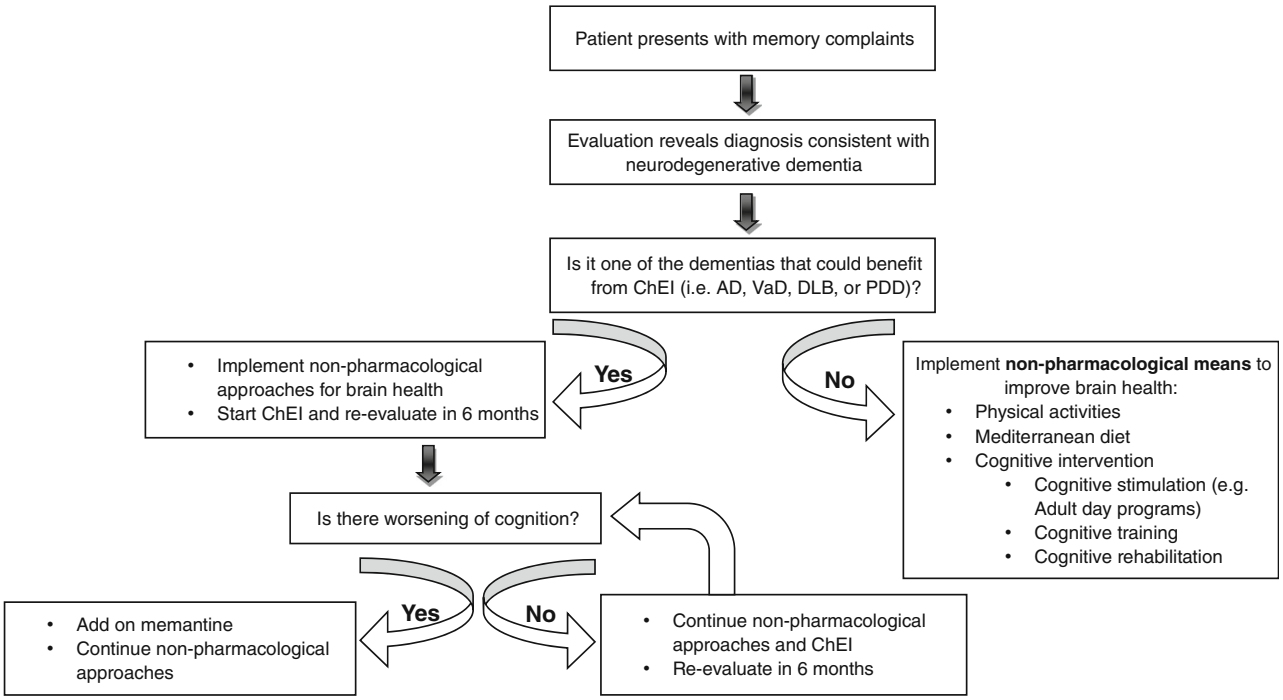

Fig. 1. Recommended algorithm of memory symptom management in dementia. Evaluation of dementia should consist of a detailed history, physical and neurological examination, cognitive assessment either bedside instruments such as MMSE and MoCA or neuropsychological assessment, laboratory studies to evaluate for potentially treatable causes of cognitive impairment, and brain imaging to correlate clinical findings. MMSE = mini-mental state examination; MoCA = Montreal Cognitive Assessment; ChEI = cholinesterase inhibitor; AD = Alzheimer's dementia; VaD = vascular dementia; DLB = dementia with Lewy bodies; PDD = Parkinson's disease dementia.

A few hypotheses exit to explain the potential positive effects of MeDi on cognition [40•, 42, 43]. One theory is that MeDi exerts its benefit via reduction of cardiovascular risk factors (e.g., lowering blood pressure, LDL choleseterol, and increasing HDL), which are also risk factors linked to cognitive decline and dementia. Another potential mechanism is the rich sources of antioxidants including vitamin C, vitamin E, and polyphenols contained within MeDi that could counteract against oxidative stress associated with neurodegeneration. Adherence to a MeDi has also been observed to result in lower levels of inflammatory markers such as C-reactive protein and IL-6. This leads to the theory that MeDi is able to decreased brain inflammation, which is another process implicated in neurodegeneration.

Conclusion

Current medication options for AD offer modest cognitive improvement. There is optimism regarding non-pharmacological interventions (i.e., physical and cognitive activities and a healthy diet) while new treatment options including disease-modifying agents and new symptomatic drugs

are being developed and tested [44•]. Optimal management of cognitive symptoms will continue to evolve, but currently the best option is to incorporate both pharmacological and non-pharmacological approaches (Fig. 1).

Compliance with Ethical Standards

Conflict of Interest
The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. American Psychiatric Association, American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013.
2. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement* 2017. 2017;13(3):325–73.
3. Budson AE, Price BH. Memory dysfunction. *NEJM*. 2005;352:692–9.
4. Mesulam M, Shaw P, Mash D, Weintraub S. Cholinergic nucleus basalis tauopathy emerges early in the aging-MCI-AD continuum. *Ann Neurol*. 2004;55(6):815–28.
5. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol*. 1981;10:122–6.
6. Villarroya M, García AG, Marco JL. New classes of AChE inhibitors with additional pharmacological effects of interest for the treatment of Alzheimer's disease. *Curr Pharm Des* 2004;10(25):3177–3184.
7. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;1:CD005593.
8. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging*. 2008;3(2):211–25.
9. Zhu CW, Livote EE, Scarmeas N, Albert M, Brandt J, Blacker D, et al. Long-term associations between cholinesterase inhibitors and memantine use and health outcomes among patients with Alzheimer's disease. *Alzheimers Dement*. 2013;9(6):733–40.
10. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc. 2003 Jul;51(7):937–44.
11. Feldman HH, Pirttila T, Dartigues JF, Everitt B, Van Baelen B, Schwalen S, et al. Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. Int J Geriatr Psychiatry. 2009 May;24(5):479–88.
12. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105–15.
13. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol. 2015 Dec;14(12):1171–81.
14. Alva G, Cummings JL. Relative tolerability of Alzheimer's disease treatments. *Psychiatry (Edgmont)*. 2008;5(11):27–36.
15. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. *Curr Med Res Opin*. 2003;19(8):707–14.
16. Bartorelli L, Giraldi C, Saccardo M, Cammarata S, Bottini G, Fasanaro AM, et al. Effects of switching from an AChE inhibitor to a dual AChE-BuChE inhibitor in

