UNIT NO. 4

PHARMACOLOGICAL TREATMENT OF DEMENTIA

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ABSTRACT

Pharmacotherapy is a vital part of the multi-pronged strategy in dementia management. All dementia patients should be evaluated for suitability of pharmacological strategies to address the underlying disease, enhance cognitive symptomatology, and treat attendant behavioural complications. Once a definitive diagnosis of dementia has been made, the choice of symptomatic treatment hinges mainly on dementia etiology and stage of severity. While skillful use of symptomatic treatment can offer tangible but modest benefits in many cases, the decision to initiate such costly treatment should be individualised and always made in conjunction with the patient and caregiver. Disease-modifying treatment which goes beyond a primary symptomatic effect to target the underlying amyloid and tau pathways are currently undergoing clinical trials.

Keywords: palliation, chronic disease, cholinesterase inhibitors, NMDA antagonists, side effects

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INTRODUCTION

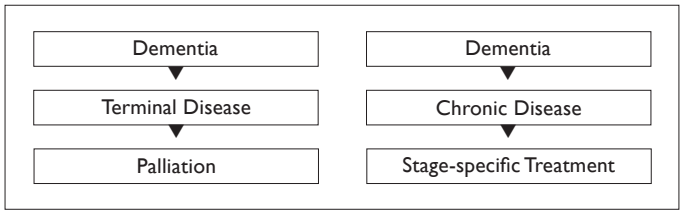
An executive report in 2006 highlighted the threat of an impending epidemic of dementia in the Asia-Pacific region in line with the greying demographic trend.[1] This has implications for Singapore, which has one of the most rapidly aging populations in the region. There is a compelling need for primary care physicians to be trained in the care and management of dementia patients to meet the projected burgeoning demand. From the standpoint of pharmacological management, it is foreseeable that the primary care physician would be involved in one of two ways:

- initiate treatment in a newly diagnosed dementia patient, or
- more commonly, continue care in dementia individuals whose treatment regimes have been initiated and stabilised by the hospital-based dementia specialist.

OVERVIEW

In the past, dementia was often perceived as a terminal illness for which the main focus of treatment is palliation. Increasingly, there is a paradigm shift towards treating dementia as a chronic disease, not unlike conditions like diabetes mellitus, where specific treatment goals can be formulated depending on the stage of the disease (Figure 1). In the mild stage, the focus is on maintenance of patient independence and autonomy, whereas in the advanced stages, carer and psychosocial issues predominate. Seen in this light, it is important to appreciate that pharmacotherapy is only one of the tenets of a comprehensive multi-pronged strategy for dementia management that encompasses other aspects such as a well-established diagnosis, education of patient and carer, non-pharmacological measures and comprehensive caregiver psychosocial intervention.

FIGURE 1: PARADIGM SHIFT IN DEMENTIA TREATMENT



Pharmacological treatment can be broadly conceptualised into three broad categories:

1. Reverse or stabilise the underlying disease.
2. Improve cognitive symptomatology, and
3. Treat behavioural and psychiatric symptoms associated with dementia.

As behavioural and psychiatric symptoms associated with dementia are covered in Unit 3, the rest of the article shall focus on the first two aspects of pharmacotherapy.

(1) Reverse or stabilise the underlying disease

Pharmacological strategies to address the underlying disease include treating identifiable reversible causes, reduction of established risk factors, and disease modifying measures to slow the rate of disease progression (Table 1).

It is now established that vascular risk factors are putative not only in vascular dementia (VaD), but also in Alzheimer's disease (AD); thus, vascular risk factors should be assiduously sought for and appropriately managed in all dementia cases. While a search for reversible causes should be undertaken in all newly diagnosed dementia patients, in truth, only a small percentage of potentially reversible abnormalities are truly reversible, most notably conditions such as depression and hypothyroidism. There is concomitant neurodegenerative causes such as AD in many of these patients. Moreover, when significant neuronal damage has occurred, treatment of potentially reversible causes often arrests the underlying pathophysiology but does not reverse the dementia.

