Minireview Article

Dementia diagnosis and alternate treatment: A recent update on treatment options

Abstract

Dementia is a global health burden identified by the World Health Organization in global action plan on the public health response to dementia 2017-2025. The objectives of our study is to determine efficacy of treatment options in different type of dementia. We searched PubMed Central and the Cochrane database for comparative trials comparing various dementia treatment options. The effectiveness of various treatment options for different types of dementia has been compared in more than 40 papers. In our analysis we have found mild to moderate cognitive dysfunction (MMSE 19 to 26) and newly diagnosed Alzheimer's disease can be treated with a trial of Cholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine); choice can be based on clinician and/or patient preference, as efficacy is similar. Moderate to advanced dementia (MMSE 10 to 18): Memantine (10 mg twice daily) is a suggested option with Cholinesterase inhibitors. Vitamin E is a reasonable option to offer, but benefits are likely to be small in mild to moderate Alzheimer's disease - more meta-analysis and review is needed to decide. Aducanumab can be used in amyloid-positive patients with mild cognitive impairments, but practices and recommendations are yet to evolve. In conclusion, it is evident that the available options for dementia medication are inherently limited, while the resources allocated to evaluate further treatment alternatives remain constrained. As a result, there is an urgent need to prioritize additional research and comprehensive assessment in this field, with a specific emphasis on engaging clinicians responsible for treating patients across the entire spectrum of mild to severe dementia categories.

Introduction & Background

Dementia is a global health burden identified by the World Health Organization in global action plan on the public health response to dementia 2017-2025 [1]. According to estimates from the Alzheimer's Association, more than 6 million Americans have Alzheimer's or another form of dementia. By 2050, that number could grow to more than 12 million people, leading to a cost of $1 trillion (about $3,100 per person in the US) annually. It is also stated that between 2000 and 2019, death from heart disease has decreased by 7.3% while death from Alzheimer's has increased by 145% [2]. Healthcare providers therefore need to consider the medications as an alternative and complementary treatment plan for dementia to improve the quality of life for patients.

Dementia: Definition and Types

Dementia can be simply defined as forgetfulness with difficulties in one or more of the following: retaining current information, handling complex tasks, reasoning, spatial orientation and ability, language, and behavior [3].

Mild cognitive impairment (MCI): MCI is defined as memory difficulty greater than expected for age and objective memory impairment, but preserved ability to function in daily life [4,5].

Alzheimer's disease typically occurs in adults 65 years and older with difficulties in executive function and insight with apraxia, sleep disturbance, and behavioral and psychologic symptoms [4-5].

Vascular cognitive impairment (VCI): A stepwise regression in processing speed and executive function due to atherosclerotic small vessel disease [4].

Lewy body dementia: The presence of Rapid eye movement (REM) sleep behavior disorder, visual hallucinations, fluctuations in level of alertness, and prominent visuospatial dysfunction with parkinsonism at the same time [4].

Parkinson's disease Dementia: Dementia appears after five to eight years of Parkinson's disease [4].

Progressive supranuclear palsy: rare disease, includes dementia and parkinsonism with distinctive early features of vertical supranuclear gaze palsy and prominent postural instability with falls [4].

Normal pressure hydrocephalus (NPH): triad of loss of cognition, gait instability and urinary incontinence [4].

Creutzfeldt-Jakob Disease: rare, but rapidly progressive dementia. Myoclonus and cerebellar deficits are also common features [4].

Review

Methods:

We have initiated a comprehensive search using the keywords 'Dementia Treatment and Management,' and subsequently refined our search to encompass three categories: vascular, mixed, and Alzheimer's dementia. To begin with, we excluded reports that were older than five years. However, we still had over 10,000 papers to review. As a result, we decided to focus our efforts on research published between 2020 and 2023, excluding studies related to 'Covid Dementia,' 'Post-Concussion Dementia,' and 'Post-Infectious Dementia.' After this, we narrowed our search to 163 papers and, of those, selected only 98 papers that were relevant to our topic.

Diagnosis of Dementia

There is no compelling evidence to recommend for or against routine screening for dementia in older adults, according to the US Preventive Services Task Force.3 There are three levels of diagnostic testing for concerns of memory and cognition difficulty: screening tools such as MoCA (Montreal Cognitive Assessment) or MMSE (Mini Mental State Examination), after that an extended Mental Status Examination and last formal level of Neuropsychiatric test.

