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REVIEW ARTICLE

Framework of treating Alzheimer's dementia

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ABSTRACT

Current treatment paradigm in Alzheimer's disease (AD) involves multiple approaches combining pharmacological and non-pharmacological intervention to mitigate the clinical symptoms, slow the progressive loss of cognitive and functional abilities, or modify the disease course. So far, beyond anti-cholinesterase inhibitors (AChEIs), donepezil, rivastigmine, galantamine, and antagonist of N-methyl-D-aspartic acid (NMDA) receptor, there are no newly approved medicines to treat AD. Under pharmacological treatment, the personal characteristic and the intra-individual therapeutic evaluations to examine various cognitive domains, behavioral and psychological problems, and global function should be considered when choosing any of AChEIs. The use of optimal dosage referring to the expected clinical outcomes and currently reported deficits from patient with AD has become an important issue in clinical treatment. Establishing and maintaining a strong therapeutic alliance to physician, patient, and caregiver is crucial and central to the comprehensive care in AD.

1 Introduction

Alzheimer's disease (AD), the most common cause of mid-to-late life dementia, is pathologically defined by deposits of amyloid-β (Aβ42)-plaques, hyper-phosphorylated tau (p-tau) tangles, and neuronal loss [1]. Although these pathological findings are well known, the complicated clinical phenotypes still make the therapeutic outcome unpredictable. Currently, there is no cure for AD, yet early diagnosis and treatment are encouraged to gain better clinical outcomes. The AD pathological processes develop over decades before symptoms manifest insidiously. This preclinical stage, which has been targeted at in research, is considered as one of the best opportunities to potentially delay the development of overt dementia stage of AD [2].

The current treatment paradigm in AD involves multiple approaches combining pharmacological

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and non-pharmacological interventions to mitigate the progressive loss of cognitive and functional abilities or modify the disease course if possible. So far, beyond the anti-cholinesterase inhibitors (AChEIs), donepezil, rivastigmine, galantamine, and antagonist of N-methyl-D-aspartic acid (NMDA) receptor, there are no new medicines approved to treat AD.

For pharmacological interventions for AD, over the last decade, multiple evidences from randomized, double-blind, and placebo-controlled trials (RCT), with prospective long-term observational cohort studies have emerged to support the clinical effectiveness of anti-AD medications, whereby in mono-, or add-on-dual combination therapy at least modestly (with small-to-medium effect sizes) mitigate symptoms and retard the expected trajectory of progressive decline [3].

Combination of non-pharmacological interventions, regarded as cocktail treatment, is one of the multifaceted managements aimed at retaining the quality of life, slowing the cognitive and functional decline, preventing behavioral and psychological symptoms of dementia (BPSD), and mitigating the burden to caregivers. The success of treatment can be expected on a strong therapeutic alliance between the clinician and the patient–caregiver dyad.

Before going on to the types of interventions presently recommended for the management of AD and the evidence for their efficacies, we classify therapeutic interventions in the following ways:

A. Disease-modifying intervention

a) Retard or stop the development of clinical AD for an individual at the pre-clinical stage.

b) Retard the progression and maintain the function of a patient with AD dementia for a longer period of time.

c) Repair or reverse damage already done to the brain.

For such purposes, these interventions may be classified as:

Pharmacological intervention

a) Target at the various established pathological mechanisms in AD by slowing the production, increasing the clearance, or preventing the aggregation of amyloid or tau. Unfortunately, so far, clinical trials targeted at amyloid or tau were disappointing.

b) Reduce inflammation and degenerative changes via other known mechanisms.

Non-pharmacological intervention

These are multi-modal training programs or lifestyle interventions, which may reduce the rate of progression or prevent the occurrence of the disease. These interventions, generally speaking, take time and great efforts to achieve their goals. Currently, there is a great need for more high-quality evidences to support these points.

