CanJPsychiatry 2014;59(12):624–631

In Review

Persistence and Adherence With Dementia Pharmacotherapy: Relevance of Patient, Provider, and System Factors

Colleen J Maxwell, PhD[1]; Kathryn Stock, BSc (MSc Candidate)[2]; Dallas Seitz, PhD, MD, FRCPC[3]; Nathan Herrmann, MD, FRCPC[4]

[1]Professor, Schools of Pharmacy and Public Health & Health Systems, University of Waterloo, Waterloo, Ontario.
Correspondence: School of Pharmacy, University of Waterloo, 200 University Avenue West, Waterloo, ON N2L 3G1; colleen.maxwell@uwaterloo.ca.

[2]Student, School of Public Health & Health Systems, University of Waterloo, Waterloo, Ontario.

[3]Assistant Professor, Division of Geriatric Psychiatry, Queen's University and Providence Care, Kingston, Ontario.

[4]Head, Division of Geriatric Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Ontario.

Key Words: cholinesterase inhibitors, memantine, Alzheimer disease, persistence, adherence

Received July 2014, revised, and accepted August 2014.

This paper provides a comprehensive review of studies examining adherence and (or) persistence with dementia pharmacotherapy during the past decade, including a summary of the key patient-, drug-, system-, and provider-level factors associated with these measures. Estimates of adherence and 1-year persistence to these drugs have ranged from 34% to 94% and 35% to 60%, respectively. Though many studies reported nonsignificant associations, there are data suggesting that patient age, sex, ethnoracial background, socioeconomic status, and region-specific reimbursement criteria, as well as the extent and quality of interactions among patients, caregivers, and providers, may influence persistence with pharmacotherapy. As many studies relied on administrative data, limited information was available regarding the relevance of patient's cognitive and functional status or the importance of caregiver involvement or assistive devices to adherence or persistence.

Persistance et observance de la pharmacothérapie de la démence : pertinence des facteurs liés au patient, au fournisseur, et au système

Cet article offre une revue détaillée des études examinant l'observance et (ou) la persistance de la pharmacothérapie de la démence au cours des dix dernières années, dont un résumé des principaux facteurs au niveau du patient, du médicament, du système et du fournisseur qui sont associés à ces mesures. Les estimations de l'observance et de la persistance d'un an à ces médicaments allaient de 34 % à 94 % et de 35 % à 60 %, respectivement. Même si de nombreuses études faisaient état d'associations non significatives, des données suggèrent que l'âge, le sexe, les origines ethnoraciales, le statut économique des patients et leurs critères de remboursement régionaux, ainsi que l'étendue et la qualité des interactions entre patients, soignants, et fournisseurs peuvent influencer la persistance de la pharmacothérapie. Comme bon nombre d'études s'appuyaient sur des données administratives, l'information disponible était limitée en ce qui concerne la pertinence de l'état cognitif et fonctionnel du patient, ou l'importance de l'implication du soignant ou des dispositifs d'assistance à l'observance ou à la persistance.

About 36 million people, worldwide, have dementia, with AD the most common cause among older adults.[1] In 2008, the estimated number of people with dementia in Canada was nearly half a million.[2] Ensuring appropriate pharmacotherapy is an important component of care for people with dementia.[3,4] ChEIs (for example, donepezil, rivastigmine, and galantamine) and the *N*-methyl-D-aspartate receptor antagonist memantine are approved for the symptomatic treatment of AD.[3,4] Recommendations made at the fourth CCCDTD (in 2012) included offering all people with AD a trial of a ChEI unless there are contraindications, using these agents for Parkinson disease dementia, and considering memantine for AD at a moderate-to-severe stage.[5]

Investigating adherence and persistence with dementia pharmacotherapy is important in understanding both the therapeutic benefits and the cost-effectiveness of these medications. As symptomatic therapies, treatment benefit will obviously be limited to those periods when these drugs are being taken.[6–9] The cognitive, functional, and (or) behavioural symptoms of dementia may worsen during either prolonged gaps in treatment or after discontinuing

these agents,[10–13] and restarting therapy may not lead to recouping what was lost.[8] In light of the modest clinical benefits observed with the available drugs for dementia,[14–18] poor persistence or adherence may undermine any economic advantage arising from therapy.[19–21] Although controversial,[22] one benefit from staying on therapy may be delayed admission to a long-term care facility.[23–25]

