Treatment of Vascular and Neurodegenerative Forms of Cognitive Impairment and Dementias

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KEYWORDS

• Alzheimer disease • Dementia • Treatment • Cognition

KEY POINTS

- Cognitive-enhancing medications, the cholinesterase inhibitors and memantine, are indicated for dementia caused by some types of neurodegenerative diseases including Alzheimer disease.
- Identifying and treating vascular risk factors may slow the rate of cognitive decline.
- Advance care planning, enhancing safety (including ability to drive), and providing home care services can increase quality of life and extend the time spent living in the community.

INTRODUCTION

The treatment of dementia has been evolving, although slowly, during the last few decades. Pharmacotherapeutic options remain limited to just a few medications, although there is hope that further research into targeted monoclonal antibodies (mAbs) may deliver new therapies for neurodegenerative diseases. As we are now able to diagnose dementia subtypes earlier by means of PET imaging or cerebrospinal fluid (CSF) biomarkers, novel treatments targeting selected patient populations have a better chance of success than we have previously known.

Because of the absence of disease-modifying therapies (DMTs), the focus of management remains on symptomatic treatments for cognition and memory. Additionally, there are many options to target other sequelae of dementia such as neuropsychiatric symptoms, as well as the hope that better cardiovascular risk factor reduction may prevent cognitive decline and that physical, social, and cognitive therapies may

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enhance cognitive reserve. Addressing auditory and visual impairments may also improve cognition.

Another important aspect of care is to optimize support for living safely with good quality of life and to support the health of informal caregivers. This includes discussions around advanced care planning, as well as assessment of other safety concerns including the risk of falls, access to firearms, and driving safety.

The aim of this article is to review the pharmacotherapies available today, as well as those emerging in research trials, and to briefly list the principles of nonpharmacological management. An overview of patient-centered dementia care is shown in **Fig. 1**.

COGNITIVE-ENHANCING MEDICATIONS FOR NEURODEGENERATIVE DISEASES

Without any proven DMTs for neurodegenerative diseases, symptomatic medications are foundational to dementia treatment. There are currently 3 cholinesterase inhibitors (ChE-I) broadly available, as well as one N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine was the last medication approved for the treatment of dementia by the Food and Drug Administration (FDA) in 2003, and there have been no new medications approved in nearly 2 decades.[1] Selection of a particular medication depends on a variety of factors including dementia type and stage of severity, ease of administration, tolerability, insurance coverage or cost, and is typically decided on an individual case basis.[2]

Cholinesterase Inhibitors

There are currently 3 different ChE-Is available: donepezil, rivastigmine, and galantamine. The efficacy profiles of each medication are similar across several meta-analyses,[3,4] and the selection of a specific medication is typically chosen based on other factors such as dosage frequency or tolerability.[2] An overview is shown in **Table 1**.

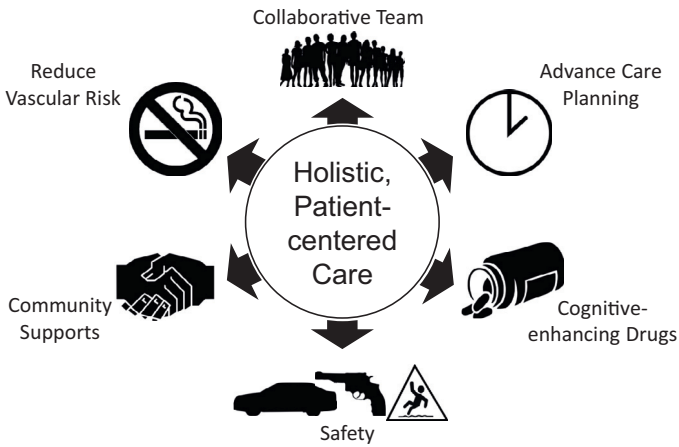

Fig. 1. Overview of Dementia Care. Collaborative team may include allied health professionals such as social workers, neuropsychologists, and occupational therapists. Advance care planning should include designation of an enduring power of attorney, will, and advance medical directives. Cognitive-enhancing drugs are summarized in **Table 1**. Safety should include assessment of driving, access to firearms, risk for falls, and wandering. Community supports may include home care programs, day programs, and support from community-based charitable organizations. Vascular risk factors should be identified and treated.