B. Symptom modification

These interventions mitigate the symptoms of AD, including cognitive dysfunction, behavioral and psychological symptoms, and impaired global function. The interventions can also be grouped into pharmacological and non-pharmacological treatments by ameliorating the following symptoms.

a) Cognitive symptoms: impairment in memory, language, orientation, concentration, executive function, judgment and abstractive thinking or others.

b) Neuropsychiatric symptoms: anxiety, depression, hallucination, delusion, appetite, apathy, aggression, apathy, agitation, or others.

c) Global function: basic activity of daily living or instrumental activities of daily living, or others.

2 Disease modifying agent

Among various pathogeneses in the development of AD, inflammation plays a critical role [4, 5].

Persistent inflammation also contributes to the development of atherosclerosis [6] and vascular contribution to cognitive impairment [7], which will subsequently lead to dementia. For these reasons, medications that suppress inflammation, such as steroid or non-steroidal anti-inflammatory drugs (NSAIDs), were considered to provide potential prevention from dementia [8–10]. However, it is not easy to test such hypothesis in real world due to several limitations. Possible evidences came from the observation of subjects having rheumatoid arthritis (RA) and developing dementia. Poor control of RA may result in joint and tissues damages, leading to disability and other cardiovascular disorders [11]. NSAIDs or other anti-inflammatory medicines were used to avoid these unwanted outcomes. Many studies have been conducted to demonstrate the association between autoimmune diseases and dementia [12–14], with heterogeneous results due to varied study designs, sample sizes, medications, and therapeutic periods.

In order to know the possible effects of anti-inflammatory agents on the prevalence or incidence of dementia, observation of patients using disease-modifying anti-rheumatic drugs (DMARDs) has provided some evidences to these issues. DMARDs used in RA patients may slow their disease progression and structure damage [11, 15–16], or reduce the risk of cardiovascular disease from inflammatory insult [17].

Recently, a large-scale study in Taiwan has provided more direct and indirect evidences to this issue—the association of using DMARDs and having dementia. In that study, patients who were newly diagnosed with RA from the year 2000 to 2005, but without a prior history of dementia, were identified from Taiwan's National Health Insurance Research Database. A total of 20,707 RA patients were recruited as study cases, and 62,121 non-RA individuals aged 20 years or older were included as controls. The RA cohort was less likely to develop dementia compared with the non-RA cohort (adjusted hazard ratio, HR, 0.63; 95% confidence interval, CI, 0.55–0.72). The effect was dose-dependent in the RA group for using DMARD (adjusted HR, 0.48; 95% CI, 0.39–0.58). The study provided the evidence for the potential protective effect of DMARD on the development of dementia [18].

3 Symptomatic management: Early treatment and adherence

Needless to say, the early treatment and keeping better therapeutic adherence are considered a high priority in the treatment of AD.

Donepezil is one of the acetyl-cholinesterase inhibitors (AChEIs) agents that are most widely used. It was shown to improve cognitive function and behavioral symptoms in patients with AD [19–21]. Beyond donepezil, in some studies, sustained use of AChEIs may delay the progression of cognitive, functional, and behavioral decline caused by AD [22, 23]. In order to have better therapeutic outcomes, therapeutic adherence is critical. However, withdrawal from treatment is frequently a barrier to effective therapy [24, 25], due to adverse effects such as anorexia, diarrhea, nausea, insomnia, urine incontinence, dizziness, or muscle cramp [26]. Another important issue for therapeutic adherence is the cost and reimbursement of insurance system that varies according to countries' guidelines for patients with AD. These published medical guidelines or government policies followed by prescribers and their prescribing practices influence the therapeutic adherence [27]. In a study done in Taiwan analyzing the clinical compliance of 273 patients with AD from February 2004 to April 2013, the mean therapeutic duration for these patients was 28.0 ± 25.9 months with a maximum of 128 months. The 12-month and 24-month adherence rates were 90.1% and 84.8%, respectively. The study

has provided an objective real-world data to the therapeutic adherence. Better baseline scores in the Mini-Mental Status Examination (MMSE) (p = 0.007), Cognitive Abilities Screening Instrument (CASI) (p = 0.003), and Clinical Dementia Rating Scale (CDR) Sum of Boxes (p = 0.011) of patients with AD taking AChEIs were associated with higher therapeutic adherence. Adherence rate was significantly higher in the CDR 0.5 group than in the CDR 2.0 group [27].