Knowledge of the determinants of adherence and persistence may inform clinicians, family caregivers, and drug plan managers of potential strategies to maintain therapy when appropriate. Note, though, at some point during the course of their illness, it may be in the patient's best interest to discontinue therapy owing to progression of their dementia to an advanced stage, intolerable adverse effects, or an unfavourable benefit-to-risk ratio.[3,5]

Highlights

- Older female patients with greater cognitive impairment may be less likely to persist with dementia pharmacotherapy and could benefit from targeted interventions.
- The quality of communication and frequency of interaction between physicians and patients and their caregivers are modifiable determinants of both persistence and adherence.
- As seen with other chronic diseases, continuity of dementia pharmacotherapy may be adversely affected by care transitions, particularly admission to hospital.
- Research is needed on the impact of patient, caregiver, and physician understanding and beliefs (including cultural influences) on adherence and persistence.

Overview of Studies Examining Persistence and Adherence

Medication-taking behaviour includes initial acceptance, execution of the proposed regimen, and persistence over time.[26] Failure at any of these levels can lead to nonadherence. There are unique challenges when treating older patients suffering from significant cognitive impairment[27–29] as they exhibit many of the characteristics associated with worse adherence (for example, impaired memory and executive functioning, depressed mood, functional limitations, comorbidities, complex drug regimens, and increased risk for adverse effects).[30–33] They are also vulnerable to contextual factors associated with poor adherence and persistence (for example, living alone, limited finances, and barriers to accessing health care).[27,28,31] Other factors contributing to a heightened risk of nonadherence in this group include limited insight (often coexisting with an inflated sense of self-efficacy),[28] comprehension difficulties, and reliance on the availability of others for assistance in the administration and monitoring of medications.[27,30]

In our paper, we review the literature on the rates and associated determinants of adherence and persistence with dementia pharmacotherapy. To date, research has largely focused on ChEI persistence (that is, how long the patient continues to follow the regimen) rather than overall measures of adherence (for example, average percentage of medication consumed during select time periods). We identified 27 English-language observational studies on persistence[34–60] and 7 reporting measures of adherence with dementia pharmacotherapy.[35,40,52,61–64] Several studies further considered the likelihood and related predictors of switching between medications and formulations.[35,36,39,47,64,65]

Abbreviations

AD	Alzheimer disease
CCCDTD	Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
ChEI	cholinesterase inhibitor
MMSE	Mini-Mental State Examination

Estimates of adherence range from 34%[35] to 94%.[61] The relatively high adherence in the report of Blais et al[61] likely reflects the degree of support provided to their participants (for example, use of weekly pill boxes with home delivery and caregiver assistance with medications).[61] Comparisons across studies are challenging, given potentially incongruent methodology and differences in the measures and time periods employed.[35,40,52,61–64] Adherence estimates may vary, both between and within patients with AD, illustrating the importance of capturing the dynamic nature of adherence behaviour.[66]

Among patients with AD, the 1-year discontinuation rate for ChEIs ranges between 40% and 65%,[34–60] with up to 90% stopping after 2 to 3 years.[44,51,53] These estimates have remained fairly consistent, even among more recent studies,[35,38] except for 2 European reports that found significantly lower 1-year discontinuation rates (10% to 20%).[34,36] These 2 studies are unique in numerous ways, limiting their generalizability. The study by Taipale et al[34] was based on a nationwide sample of patients with AD from Finland, a country with relatively less restrictive prescribing and reimbursement guidelines for ChEIs and memantine. The multi-centre study by Gardette et al[36] enrolled community-dwelling people diagnosed and followed closely in specialty AD clinics. Previous research has consistently shown relatively high rates of ChEI and memantine use in these select settings,[67,68] compared with community-based patient populations.[69]

Factors Associated With Persistence and Adherence

Online eTable 1 summarizes the associations observed between patient, drug, provider, and health system factors and either persistence or adherence with dementia pharmacotherapy. As many of these studies were based on administrative databases, they provide an informative portrayal of real-world patient populations.[70] However, most provide only limited data on the diverse range of factors potentially relevant to persistence or adherence with dementia pharmacotherapy.

