UNIT NO. 3

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 individualized and always made in conjunction with the patient and caregiver. In future, disease-modifying treatment which goes beyond a primary symptomatic effect to target the underlying disease process may be available.

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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:

- 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.

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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 and heart failure, where specific treatment goals can be formulated depending on the stage of the disease (Figure 1). For instance, in the early stages of disease, the management aims would be to delay progression of disease, maintain optimal functioning, prevent emergence of behavioural symptoms, and address relevant psychosocial issues (e.g. development of advanced directives, assessment of driving safety, and diagnostic disclosure to employer/other family members).

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 should encompass other aspects such as a well-established diagnosis, education of patient and carer, non-pharmacological measures and comprehensive caregiver psychosocial intervention.

Pharmacological treatment can be broadly conceptualized into three broad categories:

1. Reverse or stabilize 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 2, the rest of the article shall focus on the first two aspects of pharmacotherapy.

(1) Reverse or stabilize 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).

Figure 1: Paradigm shift in dementia treatment

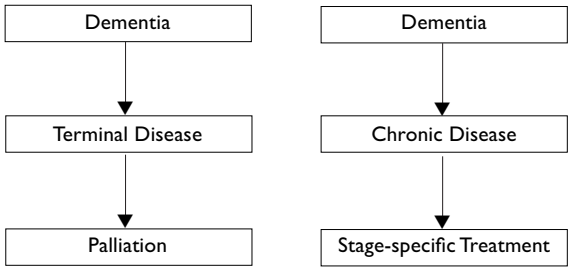

Table 1. PHARMACOLOGICAL STRATEGIES TO ADDRESS UNDERLYING DISEASE

1. Treating identifiable reversible causes • Treat depression (pseudodementia). • 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 • Hyperlipidemia, hypertension, diabetes mellitus, smoking, obesity. • Homocysteine-lowering agents e.g. folate, pyridoxine, B12. • Anti-platelet agents for secondary stroke prevention. • Anti-coagulation for atrial fibrillation and cardioembolic strokes.
3. Ancillary treatment to slow rate of disease progression • Lack of evidence in trials so far involving NSAIDS, cyclooxygenase-2 inhibitors, low dose prednisolone, oestrogen replacement therapy and statins. • High dose Vitamin E is not recommended.

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. 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.

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]. The LEADe study 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.[3] Subgroup analysis in the OmegaAD study also suggests a slower decline in Mini Mental State Examination (MMSE) in very mild AD (MMSE>27) treated with omega 3 fatty acid[4], although two RCTs reported no overall effect of omega 3 fatty acid supplementation on cognitive performance among cognitively healthy older adults[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]. The recently published Ginkgo Evaluation of Memory (GEM) study also concluded that ginkgo was not effective in preventing dementia in elderly individuals with mild cognitive impairment (MCI) or normal cognition[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.
- Selegiline and piracetam, which are both 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 randomized controlled trials of mild-to-moderate stages of AD. A recent study demonstrated the benefit of donepezil in 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).

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 ChEIs provide greater benefit when started as soon as dementia is diagnosed, rather than waiting until symptoms become more prominent. 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 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 (Table 2). 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[12]. Thus, the choice of ChEI therapy will depend 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 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 generally be avoided in those 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. The latest addition to the therapeutic armamentarium is the transdermal patch for rivastigmine. The matrix patch enables smooth continuous delivery of the drug into the bloodstream over 24 hours, resulting in less fluctuation between peak and trough drug levels than with the capsule formulation. This resulted in 3-fold decrease in side effects such as nausea and diarrhoea whilst maintaining comparable efficacy when compared with equivalent doses of the capsule formulation[13]. Skin tolerability is good and skin irritation generally is limited to mild reactions such as erythema and itch[13.] 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).

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

Table 2: DOSING RECOMMENDATIONS OF DEMENTIA DRUGS IN CLINICAL USE

Medication	Forms	Starting Dose	Titration	Example of titration
(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) 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 wks up to 6mg bid Increase to 9.5mg/24h after 4 wks	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 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 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.

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 randomized 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 treatment of MCI.

Because the costs of ChEI and memantine therapy are not subsidized, 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 institutionalization, progression of disability and cost savings for health and social services[18]. Thus, treatment decisions regarding the use of symptomatic treatment need to be individualized 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.

Fig 2. ALGORITHM FOR PHARMACOLOGICAL TREATMENT OF COGNITIVE SYMPTOMS OF DEMENTIA

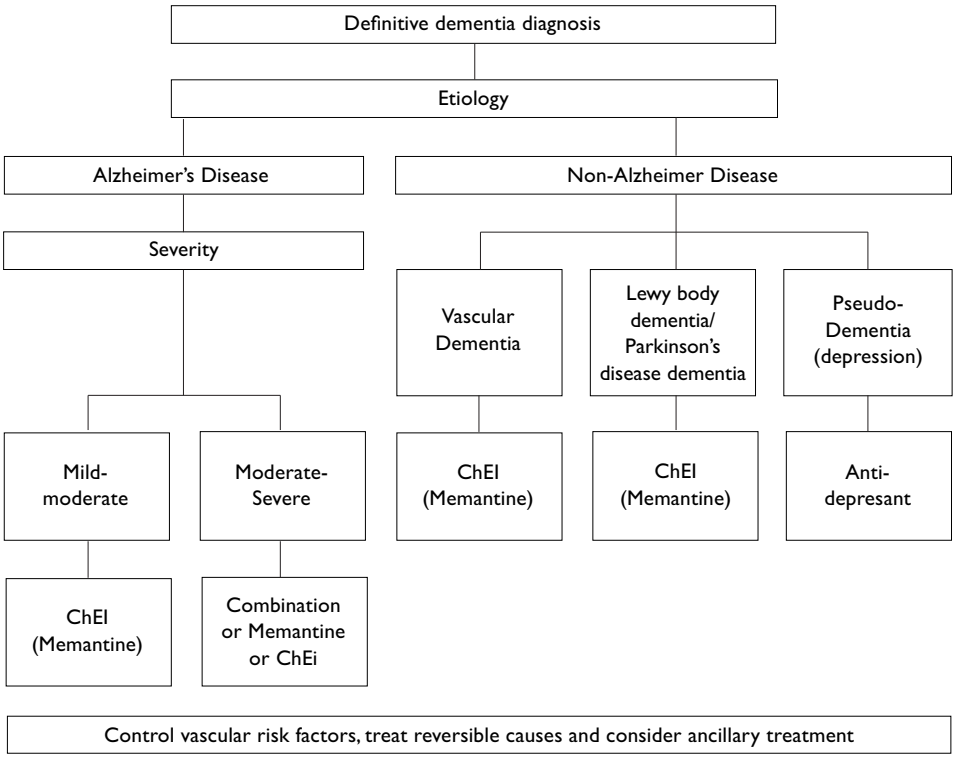

Table 3: IMPORTANT PRESCRIBING INFORMATION OF DEMENTIA DRUGS IN CLINICAL USE

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.

Table 4: SIDE EFFECTS OF DEMENTIA DRUGS

Cholinesterase inhibitors

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

Memantine

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

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 "stabilization", 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).

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?

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 standardized 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 MMSE, 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.

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.

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.

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 optimizing 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.

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[22]. With the advent of disease-modifying therapy, there will be an increasing emphasis on accurate clinical characterization 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[23].

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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 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 individualized and always made in conjunction with the patient and caregiver.**