2019

Framework of treating Alzheimer’s dementia

Yuan-Han Yang
Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Taiwan, China
Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, China
Neuroscience Research Center, Kaohsiung Medical University, Kaohsiung City, Taiwan, China

Rajka Liscic
Department of Neurology, Johannes Kepler University Linz, Austria

Jacqueline Dominguez
Institute for Neurosciences, St. Luke’s Medical Center, Quezon City, Philippines

Follow this and additional works at: https://tsinghuauniversitypress.researchcommons.org/brain-science-advances

Part of the Biomedical Engineering and Bioengineering Commons, Nervous System Diseases Commons, Neurology Commons, Neuroscience and Neurobiology Commons, Neurosciences Commons, and the Neurosurgery Commons

Recommended Citation
Yuan-Han Yang, Rajka Liscic, Jacqueline Dominguez. Framework of treating Alzheimer’s dementia. Brain Science Advances 2019, 5(2): 82-93.

This Research Article is brought to you for free and open access by Tsinghua University Press: Journals Publishing. It has been accepted for inclusion in Brain Science Advances by an authorized editor of Tsinghua University Press: Journals Publishing.
Framework of treating Alzheimer’s dementia

Yuan-Han Yang1,2,3 (✉), Rajka Liscic4, Jacqueline Dominguez5

1 Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Taiwan, China
2 Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, China
3 Neuroscience Research Center, Kaohsiung Medical University, Kaohsiung City, Taiwan, China
4 Department of Neurology, Johannes Kepler University Linz, Austria
5 Institute for Neurosciences, St. Luke’s Medical Center, Quezon City, Philippines

ARTICLE INFO
Received: 6 April, 2019
Accepted: 11 May, 2019

© The authors 2019. This article is published with open access at journals.sagepub.com/home/BSA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

KEYWORDS
donepezil, rivastigmine, galantamine, memantine, Alzheimer’s disease

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
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 acetylcholinesterase inhibitors: Optimal dose and clinical outcome, the precise treatment

#### 4.1 Donepezil

Donepezil decreases the degradation of acetylcholine, 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 \((\text{mean} \pm \text{SD} = 75.14 \pm 32.16 \text{ ng/mL})\) was significantly associated with the improvement of long-term memory \((p = 0.045; \text{odds ratio}, 0.959; 95\% \text{ CI}, 0.920–0.999)\) 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 memantine 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.

Acknowledgments

The authors are grateful for the support by Neuroscience Research Center, Kaohsiung Medical University, KMU-TC108B01.
Conflict of interests

All authors have no conflict of interests.

References

[1] Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimers Dement*. 2018, 14(4), 535–562.

[2] Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017, 390(10113), 2673–2734.

[3] Tricco AC, Ashoor HM, Soobiah C, et al. Comparative effectiveness and safety of cognitive enhancers for treating Alzheimer’s disease: systematic review and network metaanalysis. *J Am Geriatr Soc*. 2018, 66(1), 170–178.

[4] Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer’s disease. *Lancet Neurol*. 2015, 14(4), 388–405.

[5] Latta CH, Brothers HM, Wilcock DM. Neuroinflammation in Alzheimer’s disease; A source of heterogeneity and target for personalized therapy. *Neuroscience*. 2015, 302: 103–111.

[6] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002, 105(9): 1135–1143.

[7] Thiel A, Cechetto DF, Heiss WD, et al. Amyloid burden, neuroinflammation, and links to cognitive decline after ischemic stroke. *Stroke*. 2014, 45(9): 2825–2829.

[8] McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer’s disease: a review of 17 epidemiologic studies. *Neurology*. 1996, 47(2): 425–432.

[9] Chang KH, Hsu YC, Hsu CC, et al. Prolong exposure of NSAID in patients with RA will decrease the risk of dementia: a nationwide population-based cohort study. *Medicine*. 2016, 95(10): e3056.