Table 1
Cognitive-enhancing mediations for Alzheimer disease and Parkinson disease dementia

Medication	Initial Dose	Maximum Dose	Indication	Mechanisms of Action	Unique Features
Donepezil	5 mg OD	10 mg OD (23 mg tablet available in the United States)	Mild-to-severe AD	Acetylcholinesterase inhibitor	The only ChE-I approved for all stages of AD
Rivastigmine	1.5 mg bid	6 mg bid	Mild-to-moderate AD Mild-to-moderate PDD	Acetylcholinesterase inhibitor Butyrylcholinesterase inhibitor	Available in a dermal patch
Galantamine	4 mg bid	12 mg bid	Mild-to-moderate AD	Acetylcholinesterase inhibitor Possible nicotinic acetylcholine receptor modulator	Available in an extended-release formulation
Memantine	5 mg OD	10 mg bid	Moderate-to-severe AD	NMDA receptor blocker	Best tolerability over the ChE-Is

ChE-Is are reversible inhibitors of cholinesterase, preventing break down of acetylcholine in the central nervous system. Cholinergic deficits are implicated in some forms of dementia, and as cholinergic neurons are lost, this leads to worsening memory and cognitive function.[5] By stabilizing cholinergic function, modest improvements in cognition and behavioral symptoms are achieved while also temporarily delaying disease progression.[6,7]

ChE-Is are a viable treatment option for Alzheimer disease (AD) as well as Parkinson disease dementias (PDDs). Given how commonly cerebrovascular disease is accompanied by AD pathology, with data showing up to an 84% overlap, treatment with a ChE-I is reasonable in the setting of vascular cognitive impairment (VCI), although they are not labeled by the US FDA for that purpose.[8] When used for Lewy Body dementia (LBD), ChE-Is seem to improve cognition and activities of daily living (ADL), without appearing to worsen motor function.[9] There is insufficient evidence to support their use in other settings, such as mild cognitive impairment (MCI) or frontotemporal dementia variants.[10,11]

Donepezil

The oldest of the current ChE-Is, it is unique in that is approved by the US FDA for use in all stages of AD, from mild to severe.[12] Advantages include a long half-life with once daily dosing, minimal drug–drug interaction profile, and excellent drug absorption.[6] Dosing starts at 5 mg daily and can be increased to 10 mg after a period of 4 to 6 weeks.[13] In 2010, a 23-mg tablet was patented to target advanced AD. The initial trial was somewhat controversial with cognitive benefit only found in post hoc analysis, and further trials showed modest cognitive benefit in severe AD with increasing risk of adverse side effects at higher dosage.[12,14,15]

Rivastigmine

The US FDA approved rivastigmine for use in mild-to-moderate AD as well as mild-to-moderate PDD, and it is sometimes used off-label in LBD. Dosage begins at 1.5 mg twice daily and can be slowly titrated up to 6 mg twice daily as tolerated.[16] Rivastigmine is the only ChE-I available in a transdermal patch, which may be preferred in the setting of dysphagia or suspected medication noncompliance. It also seems to be better tolerated than the oral formulation.[17] Patients require education on patch placement in order to avoid skin reactions or risk of toxicity should multiple patches be applied in error.[18] Finally, rivastigmine is the only drug that also inhibits butyrylcholinesterase (BChE), another enzyme that breaks down acetylcholine. The role that BChE plays in neurodegenerative disease is not yet clear, and further study is warranted.[19]

Galantamine

The last ChE-I to be approved by the US FDA, galantamine is indicated for use in mild-to-moderate AD. It is initiated at 4 mg twice daily, increasing by 8 mg every 4 weeks to max dosage of 12 mg twice a day. An extended-release formulation is also available for once daily dosing.[20,21] It has also been described as a nicotinic ACh receptor modulator as a secondary mechanism of action, although this has recently been questioned.[22] A prodrug of galantamine, gln-1062, has been suggested to have better CNS penetration as well as reduced side effect profile.[23] An intranasal formulation was recently trialed in a small study but further research is still needed.

Memantine

As the only NMDA receptor antagonist drug approved for the treatment of moderate-to-severe AD, it is often used in combination with other ChE-Is in the later stages of

disease. The initial dose is 5 mg daily, and 5 mg can be added each week at twice daily dosing to a maximum 10 mg twice a day.[24,25] Unlike the ChE-Is, memantine maintains the highest tolerability profile at the highest dosage, whether used alone or in combination therapy. When used in combination, memantine and donepezil seemed to show the best cognitive response as well as overall cost effectiveness.[26] Interestingly, one randomized controlled trial (RCT) demonstrated diminished efficacy of galantamine and memantine as a combination therapy when compared with galantamine alone, and although the underlying reason was not clear, it was posited that this may be due to memantine's antagonism of nicotinic receptors that had been enhanced by galantamine.[27] In addition, 2 RCTs have demonstrated improvement in cognition in mild-to-moderate VCI when compared with placebo and were well tolerated in that population.[28,29]

Efficacy, Tolerability, and Duration of Therapy of Cognitive-Enhancing Medications

There are few head-to-head studies between ChE-Is but several meta-analyses during the last 20 years have shown similar efficacy profiles for improved cognition between all 3 medications.[4,30,31] Data demonstrating improvement of neuropsychiatric symptoms in dementia have been conflicting, although there is suggestion of modest benefit, particularly in combination therapy with memantine.[32] Given the comparative benefits, initial selection of a particular ChE-I can be made on other factors, such as dosage frequency or cost.

