Title	Practical approach to pharmacological treatment and nonpharmacological intervention of dementia
Author(s)	Tam, SKF; Lee, NYM; Wong, GHY
Citation	HKMA CME Bulletin, 2014, n. September, p. 9-13
Issued Date	2014
URL	http://hdl.handle.net/10722/203156
Rights	HKMA CME Bulletin. Copyright © Hong Kong Medical Association.

Practical Approach to Pharmacological Treatment and Nonpharmacological Intervention of Dementia

Dr. TAM Kui Fu, Stanley
MBBS (HK), MRCP (UK), FRCP (Edin, Glasg)
Specialist in Geriatric Medicine
Executive Committee Member, Hong Kong Alzheimer's Disease Association

Ms. LEE Nga Yee, Maggie
ROT, MMgt
Executive Director, Hong Kong Alzheimer's Disease Association

Dr. WONG Hoi Yan, Gloria
PhD
Research Assistant Professor, Sau Po Centre on Ageing, The University of Hong Kong
Honorary Research Associate, Department of Psychiatry, The University of Hong Kong

Disease-modifying therapy for dementia is not yet available. At present, treatment requires a comprehensive multidimensional approach, which includes 1) managing the disease, 2) treating the symptoms, 3) supporting the patient, and 4) supporting the caregiver. Pharmacological and non-pharmacological interventions are equally important. Given early in the course of illness, these strategies help maintain or improve functioning and quality of life.

Pharmacological Treatment

AD is a progressive degenerative brain disease. More than 200 agents have been investigated for disease-modifying potential, but none was successful. The mainstay of current management of AD involves drugs that provide symptomatic relief.[1] The US Food and Drug Administration (FDA) have approved acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonist for the treatment of cognitive symptoms in AD. For other drugs such as aspirin, steroids and non-steroidal anti-inflammatory drugs (NSAIDs), nicotine, hormone replacement and thiamine, the evidence for benefit on cognition is limited.[2-5] For Ginkgo biloba, the results are conflicting.[6] The best treatment involves concurrent application of both pharmacological and non-pharmacological modalities.

Strategic Pharmacological Intervention for Dementia: Case Illustration

History

Madam Lam, aged 81 years old, presented with progressive deterioration of short-term memory for 3 years, followed by recent problems in operating home electrical appliance, deranged cooking technique, and change in personality. She became argumentative, defensive and emotional when poor performances were pointed out by the others. Despite the cognitive deficit, she remained independent in self-care and was not depressed.

Assessment

Mini-Mental State Examination (MMSE) score was below cut-off (18/30). Neurological examination was remarkable. Targeted blood tests did not reveal any abnormality. CT scan of brain showed cerebral atrophy.

Diagnosis

Alzheimer's disease (AD) of mild-to-moderate severity.

Management

Oral rivastigmine 1.5 mg bd, gradual titration to 4.5 mg bd over 4 months.

Treatment for Mild-to-Moderate AD

The AChEIs donepezil, rivastigmine, and galantamine are available in a variety of preparations including delayed-release pills, orodispersible tablets (donepezil) and patch form (rivastigmine).

The cholinergic hypothesis[7] states that low levels of acetylcholine lead to cognitive decline. There is deficiency in cholinergic neurotransmission in AD. AChEIs inhibit the activity of acetylcholinesterase, an enzyme that breaks down acetylcholine at the synapse, resulting in increased availability of the neurotransmitter for binding to muscarinic and nicotinic receptors, and may improve memory and cognition in AD.

Statistically significant effects were shown on cognitive functions, activities of daily living and overall functioning with all three AChEIs, although the magnitude of effect is not large and not all patients benefit from the treatment. Some beneficial effects of AChEIs on behavioural symptoms were also described. A Cochrane database systemic review[8] showed that AChEIs are efficacious for mild-to-moderate AD, and they are cost-effective. Despite the slight variations in the mode of action of the three AChEIs, there are no differences between them with respect to efficacy.[9]

Strategic Pharmacological Intervention for Dementia: Case Illustration (Cont'd)

Progress

Madam Lam reported reduced appetite, weight loss of 2.5 kg after taking rivastigmine for 4 months. Systemic enquiry and physical examination were unremarkable. Blood tests and stool for occult blood were normal. She declined oesophagogastroduodenoscopy examination. Rivastigmine was stopped in view of possible gastrointestinal side effect.

She was noticed to have low mood attributed to her daughter criticizing her overtly, and her son got unemployed recently. Antidepressant was started and she was encouraged to have more daytime and outdoor activities. Dementia day care services of Hong Kong Alzheimer's Disease Association was introduced.