[10] Alisky JM. Intrathecal corticosteroids might slow Alzheimer’s disease progression. *Neuropsychiatr Dis Treat*. 2008, 4(5): 831–833.

[11] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010, 376(9746): 1094–1108.

[12] Kao LT, Kang JH, Lin HC, et al. Rheumatoid arthritis was negatively associated with Alzheimer’s disease: A population-based case-control study. *PLoS One*. 2016, 11(12): e0168106.

[13] Wotton CJ, Goldacre MJ. Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. *J Epidemiol Community Health*. 2017, 71(6): 576–583.

[14] Ungprasert P, Wijarnpreecha K, Thongprayoon C. Rheumatoid arthritis and the risk of dementia: A systematic review and meta-analysis. *Neurol India*. 2016, 64(1): 56–61.

[15] Negre C, Bojinca V, Balanescu A, et al. Management of rheumatoid arthritis: Impact and risks of various therapeutic approaches. *Exp Ther Med*. 2016, 11(4): 1177–1183.

[16] Yazici Y. Treatment of rheumatoid arthritis: we are getting there. *Lancet*. 2009, 374(9685): 178–180.

[17] Westlake SL, Colebatch AN, Baird J, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology (Oxford)*. 2010, 49(2): 295–307.

[18] Huang LC, Chang YH, Yang YH. Can disease-modifying anti-rheumatic drugs reduce the risk of developing dementia in patients with rheumatoid arthritis? *Neurotherapeutics*. 2019, 16(3): 703–709.

[19] Amuah JE, Hogan DB, Eliasziw M, et al. Persistence with cholinesterase inhibitor therapy in a population-based cohort of patients with Alzheimer’s disease. *Pharmacoepidemiol Drug Saf*. 2010, 19(7): 670–679.

[20] Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001, 57(3): 489–495.

[21] Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*. 2001, 57(3): 481–488.

[22] Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer’s disease. *Curr Neuropsychopharmacol*. 2010, 8(1): 69–80.

[23] Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer’s disease. *Curr Neuropharmacol*. 2018, 6: CD001190.

[24] Small G, Dubois B. A review of compliance to treatment in Alzheimer’s disease: potential benefits of a transdermal patch. *Curr Med Res Opin*. 2007, 23(11): 2705–2713.
[25] Lyle S, Grizzell M, Willmott S, et al. Treatment of a whole population sample of Alzheimer’s disease with donepezil over a 4-year period: lessons learned. Dement Geriatr Cogn Disord. 2008, 25(3): 226–231.

[26] Brady R, Weinman J. Adherence to cholinesterase inhibitors in Alzheimer’s disease: a review. Dement Geriatr Cogn Disord. 2013, 35(5/6): 351–363.

[27] Chang YP, Yang CH, Chou MC, et al. Clinical compliance of donepezil in treating Alzheimer’s disease in Taiwan. Am J Alzheimers Dis Other Demen. 2015, 30(4): 346–351.

[28] Burns A, Rossor M, Hecker J, et al. The effects of donepezil in Alzheimer’s disease - results from a multinational trial. Dement Geriatr Cogn Disord. 1999, 10(3): 237–244.

[29] Whitehead A, Perdomo C, Pratt RD, et al. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer’s disease: a meta-analysis of individual patient data from randomised controlled trials. Int J Geriatr Psychiatry. 2004, 19(7): 624–633.

[30] Darreh-Shori T, Meurling L, Pettersson T, et al. Changes in the activity and protein levels of CSF acetylcholinesterases in relation to cognitive function of patients with mild Alzheimer’s disease following chronic donepezil treatment. J Neural Transm (Vienna). 2006, 113(11): 1791–1801.

[31] Kanaya K, Abe S, Sakai M, et al. Changes in cognitive functions of patients with dementia of the Alzheimer type following long-term administration of donepezil hydrochloride: relating to changes attributable to differences in apolipoprotein E phenotype. Geriatr Gerontol Int. 2010, 10(1): 25–31.