The side effect profile is also similar between ChE-Is. The most common side effects are gastrointestinal (nausea, diarrhea, anorexia), although cardiovascular (bradycardia and arrhythmias) and neurologic (dizziness, headache, insomnia) symptoms are seen.[33] Of the ChE-Is, donepezil seems to have the lowest rate of discontinuation and risk of adverse events, whereas rivastigmine was associated with the highest risk of adverse events.[4,26] Memantine is the best tolerated of all, with a comparable safety profile to placebo.[34] Once an agent has been chosen, it should be continued for at least 6 months to monitor for benefit. If no benefit is seen, or the medication is not tolerated, it is reasonable to switch to a different ChE-I. However, if improvement is achieved and then wanes over time, switching to another agent is not recommended.[35]

The total duration of therapy remains unclear because most clinical trials were only 6 to 12 months in duration and clinical guidelines are variable. The AD2000 trial detected a persistent cognitive benefit with donepezil during a period of 2 to 4 years.[36] Post hoc analysis in the DOMINO-AD trial also suggested increased risk of nursing home placement in the following 12 months after donepezil withdrawal.[37] Discontinuation of therapy can be considered if a patient on therapy for more than 12 months continues to decline cognitively with or without previous benefit, if the patient enters end stage dementia, or if a patient develops intolerable side effects.[38]

Emerging Evidence for Antiamyloid Beta Monoclonal Antibodies

In the long search for DMTs for AD, mAbs targeting amyloid-beta may be the most promising approach, but not without controversy. In the setting of AD, several mAbs have been developed and are theorized to either bind amyloid proteins for phagocytosis by macrophages, to enhance the efflux of amyloid beta outside of the blood–brain barrier, or both.

Initial trials of gantenerumab and solanezumab did not find clinical benefit.[39,40] Based on evidence from 2 phase 3 trials, the US FDA granted accelerated approval for aducanumab, an anti-beta amyloid mAb, on the basis that it was proven to reduce signal on amyloid PET scans. This was the first DMT approved for AD, as well as the

newest dementia medication in more than 20 years. However, the clinical effectiveness of the drug has been questioned. Evidence for reduced functional decline emerged only after post hoc analysis of the 2 trials, which were originally terminated early due to evidence of futility.[41]

Concern over widespread use of aducanumab has been heightened by its association with amyloid-related imaging abnormalities, consisting of either vasogenic edema or intracranial hemorrhage.[42] The European Medicines Agency declined to authorize aducanumab for treatment of AD, and US Medicare decided to cover the costs of aducanumab only when it is used in clinical trials.[43,44] Currently, there seems to be little use of aducanumab in routine clinical practice in the United States. In the coming years, additional trials of aducanumab and similar antibodies such as donanemab[45] may clarify whether they will play a role in the management of early AD.

TREATMENT OF VASCULAR COGNITIVE IMPAIRMENT AND THE ROLE OF VASCULAR RISK REDUCTION

Cerebrovascular pathology is present in the brain of most persons who die of dementia, often accompanying neurodegenerative pathologic conditions such as AD. In contrast to the neurodegenerative diseases where there is not yet definitive evidence for DMTs, it is known that vascular risk factors can be reduced, and stroke can be prevented. Therefore, targeting vascular risk is currently the most promising method for preventing cognitive decline and preserving cognition. Vascular risk should be assessed, and risk should be reduced in all patients with dementia, including those diagnosed clinically with neurodegenerative causes as well as those with VCI.

Cognitive-Enhancing Medications in Vascular Cognitive Impairment

There are currently no specific pharmacologic interventions indicated by the US FDA for the treatment of cognition in the setting of VCI. Meta-analyses of ChE-Is and memantine for VCI found modest cognitive benefit for donepezil, galantamine, and memantine but treatment came at a cost of side effects; therefore, their role in the treatment of VCI has been controversial.[46,47] Their use in selected patients may be reasonable, with the strongest rationale for treating patients with VCI that have gradually progressive decline and who may also have concomitant AD pathology.[48]