patients with Alzheimer's disease. *Curr Med Res Opin*. 2005;21(11):1809–18.
17. O'Regan J, Lanctôt KL, Mazereeuw G, Herrmann N. Cholinesterase inhibitor discontinuation in patients with Alzheimer's disease: a meta-analysis of randomized controlled trials. J Clin Psychiatry. 2015 Nov;76(11):e1424–31.
18. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Rev*. 2003 Fall;9(3):275–308.
19. Lipton SA. Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. *J Alzheimers Dis*. 2004 Dec;6(6 Suppl):S61–74.
20. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev*. 2006 19;(2):CD003154.
21. Maidment ID, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. *Ann Pharmacother*. 2008;42(1):32–8.
22. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*. 2004;291:317–24.
23. Feldman HH, Schmitt FA, Olin JT. Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. *Alzheimer Dis Assoc Disord*. 2006 Oct-Dec;20(4):263–8.
24. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine MEM-MD-12 Study Group. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res*. 2008;5:83–9.
25.• Atri A, Molinuevo JL, Lemming O, Wirth Y, Pulte I, Wilkinson D. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. *Alzheimers Res Ther*. 2013;5(1):6. https://doi.org/10.1186/alzrt160. eCollection 2013.

This meta-analysis supports the use of combination therapy of cholinesterase inhibitor and memantine.

26. Davenport MH, Hogan DB, Eskes GA, Longman RS, Poulin MJ. Cerebrovascular reserve: the link between fitness and cognitive function? *Exerc Sport Sci Rev*. 2012;40(3):153–8.
27. Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. *Arch Med Res*. 2012;43(8):615–21.
28. Raji CA, Merrill DA, Eyre H, Mallam S, Torosyan N, Erickson KI, et al. Longitudinal relationships between caloric expenditure and gray Matter in the Cardiovascular Health Study. J Alzheimers Dis. 2016;52(2):719–29.
29. Dougherty RJ, Schultz SA, Kirby TK, Boots EA, Oh JM, Edwards D, et al. Moderate physical activity is associated with cerebral glucose metabolism in adults at risk for Alzheimer's Disease. *J Alzheimers Dis*. 2017;58(4):1089–97.
30. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD006489. DOI: https://doi.org/10.1002/14651858.CD006489.pub4.
31. Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. *Int Psychogeriatr*. 2014;26(1):9–18.
32. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD003260. DOI: https://doi.org/10.1002/14651858.CD003260.pub2.
33. Buschert V, Bokde AL, Hampel H. Cognitive intervention in Alzheimer disease. *Nat Rev. Neurol*. 2010;6:508–17.
34. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD005562. DOI: https://doi.org/10.1002/14651858.CD005562.pub2.
35. Huntley JD, Gould RL, Liu K, Smith M, Howard RJ. Do cognitive interventions improve general cognition in dementia? A meta-analysis and meta-regression. *BMJ Open*. 2015;5:e005247. https://doi.org/10.1136/bmjopen-2014-00524.
36. Graessel E, Stemmer R, Eichenseer B, et al. Non-pharmacological, multicomponent group therapy in patients with degenerative dementia: a 12-month randomizied, controlled trial. *BMC Med*. 2011 Dec 1;9:129. https://doi.org/10.1186/1741-7015-9-129.
37. Lauenroth A, Ioannidis AE, Teichmann B. Influence of combined physical and cognitive training on cognition: a systematic review. *BMC Geriatr*. 2016 Jul 18;16:141.
38.• Shimada H, Makizako H, Doi T, Park H, Tsutsumimoto K, Verghese J, et al. Effects of combined physical and cognitive exercises on cognition and mobility in patients with mild cognitive impairment: a randomized clinical trial. J Am Med Dir Assoc. 2017 Nov 16. pii: S1525–8610(17)30542-X. doi: https://doi.org/10.1016/j.jamda.2017.09.019.

This recent randomized clinical trial demonstrated benefits of combined physical and cognitive activities in cognition in subjects with mild cognitive impairment.

39. Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. Adherence to a Mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of

longitudinal and prospective trials. *Front Nutr*. 2016;3:22. https://doi.org/10.3389/fnut.2016.00022. eCollection 2016

40.• Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. *Adv Nutr*. 2016;7(5):889–904.

This recent systemic review provides a good summary and overview of Mediterranean diet and cognition.

41. Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. *Neurology*. 2015;85(20):1744–51.

42. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. *Arch Neurol*. 2006;63(12):1709–17.

43. Widmer RJ, Flammer AJ, Lerman LO. Lerman A3. The Mediterranean diet, its components, and cardiovascular disease. *Am J Med*. 2015 Mar;128(3):229–38.

44.• Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255–63. https://doi.org/10.1016/S0140-6736(15)60461-5.

This is one of the largest randomized controlled trial that showed a multimodal approach including diet, exercise, and cognitive stimulation could maintain or improve cognitive function in at risk subjects.