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Trials involving NSAIDS, cyclooxygenase-2 inhibitors, low-dose prednisolone and estrogen replacement therapy have yielded null findings. High dose vitamin E (2000 IU per day) is currently not recommended as ancillary treatment for dementia, because the debatable marginal benefits are mitigated by concerns about safety, especially in doses above 400 IU/day.[2] A Cochrane review of 3 RCTs did not find any significant difference in cognition or global function between statin and placebo groups.[3] The LEADe study also reported no benefit in cognition or global function when Atorvastatin 80mg/day was given to patients with mild to moderate Alzheimer's disease who were taking donepezil.[4] A recent Cochrane review did not show any benefit of omega-3 fatty acid in the prevention of dementia.[5]

(2) Medications for improving cognitive symptomatology

Currently, the established modalities for dementia treatment are considered to be primarily symptomatic rather than disease modifying in their mode of action. There are two main classes (Table 2):

- Cholinesterase Inhibitors (ChEIs) based on the cholinergic hypothesis, which states that many of the cognitive, functional and behavioural symptoms derive from an absolute or relative deficit in brain acetylcholine activity, and;
- N-methyl D-aspartate (NMDA) receptor antagonists, which protect against glutamate-mediated excitotoxicity.

Other less established treatment options for dementia include:

- Ginkgo biloba, which exhibits "inconsistent and unconvincing benefits" based on a 2007 Cochrane systematic review of 35 clinical trials and 4247 participants.[6] In a recent study with a 5-year follow up, 120 mg standardised ginkgo biloba extract did not reduce the risk of progression to Alzheimer's disease compared with placebo in elderly patients with memory complaints.[7] Practitioners who prescribe ginkgo should be aware of the variability of active ingredient among preparations and the potential for drug interactions, such as increased bleeding risk when combined with warfarin and antiplatelet agents, and the antagonism of thiazides and anticonvulsants (valproate and carbamazepine).
- Selegiline, piracetam and rosiglitazone, which are not recommended for the treatment of core cognitive symptoms of dementia.

CHOLINESTERASE INHIBITORS

ChEIs form the mainstay of dementia treatment. Most of the published data on ChEIs are derived from randomised controlled trials of mild-to-moderate stages of AD. There is evidence that ChEIs can improve cognition and preserve function in moderate to severe AD, including the more severe stages of AD (MMSE<10).[8] In general, ChEIs confer modest improvement in (1) cognition and global functioning of short-term duration (6 to 9 months), (2) activities of daily living (best described as a slowing of decline rather than an actual improvement), and (3) neuropsychiatric symptoms (delay in emergence of symptoms, improvement in apathy, and variable patterns of improvement for milder degrees of anxiety, depression and hallucination). In some open-label studies, the duration of benefit was observed to persist for as long as three years.[9]

Trials of mixed dementia and VaD reported significant improvement in cognition and to a lesser extent, global function but the benefit in activities of daily living and behaviour was less obvious. Studies of rivastigmine in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) also demonstrated cognitive, neuropsychiatric and functional benefits without worsening of motor symptoms.[10-11]

There are currently three ChEIs regularly used for the symptomatic treatment of dementia. To reduce intolerability to gastrointestinal adverse effects, ChEIs are often started at lower doses (donepezil 2.5 mg/day; galantamine 8 mg/day; rivastigmine 1.5 mg twice daily) (Table 2). Studies have consistently shown that patients who received recommended doses of ChEIs exhibited better outcomes than those who received placebo or lower doses.[12] Thus, where tolerated, ChEIs should be gradually titrated to recommended doses (5-10 mg/day donepezil; 16-24 mg/day galantamine; 6-12 mg/day oral and 4.6-9.5 mg/24hr transdermal rivastigmine). Since there is no definitive evidence to support a difference in clinical efficacy between the three available agents, the choice of ChEI therapy depends on the experience of the clinician, tolerance to side effects, ease of use, and the clinical profile of the individual to be treated (such as co-morbid diseases and drug interactions) (Table 3). For patients who require medications to be crushed due to swallowing difficulties, the capsule formulations (rivastigmine and galantamine PR) should be avoided.

