COGNITION-ENHANCING DRUGS IN DEMENTIA: TIPS FOR THE PRIMARY CARE PHYSICIAN

Print this Article

Linda Lee, MD, MClSc(FM), CCFP, FCFP, *family physician, Kitchener-Waterloo, Ontario; director of the Centre for Family Medicine Memory Clinic; assistant professor in the Departments of Family Medicine at McMaster University, the University of Western Ontario, and Queen's University*

Carlos Rojas-Fernandez, BScPharm, PharmD, *Schlegel research chair in geriatric pharmacotherapy; assistant professor at the School of Pharmacy, University of Waterloo, Waterloo, Ontario*

George Heckman, MD, MMATH, MSc, BASc, FRCPC, *Schlegel research chair in geriatric medicine; associate professor in the Department of Health Studies and Gerontology at the University of Waterloo, Waterloo; assistant clinical professor in the Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario*

Micheline Gagnon, MD, BSc, Med, FRCPC, FACP, *head of geriatrics at St. Joseph's Healthcare; professor in the Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario*

Correspondence may be directed to Dr. Lee at joelinda5@rogers.com.

With the demographic aging of the Canadian population and critical shortage of geriatricians,[1] family physicians will be expected to care for the majority of patients suffering from dementia. Studies have demonstrated, however, that many primary care physicians are not confident in their ability to manage patients with dementia.[2,3] Quality dementia care requires multi-faceted treatment interventions, and the appropriate prescribing of cognitive enhancers represents one important aspect of care. This article reviews dementia treatment objectives and provides practical tips for starting, maintaining, and stopping cognitive enhancers with the perspective of safe prescribing practice by primary care clinicians.

In *The Nature of Suffering and the Goals of Medicine*,[4] Eric Cassell writes of the three goals of medical care that are applicable to any chronic disease: (1) make all diagnostic or therapeutic plans in terms of the sick person, not the disease; (2) maximize the patient's function; and (3) minimize the suffering of the patient and the family. Suffering, according to Cassell, is defined as "the state of severe distress associated with events that threaten the intactness of a person."[5] In terms of suffering, the impact of dementia is unrivalled: patients with dementia not only suffer from a progressive, terminal illness but are also faced with loss of their social identity and a shift to a highly stigmatized social group.[6] Treatment considerations should include the degree of suffering in context of the patient's illness experience, and the goal of treatment should be to reduce suffering and improve functioning. Treatment decisions must therefore be individualized. In Canada, two types of cognitive enhancers are available that may be offered to patients with dementia: the acetylcholinesterase inhibitors (AchEIs) donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl), and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (Ebixa).

Acetylcholinesterase Inhibitors

AchEIs work by blocking the enzyme acetylcholinesterase and thereby inhibit the breakdown of acetylcholine, a neurotransmitter required for memory (Figure 1). Since the introduction of AchEIs in the 1990s, the evidence supporting their use has been questioned, largely because of conflicting study results due to methodological differences and study end points that are in hindsight questionable. Several systematic reviews have nonetheless concluded that AchEIs are modestly effective in modifying the symptoms of Alzheimer's disease in measures of cognitive functioning, activities of daily living, and behaviour.[7–9] Current Canadian consensus guidelines recommend that AchEIs be considered as viable treatment options for most patients with mild to moderate Alzheimer's disease, vascular dementia, and mixed dementia (Alzheimer's disease with vascular dementia).[8] Additionally, the recently revised consensus statement of the British Association for Psychopharmacology recommends use of AchEIs for the treatment of Lewy body dementias (Parkinson's disease dementia and Lewy body dementia).[10] AchEIs are not currently recommended for the treatment of most frontotemporal dementias. According to the recent Canadian guidelines, currently available AChEIs are "modestly efficacious for mild to moderate AD [Alzheimer's disease]" and are "all viable treatment options for most patients with mild to moderate AD."[8] Additionally, recent clinical practice guidelines from the American College of Physicians state that the decision to initiate a trial of therapy should be based on an individualized assessment.[9] Thus, physicians must consider each case in proper context when offering these medications as part of the overall treatment strategy for patients and their caregivers.