Patient-Level Factors

While many studies reported no statistically significant association between ChEI persistence and age or sex, several reports suggest that older patients (for example, aged 75 and older)[34,38,39,45,46,50,53] and female patients[34,43,44] may be more likely to discontinue ChEI therapy. An association with advanced age may reflect the impact of more advanced disease severity,[31] a perceived lack of therapeutic benefit, or concerns about a heightened risk for adverse effects. The few reports of greater ChEI persistence[44] or adherence[62] with increased age could be explained by modifying factors such as greater caregiver involvement in medication management, which has been linked with both higher ChEI use[69] and better adherence.[29,71] Unfortunately, information on the degree of caregiver involvement is generally not available in these studies. A recent Spanish study found that patients who switched from one agent to another were younger, while older patients were more likely to discontinue ChEI use altogether.[39] Previous research has shown that relative contraindications to dementia pharmacotherapy are common among real-world patients with AD who are prescribed ChEIs.[69,70,72] Many of these contraindications are more likely to be present among older, compared with younger, populations. Female patients may be more likely to discontinue or to be nonadherent because they are less likely to have a caregiver to assist with medication administration or to advocate for them.[29,69,71] There is little evidence of an association between sex and treatment outcomes with ChEIs, though women may experience more adverse effects possibly attributable to lower body weight.[73] Lower persistence among females has been noted with other therapeutic classes.[74,75]

More severe cognitive impairment was a statistically significant predictor of ChEI discontinuation in 2[44,49] of 7 studies. Among the 5 studies that failed to show a significant association, 2 found a higher risk of ChEI discontinuation in patients with AD whose MMSE scores declined by either 3 or more points[36] or 4 or more points[47] within 6 months. Stopping treatment may have occurred because of the apparent lack of effectiveness. Interestingly, the lower risk for ChEI discontinuation observed for older patients with AD in the study by Amuah et al[44] was only apparent in analyses restricted to those who remained eligible for coverage (that is, did not show evidence of decline in both their cognitive and functional abilities).

The few American studies that examined the issue have generally found worse adherence[63] and persistence[51,59] with dementia pharmacotherapy among non-Caucasian patients. Cross-sectional research has shown positive associations between ChEI use and Caucasian race as well as education level and geographic region.[71,76] These findings may reflect differential access to health services among minority groups in settings where there is no universal coverage.[77] With the exception of a small Saskatchewan study, which found no significant association between patients' ethnic background and ChEI persistence (but a significant one between less formal education and lower persistence during 6 months),[37] there have been no relevant Canadian studies exploring the role of patient race or ethnicity.

The possibility of socioeconomic barriers to dementia pharmacotherapy have been reported in Canadian[37,44] and US studies.[62,64] In the study by Amuah et al,[44] patients with AD paying for a greater proportion of their total prescription costs were significantly more likely to discontinue ChEI therapy. Studies of other drug classes have shown strong associations between worse adherence and (or) persistence and financial barriers in older, vulnerable patient groups.[78–80] During the course of the disease, patients with AD may face increasing out-of-pocket costs with continued therapy, which may adversely affect adherence and persistence with treatment.[69] As memantine is not covered by most publically funded drug benefit plans in Canada, its use would add to the costs incurred by patients and (or) their caregivers (assuming coverage is not provided by a private drug benefit plan). These findings raise concerns about equitable access and the potential for discontinuing medications owing to financial barriers rather than clinical indications.

Though again most studies showed no significant association, 2 Canadian studies reported a positive association between greater comorbidity and increased persistence with ChEI therapy.[44,50] This seemingly paradoxical finding may reflect an opportunity for more interactions with prescribers, with enhanced continuity of care leading to improved treatment persistence. Two other studies from the Netherlands[43] and the United States[62] reported lower persistence and adherence to ChEI therapy among patients with greater comorbidity. While a higher pill burden (that is, number of pills, tablets, or capsules taken on a regular basis) appeared to be unrelated to ChEI persistence, there may be a positive association between the number of medications and greater adherence to dementia pharmacotherapy.[62,64] Again this may be explained by users of multiple medications having more frequent contact with the health care system.