Aspirin

In the ASPREE trial, use of aspirin in the general elderly population did not reduce the incidence of dementia or MCI.[49] When trialed in patients with AD, aspirin did not improve cognitive outcomes and was associated with increased bleeding.[50] For patients with VCI with covert brain infarcts but no history of symptomatic stroke, the use of aspirin may be reasonable but there is no definitive evidence from clinical trials to indicate the effectiveness of this approach.[48] We recommend against using aspirin for patients with only white matter lesions because the pathogenesis of white matter lesions is uncertain and because an increased risk of intracranial bleeding was seen in one small trial.[51]

Control of Vascular Risk Factors

The primary focus of management in VCI should be on cardiovascular risk reduction and stroke prevention, with management of blood pressure, diabetes, dyslipidemia, and obesity, as well as reduction in smoking and alcohol use. For patients with VCI after a prior stroke, preventing the next stroke is the most important objective.

Given that cerebrovascular disease frequently accompanies neurodegenerative diseases, and that so many vascular risk factors are also risk factors for dementia, there should be a focus on vascular risk reduction for all patients with cognitive impairment (MCI or dementia) of any apparent cause. The American Heart Association provides guidance on primary prevention of stroke, which is applicable to all patients with dementia.[52] An earlier article in this issue reviews vascular risk reduction for dementia prevention in greater detail.

COGNITIVE TRAINING

Based in theories of cognitive reserve and neuroplasticity, various nonpharmacologic cognitive-enhancing strategies have been assessed in dementia patients.[53] Research began in the 1980s with pen and paper testing, expanding to computer programs in the 1990s, and now with smart phone and tablet programs. As technology continues to evolve, more therapies are adapting the use of augmented and virtual reality, video games, or electroceutical interventions such as transcranial magnetic stimulation.[54] These interventions rely on the assumption that by performing isolated tasks designed to stimulate a specific cognitive function (ie, verbal memory, logic, and planning), benefit can then be adapted to real-world situations, a concept known as far transfer.[55]

There are 3 main methods used: cognitive stimulation (CS), cognitive rehabilitation (CR), and cognitive training (CT). CS are nonspecific exercises that are usually done in a group setting to enhance cognition and socialization. CR is usually done in a one-on-one setting with the aim of improving a specific deficit such as speech or visual processing. Finally, CT can be done individually or in groups with the intention of improving a specific function such as memory or attention.[56]

Given the heterogeneity of different cognitive interventions that have been studied, it is difficult to systematically evaluate their overall benefits. A recent Cochrane review of 33 trials in those with mild-to-moderate dementia suggested small improvements in global cognition and verbal memory but with low quality of evidence and high risk of bias.[56] A meta-analysis of computerized CT found moderate and significant improvement in measures of global cognition, verbal and nonverbal learning, both verbal and working memory, attention, and psychosocial functioning in those with MCI. However, this was not demonstrated in those with suspected dementia.[57]

At this time, the best evidence for CT in improving cognition and delaying dementia is seen in healthy older individuals and MCI populations. More information on cognitive reserve and CT for dementia can be found in another article in this issue.

MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS

Most persons with dementia, up to 98%, will experience neuropsychiatric symptoms, especially in the later stages of disease.[58] Behavioral and psychological symptoms of dementia (BPSD) vary and can manifest as agitation, depression, sleep disorders, hallucinations, or delusions.[59] Later life emergence of persistent neuropsychiatric symptoms, known as mild behavioral impairment, can be predictive of developing cognitive decline and dementia.[60] The presence of these symptoms can affect both the patient and their caregiver(s), resulting in worsening cognitive decline, prolonged hospital stays, and earlier institutionalization.[61]

Selection of a specific agent to manage BPSD should be done carefully because many of these medications are associated with the risk of worsening cognition, falls, or adverse cardiovascular events.[62] Antipsychotics seem to increase mortality in

dementia, and this has led to warnings to providers of these drugs in several countries.[63] Drugs for BPSD should be initiated with a "low and slow" methodology and the patient closely monitored for symptomatic benefit or adverse effects. However, nonpharmacological approaches should be the first line of treatment and may include interventions such as occupational therapy, art therapy, and psychological therapy. The management of neurobehavioral and psychiatric disturbances in dementia is covered in greater detail in another article in this issue.