The decision to initiate an AchEI begins with ensuring that an adequate baseline cognitive and functional assessment has been performed using validated tools such as the Montreal Cognitive Assessment[11] and Functional Activities

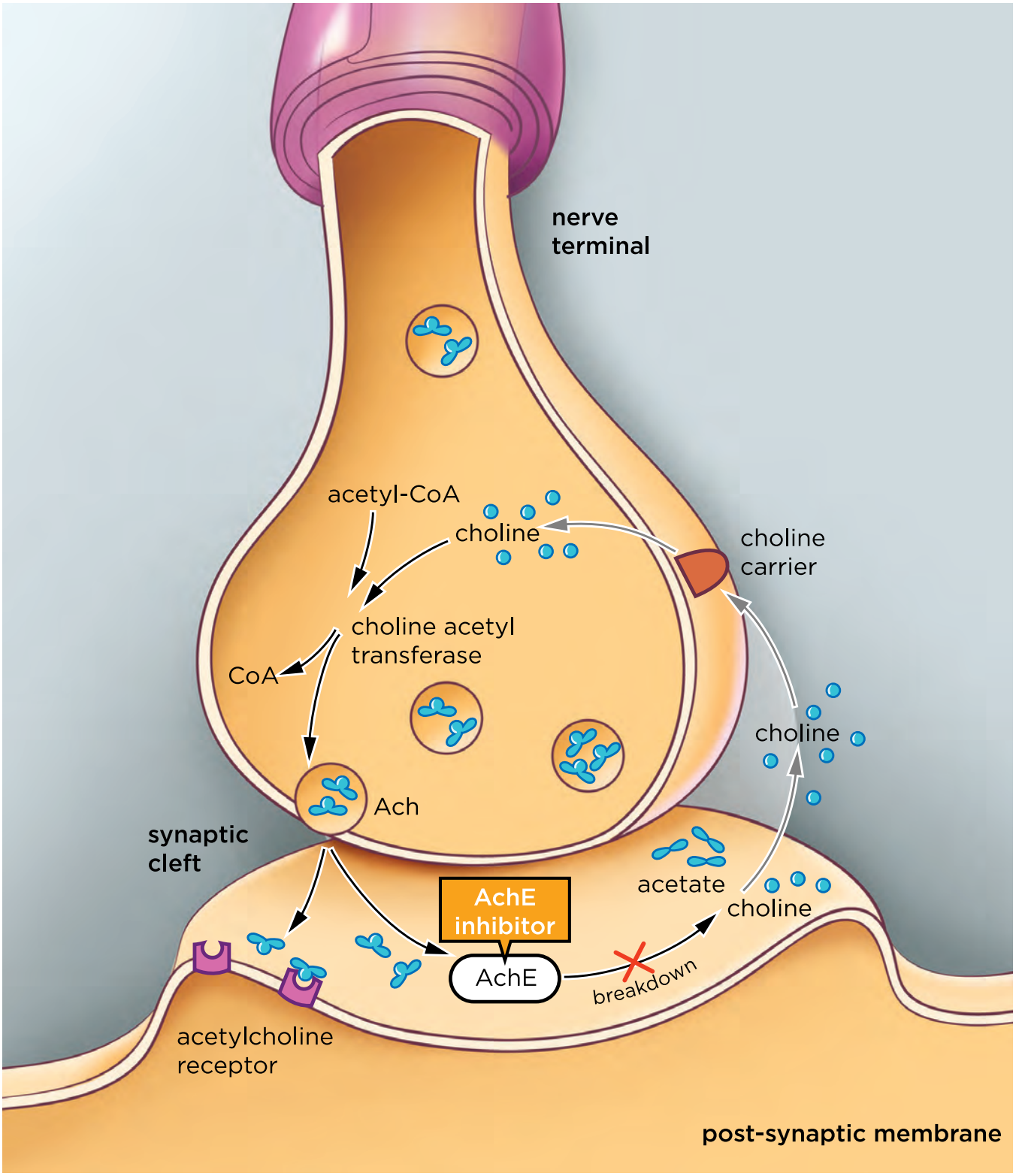

Figure 1. Mechanism of action of acetylcholinesterase inhibitors (AchEIs).
CoA = coenzyme A.