Concurrent use of particular medications may be a more important determinant of adherence and persistence, although a consistent pattern has not emerged. Generally, the concurrent use of drugs with moderate-to-severe anticholinergic effects is associated with worse persistence with dementia pharmacotherapy.[47,55,59] Conversely, persistence appears to be higher with concurrent use of various antidepressants, a number of which can have anticholinergic effects.[43,45] Previous cross-sectional research suggests a higher likelihood for ChEI use among patients concurrently exposed to antidepressants and antipsychotics.[69,72] Possibly, all 3 classes are being prescribed to treat patients with AD with more severe mood or behavioural difficulties.[38,67]

The relatively inconsistent associations noted between comorbidity and drug use with persistence and (or) adherence to dementia pharmacotherapy raises questions. One may expect that patients with greater comorbidity and using multiple medications would be more vulnerable to the potential health risks posed by ChEIs and (or) memantine.[81–84] The mixed findings in the studies examined

may be explained by an inability to account for potentially important confounding or effect modifying variables, such as the functional status of the patient and the involvement of informal (and formal) caregivers.[67,69,71]

Drug-Related Factors

Though many studies summarized in eTable 1 failed to show significant differences, numerous showed greater persistence with once-daily donepezil and extended-release galantamine, compared with twice-daily rivastigmine capsules. Higher persistence was seen with galantamine, compared with donepezil, in 5 of 11 studies, with the others showing either no difference (n = 4) or higher persistence with donepezil (n = 2). Relatively few studies have examined predictors of switching (or discontinuation following a switch) between drug types or formulations.[36,39,47,64] One study suggested that switching to the rivastigmine patch (especially if done earlier in the course of treatment) predicted greater 1-year adherence, compared with oral donepezil.[64] The rivastigmine patch has been associated with increased patient[85] and caregiver[86] satisfaction, possibly owing to improved gastrointestinal tolerability[87] and greater ease of use.[65,88] Direct comparison studies do not suggest there are significant differences between ChEIs.[89] Selection of which agent to be used will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.[5]

There was an increased risk for early discontinuation[36,43] (and switching)[36,47] with subtherapeutic dosages of the ChEIs, as well as evidence of increased persistence in patients with AD using memantine (with[38] or without[35] a ChEI). The latter finding may be explained by greater caregiver involvement in drug administration coupled with a decision to aggressively pursue therapy.[35]

Health System and Provider Factors

Greater persistence with ChEI therapy (and adherence with other medications)[32,78] is associated with more frequent physician visits.[44,55] Increased contact may be associated with improved continuity of care[90] and better communication between physicians, patients, and caregivers.[55] Higher levels of ChEI persistence have also been observed among patients in long-term care facilities, compared with those in the community.[46,54,59] This presumably reflects a more consistent approach to prescribing, dispensing, and monitoring medications in these settings.[91]

As a proxy for greater health care system exposure, having one or more hospitalizations may be expected to show a positive association with persistence.[50] However, most studies on this topic show a higher likelihood of discontinuing therapy.[36,47,92] Cross-sectional research has also shown lower use of ChEI and (or) memantine among older adults with dementia with one or more recent hospitalizations.[69,77,93] Poor communication across settings may result in unintended medication changes. Additionally, hospitalization provides an opportunity to re-evaluate the relative risks and benefits of continued pharmacotherapy during a period of health instability.[47] The increased likelihood of ChEI discontinuation among AD patients following admission to hospice care in the study by Mansour et al[42] probably reflects a more appropriate focus on quality of life and reduced treatment burden in this patient population.