[32] Choi SH, Kim SY, Na HR, et al. Effect of ApoE genotype on response to donepezil in patients with Alzheimer’s disease. Dement Geriatr Cogn Disord. 2008, 25(5): 445–450.

[33] MacGowan SH, Wilcock GK, Scott M. Effect of gender and apolipoprotein E genotype on response to anticholinesterase therapy in Alzheimer’s disease. Int J Geriatr Psychiatry. 1998, 13(9): 625–630.

[34] Cacabelos R, Llovo R, Fraile C, et al. Pharmacogenetic aspects of therapy with cholinesterase inhibitors: the role of CYP2D6 in Alzheimer’s disease pharmacogenetics. Curr Alzheimer Res. 2007, 4(4): 479–500.

[35] Pilotto A, Franceschi M, D’Onofrio G, et al. Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease. Neurology. 2009, 73(10), 761–767.

[36] Haywood WM, Mukaetova-Ladinska EB. Sex influences on cholinesterase inhibitor treatment in elderly individuals with Alzheimer’s disease. Am J Geriatr Pharmac-other. 2006, 4(3): 273–286.

[37] Csernansky JG, Wang L, Miller JP, et al. Neuroatomic predictors of response to donepezil therapy in patients with dementia. Arch Neurol. 2005, 62(11): 1718–1722.

[38] Yang YH, Wu SL, Chou MC, et al. Plasma concentration of donepezil to the therapeutic response of Alzheimer’s disease in Taiwanese. J Alzheimers Dis. 2011, 23(3): 391–397.

[39] Yang YH, Chen CH, Chou MC, et al. Concentration of donepezil to the cognitive response in Alzheimer disease. J Clin Psychopharmacol. 2013, 33(3): 351–355.

[40] Corey-Bloom JP. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer’s disease. Int J Geriatr Psychopharmacol. 1998, 1: 55–65.

[41] Farlow M, Lane R, Kudaravalli S, et al. Differential qualitative responses to rivastigmine in APOE epsilon 4 carriers and noncarriers. Pharmacogenomics J. 2004, 4(5): 332–335.

[42] Birks JS, Evans JG, Lakovidou V, Tsolaki M. Rivastigmine for Alzheimer’s disease. Cochrane Database Syst Rev, 2009, 2: CD001191.

[43] Frankort SV, Appels BA, de Boer A, et al. Identification of responders and reactive domains to rivastigmine in Alzheimer’s disease. Pharmacoepidemiol Drug Saf. 2007, 16(5): 545–551.

[44] Cutler NR, Polinsky RJ, Sramek JJ, et al. Dose-dependent CSF acetylcholinesterase inhibition by SDZ ENA 713 in Alzheimer’s disease. Acta Neurol Scand. 1998, 97(4): 244–250.

[45] Gobburu JV, Tammara V, Lesko L, et al. Pharmacokinetic-pharmacodynamic modeling of rivastigmine, a cholinesterase inhibitor, in patients with Alzheimer’s disease. J Clin Pharmacol. 2001, 41(10): 1082–1090.