MANAGING SAFETY CONCERNS

Wandering and Pacing

Wandering is a common symptom seen in patients with dementia and is a seemingly aimless or disoriented ambulation, also characterized as lapping or pacing. This behavior can lead to patients becoming lost, cause injuries due to falls, or result in fatigue, weight loss, and earlier institutionalization.[64] Treatment can be challenging. Medications such as ChE-Is, SSRIs, or atypical antipsychotics have been tried. Nonpharmacologic interventions may include exercise or music therapy, personal tracking devices, or camouflaging doorways to reduce elopement.[65]

Falls

Although falls in elderly patients are common, those with cognitive impairment are twice as likely to fall and are 5 times more likely to be admitted to institutional care. Falls may also result in injury such as fractures and concussions.[66] The first step is to review patients for evidence of orthostatic hypotension or visual impairment, as well as any contributing medications such as antipsychotics or benzodiazepines.[67] Although encouraging physical activity is advisable, it is unclear as to which exercises are recommended to reduce the risk of falling.[68,69] Other safety precautions could include the use of hip protectors and low impact flooring, although poor compliance and costs may prohibit their implementation.[70]

Driving Safety

Patients with dementia have a higher risk of becoming involved in a traffic accident when compared with those without. Although people with neurodegenerative cognitive impairment may be capable of driving for some time, given the progressive nature of their disease, it is reasonable to review their driving ability every 6 to 9 months.[71] Evaluation of driving safety can be difficult and varies widely in practice. Asking informants about any recent accidents or traffic violations, as well as their perspective on the safety of the patient's driving, can be helpful.[72] Safe driving correlates with several cognitive domains including visuoconstructional, visuospatial, attention, and executive functioning. Although no single cognitive test can predict driving safety in isolation, some tools that may be helpful include both Trail Making Tests A and B, Symbol Digit Modality Test, clock drawing, as well as intersecting pentagon figure copying.[71,73] Discussion of safe driving in the setting of dementia should be done early in the disease course, and if any concerns are identified then driving cessation or on-road testing is warranted.[74]

Firearm Safety

Around 20% of home caregivers experience aggression or violence from those with dementia, and the presence of a gun in the home adds another layer of risk.[75] People diagnosed with dementia may have an increased risk of suicide, and accessibility to a gun increases that risk.[76] If a firearm is accessible, care providers should ask about the "5 Ls": is the gun *loaded*, is it *locked*, are there *little* children in the home, is the patient

feeling *low*, and has the patient properly *learned* how to use the weapon.[77] Although rules regarding firearm possession in those with dementia varies by location, discussion and education of gun safety with patients and caregivers is important in reducing risks to them and society at large.

SUPPORTING QUALITY OF LIFE AND ADVANCED CARE PLANNING

Advanced Care Planning

Given that informed capacity and decision-making will probably be lost as cognition declines, discussions around care planning should happen early and be revisited as patient needs change over time. These discussions should include not only medical care but also estate and financial planning, includinng designation of an enduring power of attorney.[78] Unfortunately, advanced care planning in those with dementia is often neglected and only hoccurs in an estimated 3% to 39% worldwide.[79] Because it is a sensitive topic, approaching it in an individual, patient-centered way is advisable.[80] Advanced care planning increases satisfaction of care for both patients and their caregivers, and may reduce rates of hospitalization or stress for families who find themselves making emergent decisions on behalf of their loved ones.[81] Provision of educational materials on these documents at clinic visits and referral to social work can help families navigate the complexities unique to their situation and respective legal systems.

Community Resources

Most dementia care is provided by informal caregivers, typically spouses or other family members. Caregiver burnout increases with worsening disease severity, particularly when BPSD symptoms are present, such as aggression or delusions, and can result in increased rates of depression and hypertension in caregivers.[82]

Support groups are a great resource for caregivers and have been shown to be effective in reducing stress, depression, and feelings of resentment, as well as improving handling skills and quality of life.[83] Adult day programs can also mitigate caregiver burnout by providing respite, reducing patient behavioral symptoms, and keeping patients engaged in their community who would otherwise be isolated.[84] Other resources that could be explored include speech therapy for those with aphasia or dysarthria, and occupational and physical therapy for those with motor impairment and poor balance.[85–87] Nonprofit organizations—such as the Alzheimer's Association (USA), Alzheimer's Society of Canada, and Alzheimer's Society (UK)—may be able to provide additional services and support.

SUMMARY

Given the lack of DMTs in dementia, a holistic and patient-centered approach is required to provide the excellent care that patients deserve. As these patients are mainly elderly and likely to have other comorbidities, medication reconciliation is pertinent to reduce possible offending drugs, and introduction of new medications should be done slowly and in a supervised fashion to ensure treatment goals are attained. Vascular risk factors should be identified and treated in all patients. Patient and caregiver education and support can allow persons with dementia to live independently in their communities for longer. New therapeutics are emerging that may in the future provide new tools to modify the course of AD and enhance cognition.