The side effects of the three ChEIs are broadly similar (Table 4). The most common side effect is gastrointestinal (nausea, vomiting, diarrhea, anorexia), which is dose-related, transient, and often alleviated to a large extent by a slower titration and taking the medication with food. Using healthcare databases from Ontario, Canada, Gill et al reported that the use of AChEI is associated with increased rates of hospital visits for syncope, bradycardia, pacemaker insertion and hip fracture in older adults with dementia.[13] Thus although cardiovascular side effects (such as symptomatic bradycardia and syncope) are generally not frequent, ChEIs should be avoided in patients with significant bradycardia, sick sinus syndrome or cardiac conduction disturbances. Other uncommon side effects that have been reported (with donepezil, in particular) include muscle cramps, insomnia and vivid dreams; the latter can be avoided by ingestion of donepezil in the morning. Weight should be regularly monitored as weight loss is not uncommon.

TABLE 2. DOSING RECOMMENDATIONS OF DEMENTIA DRUGS IN CLINICAL USE

Medication	Forms	Starting Dose	Titration	Example of titration schedule
(1) Cholinesterase inhibitors				
Donepezil (Aricept ®)	Tablet (5mg, 10mg)	2.5-5mg once daily	Increase to 10mg/day after 4-8 weeks	2.5mg om → 5mg om → 10mg om
Rivastigmine (Exelon ®)	Capsule (1.5mg, 3mg, 4.5mg, 6mg) Patch (4.6mg/24h, 9.5mg/24h)	1.5mg bid after meals 4.6mg/24h once daily	Increase by 1.5mg bid every 2-4 weeks up to 6mg bid Increase to 9.5mg/24h after 4 weeks	1.5mg bid → 3mg bid → 4.5mg bid → 6mg bid 4.6mg/24h → 9.5mg/24h
Galantamine (Reminyl ®)	IR Tablet (4mg, 8mg, 12mg)* PR Capsule (8mg, 16mg and 24mg)* Solution (4mg/ml; 100ml bottle)†	4mg bid after meals‡	Increase by 4mg bid every 4 weeks up to 12mg bid‡	4mg bid → 8mg bid → 12mg bid‡
(2) NMDA antagonists				
Memantine (Exiba ®)	Tablet (10mg)	5mg once daily	Increase by 5mg every 1-2 weekly up to 10mg bid Increase by 5mg every 1-2 weekly up to 20mg om	5mg om → 5mg bid → 10mg om 5mg at 2pm → 10mg bid 5mg om → 10mg om → 15mg om → 20mg om

** IR: immediate release; PR: prolonged release once-a-day formulation.*

† Solution can be mixed with non-alcoholic beverage, but must be consumed immediately.

‡ Dose expressed in terms of immediate release formulation. To calculate the equivalent dosing for the PR formulation, simply add up the total daily dose e.g. galantamine 4mg IR tab bid = galantamine 8mg PR cap once daily; galantamine 8mg IR tab bid = galantamine 16mg PR cap once daily.

TABLE 3. IMPORTANT PRESCRIBING INFORMATION OF DEMENTIA DRUGS IN CLINICAL USE

Medication	Dose adjustment		Significant drug interactions
	Hepatic impairment	Renal impairment	
Donepezil	None	None	None
Rivastigmine	None	None	None
Galantamine	Child-Pugh score 7-9: max 16mg/day Child-Pugh score 10-15: use not recommended	Moderate renal impairment: max 16mg/day CrCl < 9ml/min: use not recommended	Amitriptylline, ketoconazole, prosac (fluoxetine), faverin (fluvoxamine) and paroxetine decrease galantamine clearance.
Memantine	None	CrCl 40-60 ml/min: 10mg/day Severe: use not recommended	Concomitant use of amantadine, ketamine or dextromethorphan should be avoided. Effects of L-dopa and dopaminergic agents may be enhanced. Caution is recommended with patients suffering from epilepsy.