Mild dementia: MMSE 19 to 26; MoCA 12 to 16

Moderate dementia: MMSE 10 to 18; MoCA 4 to 11

Severe dementia: MMSE < 10; MoCA < 4

These tests quantify the level and severity of dementia along with relevant history and physical examination. Other subsequent routine tests include: Screening for depression, Serum Vit B12 level, TSH, ionized Calcium, Screening for Syphilis in high-risk patients, and red blood cell folate in a patient with alcoholism. The neuroimaging MRI is more effective than a non-contrast CT scan to diagnose structural abnormalities and treatable causes of dementia such as subdural hematoma, thrombotic stroke, normal pressure hydrocephalus and cancer [4]. It is recommended by AAN to do routine neuroimaging in all patients with dementia, which is also reassuring for patients and families [2].

Current Treatment Options for Dementia

Cholinesterase Inhibitor. Donepezil, Rivastigmine and Galantamine increase acetylcholine and cortical cholinergic function by inhibiting cholinesterase at the synaptic cleft. However, there is small improvement in cognition, neuropsychiatric symptoms, and activities of daily living in patients with mild to moderate dementia [6-13]. The AD200 study found no significant difference in entry to institutional care and progression of disability with Donepezil as compared to placebo [14].

Memantine. Memantine is an NMDA receptor antagonist which is neuroprotective. Glutamate activate NMDA receptor which is important for learning and memory [15]. Treatment decision with Memantine should be individualized as there is no clear clinical significance of cognition improvement [16]. According to a recent meta-analysis conducted in 2017, encompassing data from 10 distinct research studies, it was observed that 8 of these studies reported varying degrees of cognitive and behavioral improvement in individuals with Alzheimer's disease.

Moderate to severe dementia. Treatment option is Memantine with Cholinesterase inhibitor, which has better outcome than placebo plus Donepezil to improve cognition [17].

Recent Treatment Option

Aducanumab. The US Food and drug administration approved this monoclonal antibody for the treatment of Alzheimer’s disease using the accelerated approval pathway after one of the two pivotal phase 3 trials [18].

Patient selection. Alzheimer's disease with mild cognitive impairment who has proven Amyloid plaques in PET scan or Lumber Puncture [19]. Due to uncertainty of its benefits, risk and burdens using this medication is now depending on individual choice. It is recommended to follow the safety guideline such as a recent MRI prior to initiate treatment.

Aducanumab is administered by intravenous infusion every four weeks. Monitoring of symptoms like headache, confusion, and visual impairment with Brain MRI is advised [19].

Summary of Clinical Trials

In a dose escalation trial of 165 Alzheimer's patients with mild cognitive impairment have PET scan which is showing reduction of Amyloid plaques in dose and time dependent manner [20].

EMERGE trial (1638 patients), patients treated with high dose have shown small but significant statistical benefit but uncertain clinical significance with absolute difference of 0.39 [21].

ENGAGE trial (1647 patients): no clinical significance found compared to placebo; other outcome analysis was not taken into consideration [22].

In both trials, it is evidenced that subsequent reductions of amyloid plaque by PET scan, however, trails are stopped early after a planned futility analysis. Moreover, full results of these papers have not been published in peer-reviewed form [19-21].

Adverse effect: There are 44% patients with Amyloid related imaging abnormalities (ARIA) include edema and or microhemorrhage on MRI on first eight doses, but it is resolved with time in 88% of patients [23-24].

Medications	Treatment difference or point improvement in comparison with placebo	Compared to Placebo on ADAS - Cog
In Mixed Dementia		
Galantamine	2.7	1.7 point improvement
Rivastigmine	3.3	0.4 point Improvement
In Alzheimer's Disease		
Donepezil	2.9	1.1 point improvement
Memantine	2.2	3.2 point improvement
Vit E	230 day delay in progression to severe dementia	Vit E No significant change on ADAS -cog

Table 1: Table of efficacy of different cholinesterase in Mixed Dementia and Alzheimer's disease:

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) was developed in the 1980s to assess the level of cognitive dysfunction in Alzheimer's disease. (Kueper, J. K., Speechley, M., & Montero-Odasso, M. (2018). The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. Journal of Alzheimer's disease : JAD, 63(2), 423–444. https://doi.org/10.3233/JAD-170991)

Complementary Options: Antioxidants

Vitamin E. Considering its tolerability and safety profile, but modest benefit with mixed results, Vitamin E is a reasonable option in patients with mild to moderate cognitive dysfunction [25]. It is not recommended for prevention but could be offset by combination therapy with Memantine.