CLINICS CARE POINTS

- Cognitive-enhancing medications, including the cholinesterase inhibitors and memantine, are indicated for AD and PDD, with moderate-quality evidence for vascular dementia and LBD.
- There is hope that the course of AD can be modified by monoclonal antibodies that target amyloid beta, although further clinical trials are needed.
- Vascular risk factors should be identified and treated in all patients.
- Multidisciplinary care should include identifying and treating neuropsychiatric symptoms, offering cognitively stimulating activities, planning in advance for loss of capacity to make decisions, and supporting safe living in the community.

DISCLOSURE

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REFERENCES

1. Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Syst Rev 2005;(2):CD003154.
2. Graham L. AAFP and ACP release guideline on dementia treatment. Am Fam Physician 2008;77(8):1173–5.
3. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;2006(1):CD005593.
4. Kobayashi H, Ohnishi T, Nakagawa R, et al. The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis. Int J Geriatr Psychiatry 2016;31(8):892–904.
5. Bartus RT, Dean RL 3rd, Beer B, et al. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982;217(4558):408–14.
6. Adlimoghaddam A, Neuendorff M, Roy B, et al. A review of clinical treatment considerations of donepezil in severe Alzheimer's disease. CNS Neurosci Ther 2018;24(10):876–88.
7. Xu H, Garcia-Ptacek S, Jönsson L, et al. Long-term effects of cholinesterase inhibitors on cognitive decline and mortality. Neurology 2021;96(17):e2220–30.
8. Attems Johannes, Jellinger Kurt. The overlap between vascular disease and Alzheimer's disease – lessons from pathology. BMC Med 2014;12:206.
9. Matsunaga S, Kishi T, Yasue I, et al. Cholinesterase inhibitors for Lewy Body disorders: a meta-analysis. Int J Neuropsychopharmacol 2015;19(2):pyv086.
10. Liu Mu-N, Chi-Ieong Lau, Ching-Po Lin. Precision medicine for frontotemporal dementia. Front Psychiatry 2019;10. https://doi.org/10.3389/fpsyt.2019.00075.
11. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database Syst Rev 2012;2012(9):CD009132.
12. Lee J-H, Jeong S-K, Kim BC, et al. Donepezil across the spectrum of Alzheimer's disease: dose optimization and clinical relevance. Acta Neurol Scand 2015;131(5):259–67.
13. Pfizer Inc. Aricept (donepezil hydrochloride) [package insert]. U.S. Food and Drug Administration website. 2012. https://www.accessdata.fda.gov/

drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf. [Accessed 31 August 2022].
14. Knopman DS. Donepezil 23 mg: an empty suit. Neurol Clin Pract 2012;2(4):352–5.
15. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2018;6(6):CD001190.
16. Novartis. Exelon (rivastigmine tartrate) [package insert]. U.S. Food and Drug Administration website. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020823s036,021025s024lbl.pdf. [Accessed 31 August 2022].
17. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2015;(4):CD001191.
18. Khoury R, Rajamanickam J, Grossberg GT. An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. Ther Adv Drug Saf 2018;9(3):171–8.
19. Nordberg A, Ballard C, Bullock R, et al. A review of butyrylcholinesterase as a therapeutic target in the treatment of Alzheimer's disease. Prim Care Companion CNS Disord 2013;15(2). PCC.12r01412.
20. Ortho-McNeil Neurologics. Razadyne (galantamine hydrobromide) [package insert]. U.S. Food and Drug Administration website. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021615s021lbl.pdf. [Accessed 31 August 2022].
21. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2006;2006(1):CD001747.
22. Kowal NM, Ahring PK, Liao VWY, et al. Galantamine is not a positive allosteric modulator of human α4β2 or α7 nicotinic acetylcholine receptors. Br J Pharmacol 2018;175(14):2911–25.
23. Bakker C, van der Aart J, Hart EP, et al. Safety, pharmacokinetics, and pharmacodynamics of Gln-1062, a prodrug of galantamine. Alzheimers Dement (N Y) 2020;6(1):e12093.
24. Forest Laboratories. Namenda (memantine HCl) [package insert]. U.S. Food and Drug Administration website. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf. [Accessed 31 August 2022].
25. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. Cochrane Database Syst Rev 2019;3(3):CD003154.
26. Dou KX, Tan MS, Tan CC, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimer's Res Ther 2018;10(1):126.
27. Hager K, Baseman AS, Nye JS, et al. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. Neuropsychiatr Dis Treat 2014;10:391–401.
28. Wilcock G, Möbius HJ, Stöffler A. MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002;17(6):297–305.
29. Orgogozo JM, Rigaud AS, Stöffler A, et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002;33(7):1834–9.
30. Tan C-C, Yu J-T, Wang H-F, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzhemiers Dis 2014;41:615–31.