There is a transdermal preparation for rivastigmine, which allows smooth continuous delivery of the drug to result in less fluctuation between peak and trough drug levels. This can reduce by 3-fold side effects such as nausea and diarrhea whilst maintaining comparable efficacy when compared with equivalent doses of the capsule formulation Skin tolerability is good and skin irritation generally is limited to mild reactions such as erythema and itch. The patch is available in two doses: 4.6mg/24 hours and 9.6 mg/24 hours (Table 2). It should be applied every 24 hours at a consistent time each day to the upper back, upper arm or chest; application to other body sites may result in reduced absorption. Indications for the patch include: gastrointestinal side effects during titration to higher doses, non-compliance and when a smooth drug delivery is desired (e.g. presence of co-morbidity such as epilepsy).

TABLE 4. SIDE EFFECTS OF DEMENTIA DRUGS

Cholinesterase inhibitors

Common	*Less common*
• Nausea	• Bradycardia
• Vomiting	• Syncope
• Diarrhoea	• Weight loss
• Anorexia	• Fatigue
• Abdominal pain	• Urinary incontinence
• Headache	• Vivid dreams, insomnia
• Dizziness	• Muscle cramps

Memantine

Common	*Less common*
• Headache	• Anxiety
• Dizziness	• Vomiting
• Fatigue	• Cystitis
• Diarrhoea	• Increased muscle tone
• Hallucination	
• Confusion	

NMDA ANTAGONISTS

Although memantine has been used in Germany for over 20 years, it is only in recent years that it has been approved in the US and UK for the symptomatic treatment of moderate-to-severe AD. Memantine appears to be beneficial alone or in combination with donepezil for moderately advanced AD.[14] In an industry sponsored study in moderately severe AD patients (MMSE 5-14) on stable doses of donepezil, the addition of memantine 20mg a day slightly improved cognitive, functional and global scores in comparison with patients adding placebo.[15] The cost-effectiveness of memantine therapy in moderately advanced AD remains to be established. There is also evidence of benefit in mild to moderate AD and VaD, but of a smaller magnitude compared with ChEI therapy. A small randomised controlled study of PDD and DLB patients reported that memantine produced cognitive and global benefits, although there were earlier case reports that memantine can worsen confusion in patients with DLB.

The initial dose is 5mg once a day, with 5mg increments at intervals of at least one week until a maximum of 10mg twice a day is achieved (Table 2). A recent study reported that a once-daily 20mg regime titrated over 4 weeks is equally efficacious and better tolerated compared with the b.i.d. dosing (Table 2).[16] Memantine should be used with caution in patients with epilepsy and renal impairment, and the clinician should be aware of interactions involving commonly prescribed medications such as dextromethorphan and L-dopa (Table 3).

Memantine is generally better tolerated (especially gastrointestinal-related side effects) than ChEIs. Common adverse events such as dizziness, headache, fatigue, hallucinations and confusion tend to be transient (Table 4). In clinical experience, the side effects that are most likely to lead to discontinuation are restlessness and hyperexcitation.

COMMON ISSUES IN THE USE OF DEMENTIA-SPECIFIC DRUGS

1. How should I decide whether to start symptomatic dementia treatment?

Dementia-specific treatment should only be contemplated in patients with a definitive diagnosis of dementia. ChEI therapy did not delay progression to dementia nor confer any consistent cognitive, global or functional benefits in the pre-dementia stage of mild cognitive impairment (MCI); there was also a higher prevalence of side effects (including cases of sudden deaths) in the treatment group.[17] Thus, ChEIs are presently not recommended in the routine treatment of MCI.