Table 1. Dosing Guidelines for Cognitive Enhancers and Pharmacokinetic and Pharmacodynamic Parameters

Drug	Selectivity	Half-Life	Predominant Route of Elimination	Starting Dosage	Minimal Effective Dosage	Usual Dosage
Donepezil (Aricept)	AchEI	70–80 h	Hepatic	5 mg qam	5 mg qam	10 mg qam
Rivastigmine* (Exelon)	AchEI and BuChEI	2 h	Renal	1.5 mg bid	3 mg bid	4.5 mg bid
Galantamine (Reminyl)	AchEI and nicotinic modulator	10 h	Hepatic, some renal	8 mg od	16 mg od	16–24 mg od
Memantine (Ebixa)	NMDA receptor antagonist	60–100 h	Renal	5 mg qam	10 mg bid	10 mg bid

AchEI = acetylcholinesterase inhibitor; BuChEI = butyrylcholinesterase inhibitor; NMDA = *N*-methyl-D-disparate.
*Exelon Patch 5 is equivalent to rivastigmine 3 mg bid oral dosage; Exelon Patch 10 is equivalent to rivastigmine 6 mg bid oral dosage.
Adapted, with permission, from a table created by William B. Dalziel, MD, The Ottawa Hospital.

Questionnaire.[12] In discussing treatment with an AchEI, it is critical to set realistic patient and caregiver expectations. It should be made clear to patients and their caregivers that AchEIs treat symptoms but are not curative. The anticipated benefit of these drugs for most patients is to stabilize cognitive functioning for a period of time; a minority of patients may demonstrate a temporary improvement over baseline.[13] For example, from a practical perspective, clinicians and caregivers may notice improvements in apathy, attention, and the ability of patients to engage in functional activities.[14] It is also useful to consider other benefits of these drugs, including the potential for delayed time to nursing home placement, higher retention in assisted-living facilities (versus progression into full nursing care), and a higher likelihood of slower progression.[15–18]

The next step before initiating these drugs entails assessing relevant safety considerations. In our training program for family physicians,[19] we recommend obtaining a baseline electrocardiogram (ECG). Because of the known effect of these drugs on cardioinhibition and bradyarrythmia, which can increase the risk of syncope,[20] we suggest that the opinion of a specialist (internist, cardiologist, or geriatrician) be sought prior to initiating an AchEI in the following conditions: left bundle branch block, second- or third-degree heart block, sick sinus syndrome, or bradycardia with heart rate <50 beats per minute. In first-degree atrioventricular (AV) block with P–R intervals of 0.26 or less, AchEIs can be initiated with consideration of repeating an ECG a few weeks later to ensure no further widening of the P–R interval. Other contraindications to AchEIs include uncontrolled asthma, severe chronic obstructive pulmonary disease, and angle-closure glaucoma. Patients should be warned of common, dosage-related, often-transient side effects of AchEIs, which include gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea), sleep disturbances, vivid dreams or nightmares, dizziness, urinary frequency, muscle cramps, and fatigue. If renal or hepatic dysfunction exists, the choice of AchEI can be guided by the predominant route of elimination (Table 1).

Dosage escalations are generally made every 4 weeks with an aim to achieve a minimally effective target dosage (Figure 2). It is recommended that the patient be reassessed prior to each dosage escalation to monitor for side effects, particularly syncopal symptoms,[20] and to ensure that blood pressure and heart rate are maintained. In persons with renal impairment, it is unclear based on published literature whether target dosages needs to be modified when using AchEIs that are less dependent on renal clearance (e.g., donepezil and galantamine); however, in Table 2 we offer a conservative approach for the family physician (also see below, under "NMDA Receptor Antagonist"). As noted, it may be prudent to warn patients with significant renal impairment about symptoms suggestive of cholinergic excess (nausea, diarrhea, rhinorrhea) when escalating the dosage of an AchEI. If these symptoms develop, they often occur within days of the dosage increase, and patients should reduce the dosage of the AchEI to the previously tolerated dosage. A repeat ECG may also be considered to ensure that there is no widening of the P–R interval or development of other types of heart block.