4 Pharmacological treatment and acetyl-cholinesterase inhibitors: Optimal dose and clinical outcome, the precise treatment

4.1 Donepezil

Donepezil decreases the degradation of acetyl-choline, and has been approved for the treatment of mild, moderate, and severe stage of AD. Recently, a higher dose has been promoted in order to achieve better improvement in cognition [28, 29]. Individuals taking donepezil 10 mg/d have higher concentrations of donepezil in plasma and cerebrospinal fluid compared with those taking 5 mg/d, and could have a greater improvement in cognition [30], possibly with more inhibition of acetyl-cholinesterase to have higher concentration of acetylcholine in brain tissue.

However, not every cognitive domain will have the same response to the treatment for the possibly varied deficiencies and needs of acetylcholine in different cerebral cortex areas. A longitudinal study examined the cognitive response of AD patients treated with donepezil 5 mg/d using the ADAS-cog, and found a significant improvement in the subscale of immediate word recall, but not in others [31]. Furthermore, several studies have reported various therapeutic response rates in patients with AD taking donepezil, which may be due to the effects of apolipoprotein E (*APOE*) gene status [32–33], cytochrome P450 2D6 (CYP2D6) gene polymorphism [34, 35], sex [36], and neuroanatomical characteristics [37]. In other words, many other factors affect therapeutic outcomes and should be clarified.

Previous studies addressing the clinical therapeutic response to donepezil in patients with AD only evaluated medication dose, but did not measure the donepezil plasma concentration. The plasma concentration of donepezil is more directly associated with therapeutic outcome and therefore should be measured for treatment to be precise. Contrary to reports that taking higher dosage of donepezil have better cognitive outcome, in our previous work, we have found that a higher plasma concentration of donepezil was not associated with improved MMSE score [38], but looking into the nine cognitive domains of the CASI, long-term memory had the highest improvement ratio (81.1%) compared with the other domains. An increased donepezil plasma concentration (mean ± SD = 75.14 ± 32.16 ng/mL) was significantly associated with the improvement of long-term memory (p = 0.045; odds ratio, 0.959; 95% CI, 0.920–0.999) after adjusting age, sex, education, and *APOE* genotype. These findings have highlighted the importance of plasma concentration of donepezil, apart from dosage taken, to the therapeutic clinical outcomes [39].

4.2 Rivastigmine

Rivastigmine is a carbamate-type dual inhibitor of the brain cholinesterases, acetylcholinesterase (AChE) and butyl-cholinesterase (BuChE), with efficacy in the symptomatic treatment of mild-to-moderate AD [40]. Previous research has identified greater improvements in *APOE4* carriers than in non-*APOE4* carriers following rivastigmine treatment [41]. Although published clinical trials have shown the benefits of rivastigmine treatment in AD [42], only a few studies have examined its specific cognitive effects such as language,

attention, calculation, abstract thinking, or perception [43], and measure its plasma concentration to reflect the therapeutic response from rivastigmine. When taken orally, rivastigmine is extensively metabolized to (S)-3-(1-dimethylaminoethyl) phenol, NAP 226-90, by cholinesterase-mediated decarbamylation. This is the principal step required for cholinesterase inhibition [44], and thus, the concentration of NAP 226-90 reliably reflects the extent of enzyme inhibition [45], which should be evaluated when treating AD patients.

Previous studies have, indeed, shown that increased NAP 226-90 concentration correlated well with cholinesterase inhibition [44, 45]. Clinical trials of rivastigmine on patients with AD have suggested that increasing the therapeutic dosage would improve the clinical response due to evidence of dose-dependent effects [40, 46]. Similar designs in other dose-related clinical studies on rivastigmine have found that only a few studies [44–46] addressed the plasma concentration of rivastigmine apart from the dosage. If we are going to have more objective evidences of relationships between therapeutic function and medicine dosage, the drug plasma concentration is needed.