Because the costs of ChEI and memantine therapy are not subsidised, the greatest challenge of whether to initiate cognitive enhancers resides in the cost-effectiveness, especially in the more severe stages of dementia where the benefit of costly symptomatic treatment is going to be even more marginal. In the AD 2000 study, despite the small but measurable improvements in cognition and activities of daily living, there were no benefits for donepezil in institutionalisation, progression of disability and cost savings for health and social services.[18] Thus, treatment decisions regarding the use of symptomatic treatment need to be individualised for each patient, with a conjoint decision reached after careful discussion of the pros and cons of treatment. For instance, where financial resources are limited, the opportunity cost of employing a maid to look after a patient requiring help with activities of daily living may override the modest benefits of symptomatic therapy.

To avoid unrealistic expectations, it is important to communicate with the patient and his caregiver/family from the onset that:

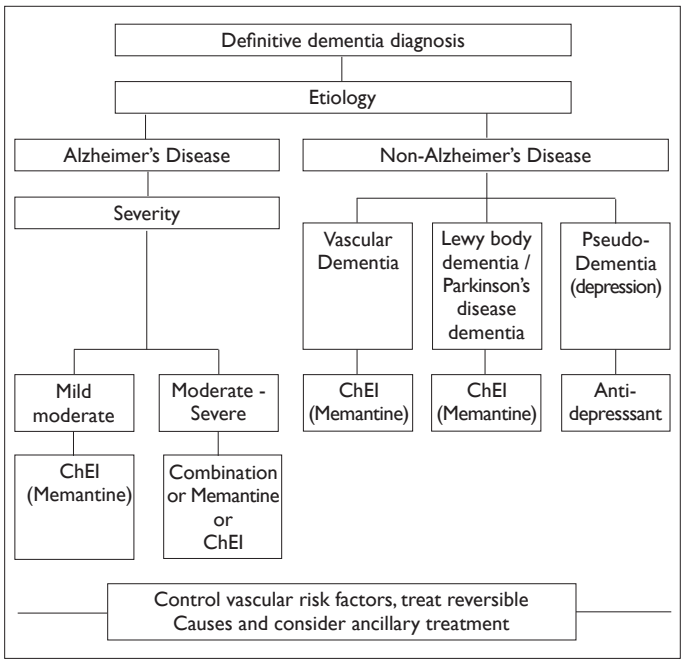
- The medications are not a cure.
- The medications do not work for everyone. The principle of one-thirds generally applies: one- third improve, one-third remain stable, while the remaining one-third deteriorate at a rate as if untreated.
- Although there may be a response in terms of modest improvement or "stabilisation", symptomatic therapy does not prevent progression of disease and cognitive decline will continue even with treatment.
- The medication will be discontinued if the patient does not respond after an adequate trial of 3-6 months.

2. Which modality should I choose?

Once a definitive diagnosis of dementia has been made, the choice of treatment modality is dependent on 2 key factors (Figure 2):

- Etiology of dementia, which can be broadly classified into AD and non-AD categories.
- Stage of dementia severity, which can be easily ascertained using functional-based scales such as the DSM-IIIR criteria (Table 5).

FIGURE 2. ALGORITHM FOR PHARMACOLOICAL TREATMENT OF COGNITIVE SYMPTOMS OF DEMENTIA



For AD individuals, ChEIs remain the preferred modality in the mild-moderate stages. Memantine is an option if ChEIs are contraindicated, not tolerated, or if there is disease progression despite an adequate trial of ChEI therapy. In the moderate-severe stages, although combination therapy appears to have the best benefit, the cost remains prohibitive. Memantine has more robust data of benefit in the more severe stages compared with ChEI.[14-15]

With regards to non-AD etiologies, the choice of treatment depends on the underlying etiology. ChEI therapy is the preferred modality in vascular dementia, as well as the synucleinopathy-based dementias such as DLB and PDD. While memantine offers a viable option in vascular dementia, it should be used with great caution in DLB and PDD, since there are reports of worsening confusion and behaviour (delusions and hallucinations) with memantine therapy in this group of dementias.[19] Conversely, there are reports of worsening behaviour in patients with frontotemporal dementia treated with ChEIs.[20]