Four weeks later, her mood and appetite improved. AChEIs was restarted with rivastigmine patch 4.6 mg/d and dose stepped up to 9.5 mg/d in 1 month. Her bodyweight returned to normal level.

All AChEIs have similar side effect profile. Patients most commonly complain of nausea, vomiting, insomnia and diarrhoea. They are more likely to occur at the commencement of therapy or when the dose of the agent is increased. These side effects are dose-related and tend to be transient. Introducing AChEIs at low doses, increasing the dose gradually, and administering the medication with meals may limit gastrointestinal side effects.

Physicians should be aware of their direct anticholinergic and vagotonic actions, especially when prescribing for patients with cardiac conduction abnormalities and chronic obstructive pulmonary disease.

It is advised to look for organic cause of weight loss and depression, before attributing to drug side effect. The patch formulation of rivastigmine allows the convenience of once-daily administration, and has fewer gastrointestinal adverse effects than its oral preparation.

Although memantine is approved for moderate to severe AD only, it is frequently prescribed off-label for mild AD. In an independent review of three clinical trials on memantine for mild AD, Schneider et al[10] found no differences between memantine and placebo on any outcome for patients with mild AD.

Strategic Pharmacological Intervention for Dementia: Case Illustration (Cont'd)

Follow-up at 4 Years After Starting Treatment

Madam Lam became mostly home bound. She required assistance from her daughter in self-care and going outdoor. Her AD has progressed to severe stage, with an MMSE score of 11/30, compared with 18/30 4 years ago. Memantine 10 mg/d was added on top of rivastigmine patch 9.5 mg/24 h.

Treatment for Moderate-to-Severe AD

Apart from indication for mild-moderate AD, the US FDA has approved donepezil and rivastigmine transdermal system (patch) for severe stage of AD. Memantine was approved for the treatment of moderate to severe AD. Memantine is an NMDA receptor antagonist that prevent the excitotoxic effects of glutamate in the brain. In AD, glutamate receptors of the NMDA type are over-activated, leading to neuronal damage and impairment of learning. Overall, patients with moderate-to-severe AD who received memantine performed better on behavioural measures than those treated with placebo.[11]

Both AChEIs and memantine are licensed as monotherapy for AD. Theoretically, combining the two drugs could potentiate their benefits. While evidence for combination therapy with memantine and AChEIs is inconsistent, combination therapy is still regarded as 'gold standard' by some authors and is commonly prescribed in daily practice.

Table 1. Drug Therapy for Alzheimer's Disease

Acetylcholinesterase Inhibitors (AChEI)	
Donepezil (pill or orodispersible tablets)	• Start with 5 mg once daily, then increase to 10 mg/d after 4 to 6 weeks. If tolerate after >3 months of 10 mg/d, may gradually step up to 23 mg/d when there are further cognitive deterioration and/or functional decline
Rivastigmine	• Pill: start with 1.5 mg twice daily initially, then titrate by 1.5 mg every 4 weeks up to 6 mg twice daily • Patch: start with 4.6 mg/24 h, then 9.5 mg/24 h after 4 weeks. If tolerate after >6 months of 9.5 mg/24 h, may step up to 13.3 mg/24 h when there are further cognitive deterioration and/or functional decline
Galantamine ER	• Start with 8 mg daily, titrate by 8 mg/d every 4 weeks up to 24 mg/d
NMDA Receptor Antagonists	
Memantine	• Start with 5 mg/d, then increase by 5 mg every 1 to 2 week up to 20 mg/d

Non-pharmacological Interventions

For the Patient

The list of non-pharmacological interventions that has been developed is long. Evidence is accumulating particularly regarding the efficacy of the more commonly used therapies.[12-15]

Cognitive stimulation is by far showing the strongest evidence in efficacy. The intervention typically involves engaging in a range of enjoyable activities that require cognitive processing within a group-based social context. There is evidence of cognitive, quality of life and wellbeing benefits.[14] The cognitive enhancing effect is similar to pharmacological treatment[16] and appears to add onto the benefits of AChEI.[17] The UK National Institute for Health and Care Excellence (NICE) and Social Care Institute for Excellence (SCIE) Guideline recommends offering the intervention to all patients with mild-to-moderate dementia irrespective of their medical treatment.[18]

Structured cognitive training has not been associated with cognitive benefits, in particular benefits beyond the specific tasks trained. More individualized cognitive rehabilitation showed some promise, but evidence is currently limited. There is limited evidence to support cognitive effects of reminiscence therapy.[16, 18]

Exercise programmes appear to improve cognitive functioning and activities of daily living in people with dementia.[15] Current evidence is insufficient to allow recommendation on specific programme designs, such as the type (e.g., aerobic, resistance, balance) of exercise. Possible mechanisms include neuroprotective neurotrophic factors, neuroplasticity, and reduction of cerebrovascular burden.[19] Patients at different stage of dementia are capable of taking part in physical activity interventions, also for the associated strength, balance, and mobility benefits.[16,20] Continued moderate-intensity physical exercise should be considered as an important therapeutic strategy.

