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 skilful 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.

INTRODUCTION

Congruent with the ageing demographic trend of the population, the local prevalence of dementia is expected to increase exponentially over the next 30 years. Primary care physicians will be increasingly called upon to participate in the care and management of dementia patients to meet this burgeoning need. This article focuses on one key aspect of dementia management: pharmacological treatment.

OVERVIEW

The primary care physician could be involved in the pharmacological management of dementia individuals in one of two ways:

- initiation of treatment in a newly diagnosed dementia patient or
- more commonly, continuation of treatment in dementia individuals whose treatment regimes have been initiated and stabilized by the hospital-based dementia specialist.

It cannot be overemphasised that pharmacotherapy is not a substitute for a well-established diagnosis, education of patient and carer, and supportive programs.

Pharmacological treatment can be broadly conceptualised into the following categories:

- Reverse or stabilise the underlying disease
- Improve cognitive symptomatology
- Treat behavioural, mood or psychiatric symptoms associated with dementia

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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 important to appreciate that when significant neuronal damage has occurred; treatment of potentially reversible causes often arrests the underlying pathophysiology but does not reverse the dementia.

Table 1. Pharmacological Strategies to Address Underlying Disease

1. Treating identifiable reversible causes
   - Replace deficiency states (e.g. B12 deficiency, hypothyroidism)
   - Correct metabolic abnormalities (e.g. hypercalcemia, hypoglycemia)
   - Treat infections (e.g. neurosyphilis, HIV-associated dementia)
2. Reduction of vascular risk factors
   - Treatment of hyperlipidemia, hypertension, diabetes mellitus, and smoking cessation
   - Homocysteine-lowering agents e.g. folate, pyridoxine, B12
   - Anti-platelet agents for secondary stroke prevention
   - Anti-coagulation for atrial fibrillation and cardioembolic strokes
3. Slowing rate of disease progression (disease modifying)
   - Anti-oxidants e.g. alpha- tocopherol
   - Multimodal mechanisms e.g. statins, supplemental omega-3 fatty acids, estrogens for postmenopausal women
   - Anti-inflammatory agents e.g. NSAIDS, cyclo-oxygenase 2 inhibitors

Thus, only a small percentage of potentially reversible abnormalities are truly reversible, most notably conditions such as hypothyroidism and vitamin B12 deficiency. 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 managed in all dementia cases. The evidence for currently available disease-modifying strategies is tentative at best. The data for homocysteine-lowering agents, statins and supplemental omega 3 are preliminary, while trials involving NSAIDS, cyclooxygenase-2 inhibitors, low-dose prednisolone and estrogen replacement therapy have yielded null findings.

To date, only high dose vitamin E (2000 IU per day) has been shown to have a modest benefit in retarding progression in moderately severe dementia. However, a recent meta-analysis reported a small but significant risk for all-cause mortality with vitamin E supplementation, especially with doses of 1000 IU or greater a day (risk ratio 1.06, 95% CI 1.00 to 1.11)[1]. Some authorities suggest avoiding high dose vitamin E (e.g. > 400 IU a day) in the management of dementia until further randomized, controlled clinical trials can evaluate its efficacy and safety[2].

Behavioural and Psychological Symptoms of Dementia

Treatment for *behavioural and psychological symptoms of dementia* will be covered elsewhere. The rest of this article will be devoted to the discussion of available treatments for *improving cognitive symptomatology*.

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 wks	2.5mg om → 5mg om → 10mg om
Rivastigmine (Exelon®)	Capsule (1.5mg, 3mg, 4.5mg, 6mg)	1.5mg bid after meals	Increase by 1.5mg bid every 2-4 wks up to 6mg bid	1.5mg bid → 3mg bid → 4.5mg bid → 6mg bid
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 wks 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	5mg om → 5mg bid → 10mg om 5mg at 2pm → 10mg bid

* 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.

Medications for Improving Cognitive Symptomatology

Currently, the established modalities for dementia treatment are considered to be 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 treatment options for dementia include:

- *Ginkgo biloba*, which exhibits mixed results in trials. Overall, the treatment benefit is smaller than that of ChEIs.
- *Selegiline*, which confers a small but clinically insignificant benefit in cognition and activities of daily living in the short term.

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 (which corresponds to stages 3 to 5 on the Functional Assessment Staging [FAST]) (Table 3). There is some evidence to suggest that ChEI therapy is beneficial in the more severe stages of AD (FAST 5 to 6c)[3-4]. 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). Patients who received higher doses had a better long-term outcome than those who received placebo or low doses. Although the placebo and low-dose groups did show improvement when switched to high doses during the open-label extensions of double-blind pivotal trials, they did not "catch up" with the group that received high-dose ChEI since trial inception, suggesting that

Table 3. 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)

Functional Assessment Staging (FAST) †

1. No difficulties, either subjectively or objectively.
2. Complains of forgetting location of objects; subjective work difficulties.
3. Decreased job functioning evident to co-workers; difficulty in travelling to new locations.
4. Decreased ability to perform complex tasks (e.g. planning dinner for guests, handling finances, marketing).
5. Requires assistance in choosing proper clothing.