[46] Lefèvre G, Sede G, Jhee SS, et al. Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules.
in Alzheimer’s disease patients. Clin Pharmacol Ther. 2008, 83(1): 106–114.
[47] McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000, 356(9247): 2031–2036.
[48] Gauthier S, Juby A, Rehel B, et al. EXACT: rivastigmine improves the high prevalence of attention deficits and mood and behaviour symptoms in Alzheimer’s disease. Int J Clin Pract. 2007, 61(6): 886–895.
[49] Chou MC, Chen CH, Liu CK, et al. Concentrations of rivastigmine and NAP 226-90 and the cognitive response in Taiwanese Alzheimer’s disease patients. J Alzheimers Dis. 2012, 31(4): 857–864.
[50] Chou PS, Jhang KM, Huang LC, et al. Skinfold thickness for rivastigmine patch application in Alzheimer’s disease. Psychopharmacology (Berl). 2019, 236(4): 1255–1260.
[51] Lilienfeld S. Galantamine—a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer’s disease. CNS Drug Rev. 2002, 8(2): 159–176.
[52] Wattmo C, Jedenius E, Blennow K, et al. Dose and plasma concentration of galantamine in Alzheimer’s disease-clinical application. Alzheimers Res Ther. 2013, 5(1): 2.
[53] MacGowan SH, Wilcock GK, Scott M. Effect of gender and apolipoprotein E genotype on response to anticholinesterase therapy in Alzheimer’s disease. Int J Geriatr Psychiatry. 1998, 13(9): 625–630.
[54] Haywood WM, Mukaetova-Ladinska EB. Sex influences on cholinesterase inhibitor treatment in elderly individuals with Alzheimer’s disease. Am J Geriatr Pharmacother. 2006, 4(3): 273–286.
[55] Lin YT, Chou MC, Wu SJ, et al. Galantamine plasma concentration and cognitive response in Alzheimer’s disease. PeerJ. 2019, 7: e6887.
[56] Kishi T, Matsunaga S, Oya K, et al. Memantine for Alzheimer’s disease: an updated systematic review and meta-analysis. J Alzheimers Dis. 2017, 60(2): 401–425.
[57] Joshi I, Yang YM, Wang LY. Coincident activation of metabotropic glutamate receptors and NMDA receptors (NMDARs) downregulates persynaptic/extrasynaptic NMDARs and enhances high-fidelity neurotransmission at the developing calyx of Held synapse. J Neurosci. 2007, 27(37): 9989–9999.
[58] Sani G, Serra G, Kotzalidis GD, et al. The role of memantine in the treatment of psychiatric disorders other than the dementias. CNS Drugs. 2012, 26(8): 663–690.
[59] Ueda T, Suzukamo Y, Sato M, et al. Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. Ageing Res Rev. 2013, 12(2): 628–641.
[60] Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012, 344: e977.
[61] Hogan M. Physical and cognitive activity and exercise for older adults: A review. Int J Aging Hum Dev. 2005, 60(2): 95–126.
[62] Wayne PM, Walsh JN, Taylor-Piliae RE, et al. Effect of Tai Chi on cognitive performance in older adults: systematic review and meta-analysis. J Am Geriatr Soc. 2014, 62(1): 25–39.
[63] Lam LC, Chan WM, Kwok TC, et al. Effectiveness of Tai Chi in maintenance of cognitive and functional abilities in mild cognitive impairment: a randomised controlled trial. Hong Kong Med J. 2014, 20(3 Suppl 3): 20–23.
[64] Fagarty JN, Murphy KJ, McFarlane B, et al. Taoist Tai Chi® and memory intervention for individuals with mild cognitive impairment. J Aging Phys Act. 2016, 24(2): 169–180.
[65] Wu G, Milon D. Joint kinetics during Tai Chi gait and normal walking gait in young and elderly Tai Chi Chuan practitioners. Clin Biomech (Bristol, Avon). 2008, 23(6): 787–795.
[66] Lan C, Lai JS, Wong MK, et al. Cardiorespiratory function, flexibility, and body composition among geriatric Tai Chi Chuan practitioners. Arch Phys Med Rehabil. 1996, 77(6): 612–616.
[67] Lan C, Chen SY, Lai JS, et al. Tai Chi Chuan in medicine and health promotion. Evid Based Complement Alternat Med. 2013: 502131.
[68] Kao HSR. Shufa: Chinese calligraphic handwriting (CCH) for health and behavioural therapy. Int J Psychol. 2006, 41(4): 282–286.
[69] Guo NF, Kao HSR., Liu X. Calligraphy, hypertension and the type-A personality. Ann Behav Med. 2001, 23: S159.
[70] Kao HSR, Ding BK, Cheng SW. (2000). Brush handwriting treatment of emotional problems in patients with Type II diabetes. *Int J Behav Med.* 2000, 7:50.