For the Caregiver

Dementia inflicts on both the patient and the family caregivers. Due to its effects on the patient's self-care ability and the losses for caregivers that can be compared to bereavement, dementia caregivers are at risk of poor physical health, depression, anxiety burnout, and increased mortality.[21,22] These contribute to unnecessary or premature institutionalization of the patient.[23]

Multicomponent interventions targeting caergivers reduce burden and depression and delay institutionalization, mainly through reduced frequency and severity of behavioural and psychological symptoms of dementia (BPSD).[24] Successful interventions typically last about nine to 12 tailored sessions delivered individually over 3 to 6 months with regular follow-up. Examples include the Resources for Enhancing Alzheimer's Caregiver Health (REACH) in the US[25] and the STrAtegies for RelaTives (START) study in the UK.[26] The former has been piloted in Hong Kong.[27]

For Both Patient and Caregiver

The Alzheimer's Disease International (ADI) noted in its 2011 report that successful interventions involve both the patient and the caregiver.[16] These interventions should target family needs on educational information, emotional support, practical advice on disability benefits, financial and legal issues started early in the disease course.

Existing programmes mainly involve case management approaches with initial evidence for improved outcomes. However, there was large variation in protocols, and few programmes were specifically tailored for families facing early dementia.[16] Programmes with a high degree of integration between health and social care providers are particularly beneficial.[28]

Recently, the Hong Kong Alzheimer's Disease Association (HKADA) and ADI co-developed in collaboration with The University of Hong Kong the curriculum of Certificate Dementia Care Planner (CDCP), with a family focus and comprehensive advance care planning element, targeting to help families once a diagnosis is made. CDCPs have a role similar to a case manager but equipped with comprehensive knowledge of all aspects of dementia care, including mental and physical health, social, legal, financial, advance planning and environmental design.

Integrated Multidisciplinary Community Strategies

Dementia is a complex disorder affecting both the patients and their caregivers. Its management requires integrated multidisciplinary strategies. The DSM-5 proposes a bio-psycho-social-cultural approach;[29] a compatible community model puts emphases in a reverse order and entails:

1) Cultural: Development of a dementia-friendly community, in which dementia should be every family's business;

2) Social: Provision of supportive programmes in the community (e.g., day centres), and mainstreaming dementia care into social services;

3) Psychological: Facilitate positive caregiving with a person-centred approach, including individualized advance care planning; and

4) Biological: Early diagnosis and treatment to reduce hospital admission and stay due to crisis.

In line with this, local efforts have been made:

1) Public awareness in the community, including a collaborative destigmatization initiative by 10 NGOs and five colleges of the Hong Kong Academy of Medicine to revise the Chinese term for dementia;[30]

2) Dementia day centres and other community-based services, including the development of a culturally appropriate framework (the Chinese Six Arts) for multimodal non-pharmacological intervention, incorporating cognitive stimulation and physical activities for delivery in day centres;

3) Comprehensive family support programme with knowledge, counselling, care coordination and advance care planning through training of CDCPs, who work with dementia care specialists and families with dementia to design conducive care plan, arrange necessary services, monitor intervention outcome, and help the family to make informed decisions about their future care while they still have the capacity;

4) Pre-consultation assessment to triage help-seekers and facilitate timely diagnosis, which involves trained allied healthcare professionals and primary care doctors in early detection, early diagnosis and treatment programmes with specialist support.

Best care for dementia mandate health and social services, drawing on the combined knowledge and evidence base of both systems.[18] Primary care doctors have a pivotal role in the best practice of dementia care by connecting with the family for medico-social support in the locality.