6a. Difficulty in putting clothing on properly.
6b. Unable to bathe properly; may develop fear of bathing.
6c. Inability to handle mechanics of toileting (i.e. forgets to flush, doesn't wipe properly).
6d. Urinary incontinence.
6e. Faecal incontinence.

7a. Ability to speak limited (1 to 5 words a day).
7b. All intelligible vocabulary lost.
7c. Non-ambulatory.
7d. Unable to sit independently.
7e. Unable to smile.
7f. Unable to hold head up.

* DSM III-R: *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised.
† Reisberg B. Functional assessment staging (FAST). Psychopharmacology Bulletin 1988; 24: 653-9.

ChEIs provide greater benefit when started as soon as dementia is diagnosed, rather than waiting until symptoms become more prominent. The duration of benefit may persist as long as three years in some patients.

Trials of mixed dementia and VaD reported significant improvement in cognition, global function, activities of daily living and neuropsychiatric symptoms of similar magnitude to that observed in ChEI trials for AD. Recent studies of rivastigmine in Parkinson's disease dementia and dementia with Lewy bodies also demonstrated cognitive and neuropsychiatric benefits without worsening of motor symptoms[5-6].

There are currently three ChEIs regularly used for the symptomatic treatment of dementia (Table 2). Tacrine is now hardly used because of its inconvenient dosing schedule (four times a day) and potential for hepatotoxicity. With regards to the three newer agents (donepezil, rivastigmine and galantamine), there is very little to choose between them in practice in terms of core efficacy. The clinical relevance of pharmacodynamic characteristics (such as selectivity for acetylcholinesterases versus butyrylcholinesterases [rivastigmine], and allostearic modulation of nicotinic receptors [galantamine]) has not been established. Moreover, the few comparative studies are small, industry sponsored, inconsistent in results, and offer little basis to make a clinical choice[7].

Thus, the choice of ChEI therapy will depend on the experience of the clinician, tolerance to side effects, ease of use (donepezil and prolonged-release [PR] galantamine can be administered once daily), and the clinical profile of the individual to be treated (such as weight, co-morbid diseases and drug interactions) (Table 4). 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 5). The most common side effect is gastrointestinal (nausea, vomiting, diarrhoea, anorexia), which is dose-related, transient, and often circumvented to a large extent by a slower titration and taking the medication with food. Although cardiovascular side effects (such as symptomatic bradycardia and syncope) are generally not frequent, ChEIs should be used with great caution in those with 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.

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[8]. In an industry sponsored study in moderately severe AD patients (predominantly FAST 5 to 6c) 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[4]. 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 (conference abstract) and VaD, but of a smaller magnitude compared with ChEI therapy.

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). It 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 4). 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 5). In clinical experience, the side effects which are most likely to lead to discontinuation are restlessness and hyperexcitation.

Table 4: 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	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.

Table 5: Side Effects of Dementia Drugs

Cholinesterase inhibitors

Common
- Nausea
- Vomiting
- Diarrhoea
- Anorexia
- Abdominal pain
- Headache
- Dizziness

Less common
- Weight loss
- Fatigue
- Bradycardia
- Urinary incontinence
- Vivid dreams, insomnia
- Muscle cramps

Memantine

Common
- Headache
- Dizziness
- Fatigue
- Diarrhoea
- Hallucination
- Confusion

Less common
- Anxiety
- Vomiting
- Cystitis
- Increased muscle tone

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. Authorities do not recommend the use of specific therapy such as ChEIs in the pre-dementia stage of mild cognitive impairment (MCI)[2]. This is a heterogeneous clinical entity that may be attributable to reversible causes (such as depression, sleep apnoea and a variety of metabolic, nutritional or sensory impairment), and a significant proportion of MCI individuals (20-40%) revert to normal on follow-up even without treatment.

Currently, ChEI and memantine therapy are not subsidized and each costs about $6 per day (equivalent to about $180 per month). Thus, the greatest challenge of symptomatic treatment resides in the cost-effectiveness, especially in the more severe stages of dementia where the benefit of costly treatment is going to be even more marginal. In a recent UK 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. 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 rule of one-thirds 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 1):
- 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 and FAST staging (Table 3).