The effects of rivastigmine treatment on various cognitive functions, such as memory, language, or executive function in patients with AD also remain unclear. In a study on patients with Lewy-body dementia, attention was one of the cognitive subdomains which responded to rivastigmine therapy [47]. Studies have reported that attention may specifically respond to rivastigmine therapy in AD patients [43, 48]. The cognitive domain that responds to treatment may vary with study design, individual characteristics, instruments for therapeutic evaluations, ethnicities, or others. In Taiwan, we have demonstrated the association between plasma concentrations of rivastigmine and its metabolite, NAP 226-90, and cognitive function in patients with AD. Rivastigmine-treated patients with AD maintained on a fixed regimen of taking rivastigmine twice daily (6 to 12 mg/d) for ≥ 6 months. The study showed that higher rivastigmine concentration was significantly associated with improved short-term-memory (p = 0.021) and worsened abstraction/judgment (p = 0.027), but no changes in other cognitive domains. Higher NAP 226-90 concentration was significantly associated with worsened abstraction/judgment (p = 0.007), but not with changes in other domains. The report suggested that an optimal concentration of rivastigmine should be quantified for each patient because of differential response [49].

4.3 Transdermal delivery of rivastigmine

Owing to unwillingness to take oral medicine among patients with AD and possible side effect of medicine related to its fluctuating serum concentration, rivastigmine has been given by a transdermal patch to minimize adverse events for better therapeutic compliances and outcome. However, the thickness of the skin area where the patch is applied may affect rivastigmine plasma concentration because of the possible barriers to absorption of skin and subcutaneous. A previous study that examined the skin where rivastigmine transdermal patch was applied (4.6 mg/24 hours) indicated that the subscapular area was significantly negatively correlated with the NAP 226-90 serum concentration (p = 0.010) [50]. In that study, patients with subscapular skin thickness of ≥ 25 mm worsened in their MMSE score (odds ratio, 3.00; 95% CI, 1.076–8.366; p = 0.030), which could also secondarily decrease medication adherence. While rivastigmine patch may provide an alternative treatment for rivastigmine to treat AD, the skin thickness of the area where it is to be applied should be carefully evaluated.

4.4 Galantamine

Galantamine, similar to other acetylcholinesterase inhibitors (AChEIs), has been approved for the treatment of mild-to-moderate AD [51]. Various dosages of galantamine have been proposed to provide the therapeutic benefits in AD [52]. However, the response ratio varies by individual characteristics [53]. Previous studies have stated that several factors influence the treatment outcome, including gender, body weight, neuroanatomical characteristics, baseline cognitive function, genotypes such as cytochrome P450 and *APOE* [53, 54]. A study has reported that better cognitive outcome was related to higher dosages of galantamine [51]. However, a study done in Sweden has demonstrated that higher concentration of serum galantamine would result from higher dosages, but did not have significant correlation with the short-term cognitive and functional outcomes [52]. In order to examine this association among Asians with AD, a study was done in Taiwan to examine the association between cognitive outcomes and plasma concentration of galantamine in 33 patients. In the nine cognitive domains of CASI, 22 of 33 patients with AD improved in their long-term memory domain, but the improvement was not related significantly with galantamine plasma concentration [55]. Hence, for patients with AD treated with galantamine, the exact mechanisms between dosage and therapeutic outcomes may be beyond plasma concentration.

4.5 NMDA-antagonist

Memantine is one of the approved drugs for the treatment of moderate-to-severe stage of AD other than cholinesterase inhibitors [56]. One of the pharmacological mechanisms of memantine is being a noncompetitive, nonselective, and voltage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist [57]. Memantine blocks the effects of sustained and pathologically elevated levels of glutamate that leads to neuronal dysfunction [57, 58]. Memantine also upregulates NMDA receptor expression, causing activation after a stimulus [11]. Owing to these mechanisms, memantine is used to treat moderate-to-severe stage of AD. Many studies have reported various therapeutic outcomes due to their varied study designs. The clinical efficacy of memantine was recently summarized in a meta-analysis that assessed the therapeutic outcome of mematine in AD based on cognitive and behavioral outcomes [56]. Memantine showed a significant improvement in cognitive function ($p < 0.001$) and behavioral outcome ($p = 0.010$) compared with placebo. When memantine was used as an add-on to AChEIs, combined treatment was better than AChEI alone, with greater improvement in behavioral outcomes ($p = 0.020$) but only an insignificant sign of improvement in cognition ($p = 0.060$). The meta-analysis suggested the credible efficacy of memantine in treating AD when used alone or in combination with AChEIs [56].