Reference

1. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurology* 2010; **9**(7): 702-16.
2. Jaturapatporn D, Isaac MG, McCleery J, Tabet N. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. *The Cochrane Database of Systematic Reviews* 2012; **2**: CD006378.
3. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA* 2000; **283**(8): 1007-15.
4. Lopez-Arrieta JM, Rodriguez JL, Sanz F. Nicotine for Alzheimer's disease. *The Cochrane Database of Systematic Reviews* 2000; (2): CD001749.
5. Rodriguez-Martin JL, Lopez-Arrieta JM, Qizilbash N. Thiamine for Alzheimer's disease. *The Cochrane Database of Systematic Reviews* 2000; (2): CD001498.
6. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. *The Cochrane Database of Systematic Reviews* 2009; (1): CD003120.
7. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of Neurology, Neurosurgery, and Psychiatry* 1999; **66**(2): 137-47.
8. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane Database of Systematic Reviews* 2006; (1): CD005593.
9. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clinical Interventions in Aging* 2008; **3**(2): 211-25.
10. Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. *Archives of Neurology* 2011; **68**(8): 991-8.
11. McKeage K. Memantine: a review of its use in moderate to severe Alzheimer's disease. *CNS Drugs* 2009; **23**(10): 881-97.
12. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *The Cochrane Database of Systematic Reviews* 2013; **6**: CD003260.
13. Woods B, Spector A, Jones C, Orrell M, Davies S. Reminiscence therapy for dementia. *The Cochrane Database of Systematic Reviews* 2005; (2): CD001120.
14. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *The Cochrane Database of Systematic Reviews* 2012; **2**: CD005562.
15. Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S. Exercise programs for people with dementia. *The Cochrane Database of Systematic Reviews* 2013; **12**: CD006489.
16. Prince M, Bryce R, Ferri C. World Alzheimer Report 2011: The benefits of early diagnosis and intervention. London: Alzheimer's Disease International; 2011.
17. Onder G, Zanetti O, Giacobini E, et al. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *The British Journal of Psychiatry* 2005; **187**: 450-5.
18. NICE-SCIE. Dementia: A NICE-SCIE Guideline on Supporting People With Dementia and Their Carers in Health and Social Care (Revised). Leicester (UK): National Institute for Health and Clinical Excellence; 2011.
19. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clinic Proceedings* 2011; **86**(9): 876-84.
20. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Scherder EJ. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. *Dementia and Geriatric Cognitive Disorders* 2010; **30**(5): 392-402.
21. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA* 1999; **282**(23): 2215-9.
22. Sorensen S, Conwell Y. Issues in dementia caregiving: effects on mental and physical health, intervention strategies, and research needs. *The American Journal of Geriatric Psychiatry* 2011; **19**(6): 491-6.
23. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002; **287**(16): 2090-7.
24. Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues Clin Neurosci* 2009; **11**(2): 217.
25. Wisniewski SR, Belle SH, Coon DW, et al. The Resources for Enhancing Alzheimer's Caregiver Health (REACH): project design and baseline characteristics. *Psychology and Aging* 2003; **18**(3): 375-84.
26. Livingston G, Barber J, Rapaport P, et al. Clinical effectiveness of a manual based coping strategy programme (START, STrAtegies for RelaTives) in promoting the mental health of carers of family members with dementia: pragmatic randomised controlled trial. *BMJ* 2013; **347**: f6276.
27. Cheung KS, Lau BH, Wong PW, et al. Multicomponent intervention on enhancing dementia caregiver well-being and reducing behavioral problems among Hong Kong Chinese: a translational study based on REACH II. *International Journal of Geriatric Psychiatry* 2014.
28. Somme D, Trouve H, Drame M, Gagnon D, Couturier Y, Saint-Jean O. Analysis of case management programs for patients with dementia: a systematic review. *Alzheimer's & Dementia* 2012; **8**(5): 426-36.
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
30. Chiu HF, Sato M, Kua EH, et al. Renaming dementia – an East Asian perspective. *International Psychogeriatrics* 2014; **26**(6): 885-7.

Complete this course and earn **1 CME Point**

Q&A Self-assessment Questions

Answer these on page 21 or make an online submission at: www.hkmacme.org
Please indicate whether the following statements are true or false.

1) Disease-modifying agents are available for use in AD.
2) Treatment of neuropsychiatric symptoms is mandatory in all patients.
3) Pharmacological treatment is equally important as non-pharmacological treatment.
4) ChEIs should be stopped once the patient enters into severe stage.
5) ChEIs have no effects on ADL function.
6) Memantine antagonist can be used for all causes of dementia.
7) Cognitive stimulation is effective in maintaining cognition in mild-to-moderate dementia.
8) Cognitive stimulation should not be used in combination with AChEIs.
9) Physical exercise should not be recommended in moderate-to-severe dementia.
10) Multi-component caregiver interventions may improve caergivers through reducing BPSD in the patient.