3. How do I monitor the benefits of symptomatic treatment?

Patients who are started on cognitive enhancers should be assessed for cognition, mood and behaviour, and function within 3-6 months of starting therapy and thereafter, at least once yearly or as clinically indicated. Stabilisation or modest improvement above baseline may be observed with cognitive enhancers in the first 6-9 months, followed a lesser decline thereafter. During follow-up, patients should be assessed using: (i) clinical methods, via assessment of cognitive, functional and behavioural domains through interview with the patient and caregiver; and/or (ii) brief mental status tests, such as the Chinese MMSE, Abbreviated Mental Test (AMT) and Elderly Assessment Cognitive Questionnaire (ECAQ),

When a patient does not appear to be responding to ChEI therapy, and this is not due to non-compliance or other confounding conditions such as delirium, the options[12,21] include:

- Increasing the dose.
- Switching to another ChEI.
- Switching to memantine.
- Adding on memantine (i.e. ChEI-memantine combination).
- Drug holidays can be associated with clinical deterioration that may not revert to baseline even on resumption of therapy, and hence, should be discouraged.

4. When should symptomatic treatment be stopped?

A trial of treatment withdrawal should be considered when the harm outweighs the benefit. Examples include intolerable or serious side effects, and progression of disease despite optimising treatment. This should be undertaken only after careful discussion with the patient and caregiver. When attempting withdrawal, it is important to monitor closely for any deterioration so that the medication can be quickly reinstated to regain the same level of symptomatic effect. The DOMINO study in patients with moderate to severe Alzheimer's disease who had progressed despite donepezil treatment found that discontinuing donepezil was associated with slightly poorer cognition (1.2-1.9 points on the 30-item Standardised MMSE) and function at 1 year compared with continuation of donepezil or switching to NMDA antagonist (memantine).[22] Many patients, however, discontinue donepezil without obvious difficulty.

NEW FRONTIERS IN DEMENTIA TREATMENT

Recent advances in understanding disease pathogenesis have led to the development of new therapeutic approaches that might modify the underlying specific disease process (i.e. disease-modifying treatment as opposed to current symptomatic treatment). For instance, in Alzheimer's disease, a wide array of anti-amyloid and neuroprotective therapeutic approaches are under investigation on the basis of the hypothesis that amyloid beta (Aβ) protein plays a pivotal role in disease onset and progression and that secondary consequences of Aβ generation and deposition, including tau hyperphosphorylation and neurofibrillary tangle formation, oxidation, inflammation, and excitotoxicity, contribute to the disease process. Investigations are currently underway to evaluate the effectiveness of disease- modifying agents that might block the cascade of events comprising AD pathogenesis, such as anti-amyloid strategies, anti-tau strategies, limiting oxidation and excitotoxicity, and controlling inflammation.[23] With the advent of disease-modifying therapy, there will be an increasing emphasis on accurate clinical characterisation in the earlier stages of disease such as MCI, and the development of methods and trial designs to effectively identify and test promising candidate agents.[24]

TABLE 5: CRITERIA FOR THE STAGING OF DEMENTIA SEVERITY

DSM III-R* criteria
Mild: although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgement.
Moderate: independent living is hazardous, and some degree of supervision is necessary.
Severe: activities of daily living are so impaired that continual supervision is required (e.g. unable to maintain minimal personal hygiene, largely incoherent or mute).

**DSM III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revised.*

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LEARNING POINTS

- **All dementia patients should be evaluated for suitability of pharmacological strategies to address the underlying disease, enhance cognitive symptomatology, and treat attendant behavioural complications.**
- **Once a definitive diagnosis of dementia has been made, the key factors determining choice of symptomatic treatment are dementia etiology and stage of severity.**
- **The pre-requisite to skillful use of symptomatic treatment is a firm knowledge of the pharmacokinetic and dosing properties, side effect profile and expected benefits of such medications.**
- **The decision to initiate costly symptomatic treatment should be individualised and always made in conjunction with the patient and caregiver.**
- **Patients who are started on cognitive enhancers should be monitored for benefit and side effects.**