Selegiline. There are limited evidence of efficacy and not recommended to use considering expanses and no significant cognitive benefits.

Vitamin B. Randomized control trial results in 340 patients for 18 months with mild to moderate AD found no beneficial effects of cognitive impairment [26].

Omega-3 fatty acids. Observational studies have suggested association of lower risk of dementia however clinical trials have not supported a therapeutic role [27].

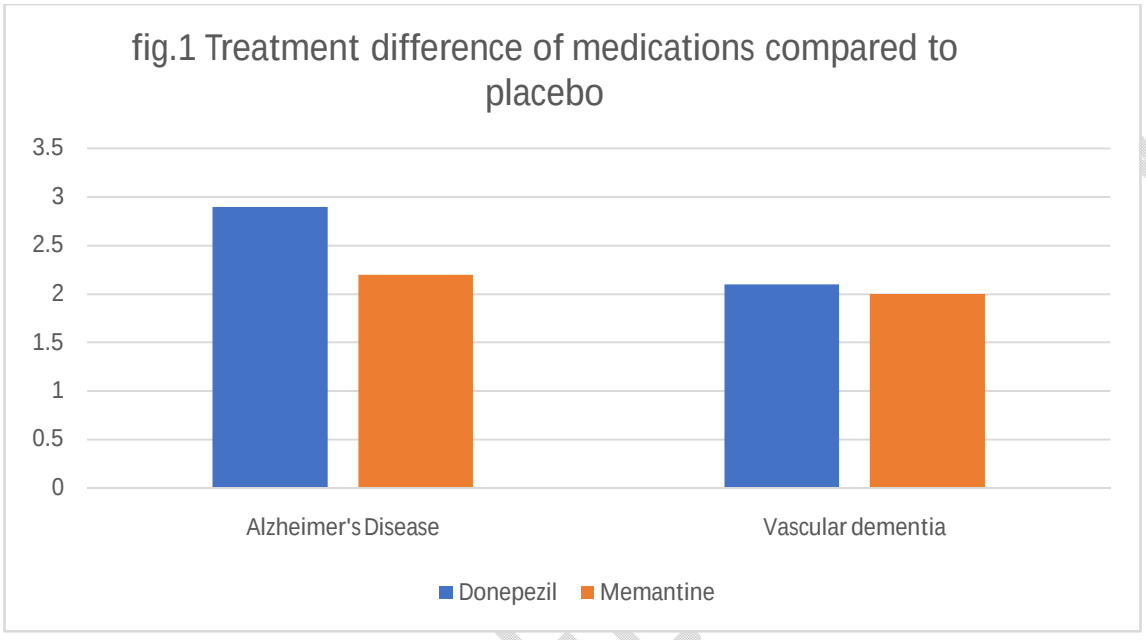
Conclusions

The comprehensive treatment plan for dementia remains a subject of debate in existing literature, primarily due to the increasing age of the patient population. The efficacy of drugs and the long-term outcomes reported in various research papers are also a matter of concern and warrant further investigation. Consequently, the development of new medications has become a priority in recent times. However, in comparison to the progression of dementia, and the effectiveness of medications in slowing down this progression, there exists a significant gap in our understanding that necessitates further research. This paper aims to provide a summary of the rationale behind initiating medications and incorporating them as part of the dementia treatment paradigm, acknowledging the limited options currently available to us.

Table 2 : efficacy of different cholinesterase in Mixed Dementia and Alzheimer's disease:

Medications	Compared to Placebo on ADAS - Cog	Treatment difference or point improvement in comparison with placebo
In Mixed Dementia		
Galantamine	1.7 point improvement	2.7
Rivastigmine	0.4 point decline	3.3
In Alzheimer's Disease		
Donepezil	1.1 point improvement	2.9
Memantine	3.2 point decline	2.2
Vit E	No significant change on ADAS -	230 day delay in progression to

	cog	severe dementia
In vascular Dementia		
Donepezil	2.2 point improvement	2.1
Memantine	0.4 point improvement	2.0



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