The patient's cognitive functioning should be reassessed after 3 months[21] of achieving a minimally effective dosage of an AchEI and, if stable, repeated yearly thereafter. Reassessment may be required sooner if the patient or family members notice a worsening of symptoms. As dementia is a progressive disease, stabilization of cognition, behaviour, or function is considered a positive treatment response. Switching to a different AchEI may be considered if patients develop intolerable side effects or if there is progressive cognitive decline. If a switch is made due to side effects, a washout period of 1 week is recommended prior to initiating a different AchEI according to the dosage titration schedule outlined in Figure 2. While there is limited evidence to support switching AchEIs due to non-response, it has been suggested that up to 50% of initial non-responders to one AchEI may respond to a different AchEI.[10] Switching in this case can be easily accomplished by replacing the AchEI with its dosage equivalent alternative: refer to Figure 2 to find the vertically aligned dosage equivalent, with no washout period suggested.

NMDA Receptor Antagonist

Unlike AchEIs, memantine works by blocking glutamatergic NMDA receptors. Memantine can be used to treat moderate to severe Alzheimer's disease either as monotherapy or in combination with an AchEI.[8] Studies have demonstrated modest benefits on cognition and behaviour.[22,23] Overall, this drug is well tolerated. In clinical trials, the most commonly reported side effects included agitation, falls, dizziness, and diarrhea, but these occurred at the same (or lower) rates as those in placebo-treated patients. Dosage adjustment is required in patients with renal impairment. In those patients with a creatinine

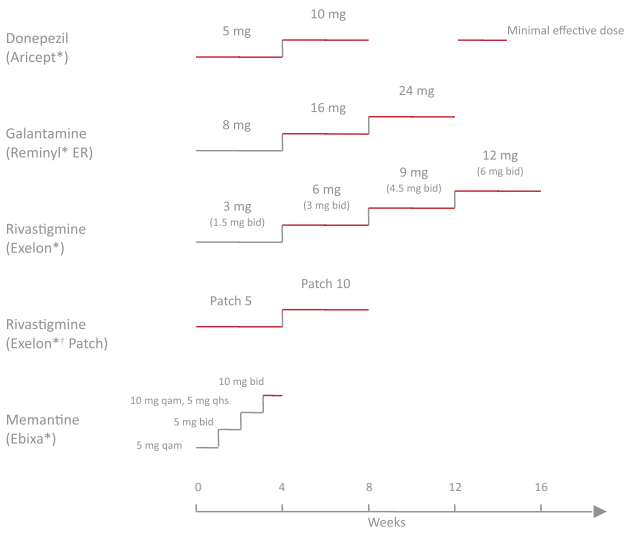

Figure 2. Dosage titration of cognitive enhancers.
*Dosage titration is generally every 4 weeks, although slower titration may be used if side effects occur. Dosage titration assumes normal renal function.
†Exelon Patch 5 is equivalent to rivastigmine 3 mg bid oral dosage. Exelon Patch 10 is equivalent to rivastigmine 6 mg bid oral dosage.
Adapted, with permission, from a figure created by William B. Dalziel, MD, The Ottawa Hospital.

Table 2. Suggested Dosing Adjustments for Renal Impairment

CrCl (mL/min)*	AchEI Dosage Adjustments
>61	Any AchEI can be used and titrated to the minimum effective dosage
40–60	Any AchEI can be used but exercise caution† when exceeding 16 mg/d of galantamine or 6 mg/d of rivastigmine
<39	Consider using donepezil as it is has mainly hepatic clearance, but exercise caution† in exceeding 5 mg/d; galantamine is not recommended for use in patients with CrCl <9 mL/min

CrCl (mL/min)*	NMDA Receptor Antagonist (Memantine) Dosage Adjustment
>50	None required
30–49	If patient tolerates 10 mg/d after 7 days, begin further titration to target 20 mg/d
15–29	Suggested dosage is 10 mg/d