5 Non-pharmacological treatment

So far, there is no cure for AD under currently available medicines. The "cocktail treatment" including pharmacological and non-pharmacological interventions has been advocated to provide multiple therapeutic approaches for AD management. Non-pharmacological interventions are recommended for treating behavioral and psychological symptoms in patients with AD, because they might have fewer side effects [59, 60]. Several non-pharmacological interventions have also been developed to lessen the functional impact of the disease [61]. Some traditional Chinese activities have been reported to improve cognitive and physical function in the elderly [62]. For example, Tai Chi is a traditional Chinese mind-body exercise with mild-to-moderate intensity,

which has been promoted extensively for its potential benefits particularly in neurological disease such as stroke, Parkinson's disease, traumatic brain injury, and multiple sclerosis, in cognitive dysfunction [63, 64], in skeletal muscle system and orthopedic diseases [65], and also in cardiovascular diseases, myocardial infarction, coronary artery bypass grafting surgery, and heart failure [66]. Tai Chi also promotes general health and well-being [67]. Chinese calligraphic handwriting and drawing require integration of the mind and body with the features of Chinese writing. Calligraphy involves visual perception of the characters, spatial structuring of the characters, cognitive planning, and maneuvering of the writing brush to follow specific characteristic configurations. Clinical research has found that calligraphy used as therapy may improve behavioral and psychosomatic disorders [68]. Calligraphy also has a therapeutic effect on hypertension and type 2 diabetes [69, 70], and therefore can reduce the risk for cardiovascular disease, which contributes to further cognitive impairment in AD. Moreover, calligraphic writing may improve attention span and concentration, and may facilitate relaxation and emotional stabilization [71]. For such effects, calligraphy has been reported to successfully enhance spatial ability, visual attention, and episodic memory in patients with AD [72, 73], and may slow cognitive deterioration in elderly people [74].

A study that examined the effects of the combination of traditional Chinese traditional activities, physical training, mental rehabilitation, and social engagement on patients with mild AD has shown impressive results. After 4 months of such intervention, there was improvement in cognitive function measured by CASI ($p = 0.007$), in the psychiatry domain of World Health Organization Quality of Life-BREF (WHOQOL-BREF) ($p = 0.042$), and in the caregiver burden measured by Zarit Caregiver Burden Scale ($p = 0.035$) compared to no intervention [75]. The study highlighted that non-pharmacological interventions should combine several modalities together to have successful outcome.

6 Summary

With the current treatment paradigm in AD, we can only aim to mitigate symptoms and slow clinical progression, but not modify the course or cure the disease. Non-pharmacological management, physical training, social engagement, and mental rehabilitation and pharmacologic therapies (AChEIs and memantine), are prescribed to minimize the disabling effects from cognitive, behavioral and functional decline.

When choosing pharmacological treatment, the patient's personal characteristic and individualized evaluation of various cognitive domains, behavior and psychological problems, and global function should be considered. Owing to varying patient response to medications, dosing has become an important issue in treatment decisions. Optimal drug dosing may be complemented by drug plasma concentration and guided by desired clinical outcomes based on reported deficits from the patient and caregiver.

Establishing and maintaining a strong therapeutic alliance that is holistic, pragmatic, involving ethical consideration, psycho-education, behavioral and environmental strategies, appropriate pharmacotherapy and non-pharmacological interventions, planning for current and future care needs, and patient–caregiver dyad psychosocial well-being is crucial and central to the comprehensive care in AD.

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Conflict of interests

All authors have no conflict of interests.

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