31. Hansen RA, Gartlehner G, Webb AP, et al. 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.
32. Guo J, Wang Z, Liu R, et al. Memantine, donepezil, or combination therapy-What is the best therapy for Alzheimer's disease? A network meta-analysis. Brain Behav 2020;10(11):e01831.
33. Campbell NL, Perkins AJ, Gao S, et al. Adherence and tolerability of Alzheimer's disease medications: a Pragmatic randomized trial. J Am Geriatr Soc 2017;65(7):1497–504.
34. Matsunaga S, Kishi T, Nomura I, et al. The efficacy and safety of memantine for the treatment of Alzheimer's disease. Expert Opin Drug Saf 2018;17(10):1053–61.
35. Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. Int Psychogeriatr 2011;23(3):372–8.
36. Courtney C, Farrell D, Gray R, et al. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363(9427):2105–15.
37. Howard R, McShane R, Lindesay J, 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;14:1171–81.
38. Ismail Z, Black SE, Camicioli R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95.
39. Ostrowitzki S, Lasser RA, Dorflinger E, et al, SCarlet RoAD Investigators. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther 2017;9(1):95.
40. Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 2018;378(4):321–30.
41. Schneider L. A resurrection of aducanumab for Alzheimer's disease. Lancet Neurol 2020;19(2):111–2.
42. Prins ND, Scheltens P. Treating Alzheimer's disease with monoclonal antibodies: current status and outlook for the future. Alz Res Ther 2013;5:56.
43. Baker J, Schott JM. AD and its comorbidities: an obstacle to develop a clinically efficient treatment? Rev Neurol (Paris) 2022. https://doi.org/10.1016/j.neurol.2022.03.001. S0035-3787(22)00546-X.
44. Dyer O. Medicare's decision not to fund Aduhelm changes the landscape for US pharma industry. BMJ 2022;377. https://doi.org/10.1136/bmj.o996.
45. Decourt B, Boumelhem F, Pope ED 3rd, et al. Critical Appraisal of amyloid Lowering agents in AD. Curr Neurol Neurosci Rep 2021;21(8):39.
46. Battle CE, Abdul-Rahim AH, Shenkin SD, et al. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. Cochrane Database Syst Rev 2021;2(2):CD013306.
47. Jin BR, Liu HY. Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis. Neural Regen Res 2019;14(5):805–16.
48. Smith EE, Barber P, Field TS, et al. Canadian Consensus Conference on diagnosis and treatment of dementia (CCCDTD)5: guidelines for management of vascular cognitive impairment. Alzheimer's Dementia (New York, N Y.) 2020;6(1):e12056.
49. Ryan J, Storey E, Murray AM, et al, ASPREE Investigator Group. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. Neurology 2020;95(3):e320–31.

50. AD2000 Collaborative Group, Bentham P, Gray R, Sellwood E, et al. Aspirin in Alzheimer's disease (AD2000): a randomised open-label trial. Lancet Neurol 2008; 7(1):41–9.
51. Thoonsen H, Riichard E, Bentham P, et al. Aspirin in Alzheimer's disease: increased risk of intracerebral hemorrhage: cause for concern? Stroke 2010; 41(11):2690–2.
52. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart association/American stroke association. Stroke 2014;45:3754–832.
53. Sara Mondini, Ileana Madella, Andrea Zangrossi, et al. Cognitive reserve in dementia: Implications for cognitive training. Front Aging Neurosci 2016;8. https://doi.org/10.3389/fnagi.2016.00084.
54. Sanches C, Stengel C, Godard J, et al. Past, present, and future of non-invasive brain stimulation approaches to Treat cognitive impairment in neurodegenerative diseases: time for a Comprehensive Critical review. Front Aging Neurosci 2021; 12:578339.
55. Zelinski EM. Far transfer in cognitive training of older adults. Restorative Neurol Neurosci 2009;27(5):455–71.
56. Bahar-Fuchs A, Martyr A, Goh AMY, et al. Cognitive training for people with mild to moderate dementia. Cochrane Database Syst Rev 2019;(3):CD013069.
57. Hill NT, Mowszowski L, Naismith SL, et al. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. Am J Psychiatry 2017;174(4):329–40.
58. Phan SV, Osae S, Morgan JC, et al. Neuropsychiatric symptoms in dementia: considerations for Pharmacotherapy in the USA. Drugs R D 2019;19(2):93–115.
59. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. JAMA 2002;288(12):1475–83.
60. Ismail Z, McGirr A, Gill S, et al. Mild behavioral impairment and Subjective cognitive decline predict cognitive and functional decline. J Alzheimers Dis 2021;80(1): 459–69.
61. Wancata J, Windhaber J, Krautgartner M, et al. The consequences of non-cognitive symptoms of dementia in medical hospital departments. Int J Psychiatry Med 2003;33(3):257–71.
62. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate medication Use in older adults. J Am Geriatr Soc 2019;67(4): 674–94.
63. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294(15):1934–43.
64. Cipriani G, Lucetti C, Nuti A, et al. Wandering and dementia. Psychogeriatrics 2014;14(2):135–42.
65. Neubauer NA, Azad-Khaneghah P, Miguel-Cruz A, et al. What do we know about strategies to manage dementia-related wandering? A scoping review. Alzheimers Demen 2018;10:615–28.
66. Montero-Odasso M, Verghese J, Beauchet O, et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc 2012;60(11):2127–36.