AchEI = acetylcholinesterase inhibitor; CrCl = creatinine clearance; NMDA = *N*-methyl-D-disparate.
*See text for further details. CrCl as estimated by the Cockcroft-Gault method:

$$\frac{\text{CrCl} = (140 - \text{Age}) \times \text{Weight (kg)} \times K,}{\text{Scr (μmol/L)}}$$

where *K* represents a constant of 1.23 for men and of 1.04 for women, and Scr indicates serum creatinine.
†Watch for symptoms of cholinergic excess (nausea, diarrhea, runny nose); usually will occur within days of dosing increase. Consider an electrocardiogram to ensure no widening of P–R interval.

clearance (CrCl) of 30–49 mL/min, it is recommended that the dosage initially be 10 mg/d and, if tolerated, increased to 20 mg/d.[24] For those with severe renal impairment (CrCl <30 mL/min), the suggested dosage is 10 mg/d. It is worth noting that these dosing guidelines as well as those for AChEIs (see Table 2) are based on estimated CrCl rates using the Cockcroft-Gault method, not estimated glomerular filtration rates (eGFRs), which are commonly reported by laboratories. For older persons, eGFRs provided by laboratories (based on the Modification of Diet in Renal Disease [MDRD] method) tends to overestimate the actual CrCl.[25] We therefore recommend that if a patient's eGFR is within 5–10 mL/min of the cut-off for dosage adjustment, CrCl be calculated using the Cockcroft-Gault method[26] (see Table 2 footnote) in order to obtain a more accurate CrCl estimation to guide dosing.

Key Points

The decision to treat with a cognitive enhancer should be based on an individualized assessment.
Realistic patient and caregiver expectations should be established.
An adequate baseline cognitive and functional assessment must be performed prior to initiating treatment.
A baseline electrocardiogram should be obtained and a specialist's referral considered in the presence of certain conduction abnormalities.
A conservative approach to dosage escalations is suggested for patients with renal impairment.

Discontinuation of Treatment

The decision to discontinue treatment must be individualized based on the balance of benefits and harm. It is reasonable to discontinue a cognitive enhancer in the following circumstances: when the patient's dementia progresses to a stage where there is no meaningful benefit from continued therapy; when the patient's overall condition is deemed palliative; when there is no beneficial response, or intolerable side effects occur; or when the patient is non-adherent and the patient or proxy decision maker decides to stop the treatement.[8,21] Sometimes when a cognitive enhancer is discontinued, a noticeable deterioration occurs,[27] reflecting positive benefits of treatment that had not been recognized. Patients should therefore be closely monitored after stopping cognitive enhancers and considered for prompt reinstatement of treatment should a significant decline in cognition, functional abilities, or behaviour occur. For some patients, interrupting therapy for prolonged periods of time (6 weeks in one study[28]) may result in the loss of treatment benefits that cannot be regained.

Conclusions

While a few considerations are required in ensuring the safe use of cognitive enhancers, these medications can be properly initiated and managed by primary care physicians. For appropriate patients, the use

of cognitive enhancers can contribute to holistic, compassionate dementia care that allows patients to maintain their quality of life and independent living for as long as possible.

Acknowledgements

Dr. Lee has received educational grants or honoraria from Pfizer, Janssen-Ortho, Novartis, Astra-Zeneca, and Solvay. Dr. Rojas-Fernandez has received consulting honoraria from Otsuka Pharmaceutical Inc (US), received grants from Pfizer, Purdue, and Astra Zeneca, and served on an expert panel for Ortho-McNeil (US). Dr. Heckman has received grant-in-aid funding from CIHR and HSFO, received salary support from HSFC, and served on advisory boards for Pfizer, Janssen-Ortho, and Novartis. Dr. Gagnon has received honoraria and served on advisory panels for Pfizer, Novartis, Lundbeck, and Janssen-Ortho, and has received research grants from Pfizer.

This article has been peer reviewed.