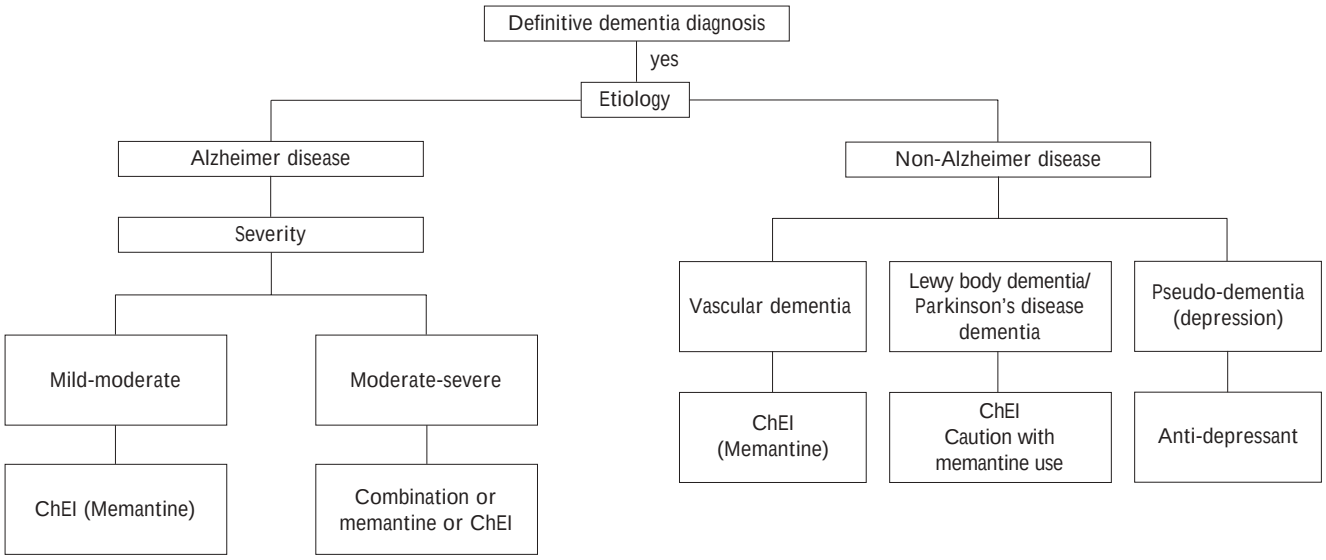
For AD individuals, ChEIs remain the preferred modality in the mild-moderate stages. Memantine is an option if ChEIs are contraindicated, not tolerated, or if there is disease progression despite an adequate trial of ChEI therapy. In the moderate-severe stages (FAST 5-6), although combination therapy appears to have the best benefit, the cost remains prohibitive. Memantine has more robust data of benefit in the more severe stages (FAST $\geq$6) compared with ChEI[4,8].

With regards to non-AD etiologies, the mainstay of treatment remains ChEI therapy. While memantine offers a viable option in vascular dementia, it should be used with great caution in synucleinopathy-based dementias such as Lewy body dementia and Parkinson's disease dementia, since there are reports of worsening confusion and behaviour (delusions and hallucinations) with memantine therapy in this group of dementias[9].

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

A range of improvement above baseline may be observed in the first 6-9 months, which can be monitored by the use of clinical methods or standardised rating scales. The former involves a clinical global impression of change after assessing the cognitive, functional and behavioural domains via interview with the patient and caregiver. The latter involves either: (a) brief mental status tests such as the Chinese Mini Mental State Examination (CMMSE), Abbreviated Mental Test (AMT) and Elderly Assessment Cognitive Questionnaire (ECAQ), or (b) more detailed psychometric testing. After 9-12 months, a lesser decline can be observed, which can be documented by patient and caregiver interview for cognitive, functional and behavioural (emergence of neuropsychiatric symptoms) features.

Figure 1. Algorithm for Pharmacological Treatment of Cognitive Symptoms of Dementia



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[7,10] 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.

REFERENCES

1. Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46.
2. Morris JC. Dementia update 2005. Alz Dis Assoc Disord 2005;19:100-17.
3. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study on donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613-20.
4. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: A randomized controlled trial. JAMA 2004;291:317-24.
5. McKeith I, Del Sen T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomized, double-blind, placebo-controlled international study. Lancet 2000;356:2031-6.
6. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004;351:2509-18.
7. Overshott R, Burns A. Treatment of dementia. J Neurol Neurosurg Psychiatry 2005;76(S):v53-v59.
8. Reisberg B, Doody R, Stoffler A, et al. Memantine Study Group. Memantine in moderate-to severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.
9. Ridha BH, Josephs KA, Rossor MN. Delusions and hallucinations in dementia with Lewy bodies: worsening with memantine. Neurology 2005;65:481-2.
10. Hake AM. The treatment of Alzheimer's disease: the approach from a clinical specialist in the trenches. Sem Neurol 2002;22:71-4.

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 skilful 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.**