67. Zhang W, Low LF, Schwenk M, et al. Review of Gait, cognition, and fall risks with Implications for fall prevention in older adults with dementia. Dement Geriatr Cogn Disord 2019;48(1–2):17–29.
68. Racey M, Markle-Reid M, Fitzpatrick-Lewis D, et al. Fall prevention in community-dwelling adults with mild to moderate cognitive impairment: a systematic review and meta-analysis. BMC Geriatr 2021;21(1):689.
69. Morello RT, Soh SE, Behm K, et al. Multifactorial falls prevention programmes for older adults presenting to the emergency department with a fall: systematic review and meta-analysis. Inj Prev 2019;25(6):557–64.
70. Lord SR, Close JCT. New horizons in falls prevention. Age Ageing 2018;47(4):492–8.
71. Lee L, Molnar F. Driving and dementia: efficient approach to driving safety concerns in family practice. Can Fam Physician 2017;63(1):27–31.
72. Breen DA, Breen DP, Moore JW, et al. Driving and dementia. BMJ 2007;334(7608):1365–9.
73. Jacobs M, Hart EP, Roos RAC. Driving with a neurodegenerative disorder: an overview of the current literature. J Neurol 2017;264(8):1678–96.
74. Stamatelos P, Economou A, Stefanis L, et al. Driving and Alzheimer's dementia or mild cognitive impairment: a systematic review of the existing guidelines emphasizing on the neurologist's role. Neurol Sci 2021;42(12):4953–63.
75. Polzer ER, Nearing KA, Knoepke CE, et al. Firearm access and dementia: a qualitative study of reported behavioral disturbances and responses. J Am Geriatr Soc 2022;70(2):439–48.
76. Schwertner E, Zelic R, Secnik J, et al. Biting the Bullet: firearm ownership in persons with dementia. A Registry-based Observational study. J Alzheimers Dis 2021;81(1):179–88.
77. Pinholt EM, Mitchell JD, Butler JH, et al. Is there a gun in the home?" Assessing the risks of gun ownership in older adults. J Am Geriatr Soc 2014;62(6):1142–6.
78. Lee S, Kirk A, Kirk EA, et al. Factors associated with having a will, power of attorney, and advanced healthcare Directive in patients presenting to a Rural and Remote memory clinic. Can J Neurol Sci 2019;46(3):319–30.
79. Sellars M, Chung O, Nolte L, et al. Perspectives of people with dementia and carers on advance care planning and end-of-life care: a systematic review and thematic synthesis of qualitative studies. Palliat Med 2019;33(3):274–90.
80. Manthorpe J, Samsi K. Person-centered dementia care: current perspectives. Clin Interv Aging 2016;11:1733–40.
81. Wendrich-van Dael A, Bunn F, Lynch J, et al. Advance care planning for people living with dementia: an umbrella review of effectiveness and experiences. Int J Nurs Stud 2020;107:103576.
82. Cheng ST. Dementia caregiver Burden: a research update and Critical analysis. Curr Psychiatry Rep 2017;19(9):64.
83. Chien LY, Chu H, Guo JL, et al. Caregiver support groups in patients with dementia: a meta-analysis. Int J Geriatr Psychiatry 2011;26(10):1089–98.
84. Tretteteig S, Vatne S, Rokstad AM. The influence of day care centres designed for people with dementia on family caregivers - a qualitative study. BMC Geriatr 2017;17(1):5.
85. Swan K, Hopper M, Wenke R, et al. Speech-language pathologist interventions for Communication in moderate-severe dementia: a systematic review. Am J Speech Lang Pathol 2018;27(2):836–52.

86. Bennett S, Laver K, Voigt-Radloff S, et al. Occupational therapy for people with dementia and their family carers provided at home: a systematic review and meta-analysis. BMJ Open 2019;9(11):e026308.
87. Zhu XC, Yu Y, Wang HF, et al. Physiotherapy intervention in Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis 2015;44(1): 163–74.