References

1. Hogan DB. Human resources training and geriatrics. Geriatr Today J Can Geriatr Soc 2001;4:7–10.
2. Hinton L, Franz CE, Reddy G, et al. Practice constraints, behavioral problems and dementia care: primary care physicians' perspectives. J Gen Intern Med 2007;22:1487–92.
3. Pimlott NJ, Persaud M, Drummond N, et al. Family physicians and dementia in Canada. Part 2. Understanding the challenges of dementia care. Can Fam Physician 2009;55:508–9.e1–7; www.cfp.ca/content/55/5/508.full.pdf+html. Accessed October 1, 2011.
4. Cassell EJ. The Nature of Suffering and the Goals of Medicine, 2nd edition. New York (NY): Oxford University Press; 2004.
5. Cassell EJ. The Nature of Suffering and the Goals of Medicine. N Engl J Med 1982;306:639–45.
6. Aminzadeh F, Byszewski A, Molner FJ, et al. Emotional impact of dementia diagnosis: exploring persons with dementia and caregiver perspectives. Aging Mental Health 2007;11:281–90.
7. Birks J. Cholinesterase inhibitors for Alzheimer's disease (edited 2009). Cochrane Database Syst Rev 2006:CD005593.
8. Hogan DB, Bailey P, Carswell A, et al. Management of mild to moderate Alzheimer's disease and dementia. Alzheimers Dementia 2007;3:355–84.
9. Qaseem A, Snow V, Cross T, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008;148:370–8.
10. O'Brien JT, Burns A. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol 2010; http://jop.sagepub.com/content/early/2010/11/17/0269881110387547.
11. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
12. Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Measurement of functional activities in older adults in the community. J Gerontol 1982;37:323–9.
13. Burns A, Yeates A, Akintade L, et al. Defining treatment response to donepezil in Alzheimer's disease. Responder analysis of patient level data from randomised, placebo controlled studies. Drugs Ageing 2008;25:707–14.
14. Rockwood K, Black S, Bedard MA, et al. Specific symptomatic changes following donepezil treatment of Alzheimer's disease: a multi centre, primary care, open label study. Int J Geriatr Psychiatry 2007;22:312–9.
15. Geldmacher DS, Provenzano G, McRae T, et al. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003;51:937–44.
16. Rosenblatt A, Samus QM, Onyike CU, et al. Acetylcholinesterase inhibitors in assisted living: patterns of use and association with retention. Int J Geriatr Psychiatry 2008;23:178–84.
17. Lyketsos CG, Samus QM, Baker A, et al. Effect of dementia and treatment of dementia on time to discharge from assisted living facilities: the Maryland assisted living study. J Am Geriatr Soc 2007;55:1031–7.
18. Lopez OL, Becker JT, Saxton J, et al. Alteration of a clinically meaningful outcome in the natural history of Alzheimer's disease by cholinesterase inhibition. J Am Geriatr Soc 2005;53:83–7.
19. Lee L, Kasperski MJ, Weston WW. Building capacity for dementia care: a training program to develop primary care memory clinics. Can Fam Physician 2011;57:e249–52.
20. Kim DH, Brown RT, Ding EL, et al. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc 2011;59:1019–31.
21. Freedman A, Ibrahiem K. Dementia. Hamilton (ON): The Foundation for Medical Practice Education; 2008.
22. McShane R, Sastre AA, Minakaran N. Memantine for dementia (edited 2009). Cochrane Database Syst Rev 2006:CD003154.
23. Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer's disease. Int Psychogeriatr 2010;22:346–72.
24. McKeage K. Memantine. A review of its use in moderate to severe Alzheimer's disease. CNS Drugs 2009;23:881–97.
25. Pequignot R, Belmin J, Chauvelier J, et al. Renal function in older hospital patients is more accurately estimated using the Cockcroft-Gault formula than the modification diet in renal disease formula. J Am Geriatr Soc 2009;57:1638–43.
26. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41.
27. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004;63:214–9.
28. Doody RS, Geldmacher DS, Gordon B, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer's disease. Arch Neurol 2001;58:427–3.Alzheimer's disease. Arch Neurol 2001;58:427–3.