[71] Yang XL, Li HH, Hong MH, et al. The effects of Chinese calligraphy handwriting and relaxation training in Chinese Nasopharyngeal Carcinoma patients: a randomized controlled trial. *Int J Nurs Stud.* 2010, 47(5): 550–559.

[72] Kao HSR, Gao DG, Wang MQ. Brush handwriting treatment of cognitive deficiencies in Alzheimer’s disease patients. *Neurobiol Aging.* 2000, 21: 14.

[73] Kao HSR, Gao DG, Wang MQ, et al. Chinese calligraphic handwriting: Treatment of cognitive deficiencies in Alzheimer’s disease patients. *Alzheimers Rep.* 2000, 3(5-6): 281–287.

[74] Bai X, Kao H, Kwok T, et al. Cognitive effects of calligraphy therapy for older people: a randomized controlled trial in Hong Kong. *Clin Interv Aging.* 2011, 6: 269.

[75] Tai SY, Hsu CL, Huang SW, et al. Effects of multiple training modalities in patients with Alzheimer’s disease: a pilot study. *Neuropsychiatr Dis Treat.* 2016, 12: 2843–2849.

Yuan-Han Yang was a research fellow at the Alzheimer’s Disease Research Center, Washington University in St Louis, MO, USA. He was awarded the First Place of Research Award by the Taiwan Dementia Society in 2010. He was listed in Marquis Who’s Who in The World in 2014 and 2015, and was honored for Albert Nelson Marquis Lifetime Achievement Award in 2017 and 2018. He has published over 200 dementia-related papers, some of which were featured in The Innovation and Impaction Papers: 2013 World Biomedical Frontiers. He initiated the Asian Society Against Dementia Collaborative Study: AD8-Asia for screening early dementia and the Registration of Alzheimer’s Disease in Asian Countries (ReAD-Asia) to foster collaboration in Asia. He has served as the Editor of *Frontiers in Bioscience*, Associate Editor of *Journal of Alzheimer’s Disease*, Associate Editor-in-Chief of *Brain Science Advances*, Lead Guest Editor of *The Scientific World Journal*, Lead Guest Editor of *Parkinson’s Disease*, and as editorial board member of many other Journals.

Rajka M. Liscic, M.D., Ph.D., as a winner of a prestigious Fulbright Scholarship, completed a 12-month education in cognitive neurology at the NIH-funded Knight Alzheimer’s Disease Research Centre (ADRC), Washington University in St. Louis, MO, USA under the supervision of Dr. J. C. Morris (M.D., Director), and became CDR (Clinical Dementia Rating) certified. Her major focus has been on frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD). She performed a project to study both clinically and pathologically the phenotypes of FTLD and AD, describing the co-existence of AD pathology in almost a quarter of FTLD cases (Liscic RM et al., *Archives of Neurology*, 2007). She has published over 60 dementia-related papers in peer-review international journals. She has also served as a reviewer for international journals including *Archives of Neurology, Annals of Neurology, European Journal of Neurology*, and she was a Guest Editor of the *Scientific World Journal* and Guest Editor of *Parkinson’s Disease*. Since 2016, she has been serving as a consultant for Hofmann-La Roche for clinical trials in Alzheimer disease.
Jacqueline Dominguez is a neurologist with special interest in aging and cognitive impairment. She graduated from the St. Louis University College of Medicine and trained in adult neurology at the St. Luke’s Institute for Neurosciences. She pursued training at Washington University in St. Louis, MO under Prof. John Morris. She was the former Research Chair in neurosciences at St. Luke’s. She established the Marikina Memory and Aging Project (MMAP) for the epidemiological study of dementia, and developed community and family-based non-pharmacologic interventions like dancing to prevent cognitive decline in persons with Mild Cognitive Impairment. She has collaborated with several colleagues in Asia regarding dementia, and is an executive member of the Asian Society Against Dementia.