A European study by Gardette et al[36] found that, compared with multidisciplinary centres and geriatric clinics, treatment at psychiatric centres was associated with a greater risk of discontinuation, while treatment at neurologic centres was associated with a lower risk. A cross-sectional study of residents in assisted living settings in France found that use of dementia pharmacotherapy was higher if the diagnosis was made by a neurologist, followed by geriatricians and psychiatrists, with a general practitioner diagnosis associated with the lowest likelihood.[93] However, another French study found no association between ChEI persistence and the specialty of the initial prescriber.[45]

Variation in ChEI adherence related to differential access to care (including the availability of physicians, specialists, pharmacists, and other support services) across geographic regions has been suggested by US research[62] but remains relatively unexplored in the Canadian context. The one Canadian study that examined potential urban and rural differences[44] reported a higher discontinuation rate among patients with AD residing in an urban setting, but this association did not remain significant in adjusted analyses.

Reimbursement and Regulatory Factors

Region- and country-specific reimbursement policies for the ChEIs and memantine appear to have a significant impact on overall use and persistence.[34,94] For example, the high rate of ChEI use (84%) and low 1-year discontinuation rate (20%) observed in a Finnish study[34] was likely due, in part, to the relatively liberal recommendations for use and reimbursement policies for ChEIs and memantine found in that country.

Eligibility for reimbursement of ChEIs through publicly funded drug benefit programs in Canada is primarily dependent on meeting province-specific criteria. Variations in the number and nature of these criteria across the country may influence treatment persistence. This is perhaps best illustrated by a comparison of findings of population-based studies using data from Ontario[54] and Saskatchewan.[44] Herrmann et al[54] reported that, among patients newly prescribed a ChEI in Ontario, the median number of days until discontinuation was 651, with 44% continuing with therapy during 58 months. For patients residing exclusively in the community, 69% discontinued therapy during this time frame. Amuah et al[44] found that among ChEI users in Saskatchewan, the median number of days until discontinuation was 279, with 76% of patients stopping by 40 months. Although this difference could be due to several factors (including more frequent physician visits evident among patients in Ontario),[54] the more restrictive reimbursement criteria in Saskatchewan, compared with Ontario during the study periods, likely

played a role.[44] A key difference included a requirement for patients in Saskatchewan to discontinue drugs with marked anticholinergic activity (as per a list provided to prescribers). Patients in Saskatchewan were also required to exhibit an initial improvement on the MMSE and Functional Activities Questionnaire, and, afterwards, to not have shown a decline greater than pre-specified levels on both measures.

Clinical and Research Implications

Appropriateness of Discontinuation

The available data cannot resolve the question of whether lower or higher persistence reflects more appropriate use of the available drugs for dementia. There is considerable uncertainty about when dementia pharmacotherapy should be discontinued because of a perceived lack of clinically meaningful benefit, and limited data on how long therapy with these agents should persist.[95–98] There are concerns that treatment may continue even when potentially inappropriate (for example, among patients on ChEIs hospitalized for bradycardia),[99] but also the possibility for underuse among eligible patients.[44] Decisions about continuing therapy need to be patient-centred, and based on clinical judgment rather than arbitrarily made.[3–5]

In the most recent CCCDTD,[5] it was noted that discontinuing ChEIs in patients with moderate-to-severe AD may lead to a worsening of cognitive function and greater functional impairment, compared with continued therapy, and that such risks should be balanced with that of the known side effects and the costs of continued therapy. It was recommended that dementia pharmacotherapy be discontinued when

1) the patient or their caregiver decide to stop (after being appraised of the relevant risks and benefits);
2) the patient refuses to take the medication;
3) the patient is sufficiently nonadherent and it is not possible to establish mechanisms to resolve the problem;
4) the patient's rate of cognitive, functional, and (or) behavioural decline is greater on treatment, compared with prior to treatment;
5) the patient experiences intolerable side effects that are definitely or probably related to the ChEI;
6) comorbidities make continued use either unacceptably risky or futile (for example, terminal illness); or
7) the patient's dementia progresses to a stage where there would be no clinically meaningful benefit from continued therapy.

When a decision has been made to discontinue therapy (because of a perceived lack of effectiveness), the dose should be tapered before stopping and the patient monitored for the next 1 to 3 months for evidence of significant decline. If this occurs, consideration should be given to reinstating therapy.[5]

Strategies to Improve Adherence and Persistence

Unfortunately, the lack of research in this area undermines our ability to make strong evidence-based recommendations.[28] A clear first step is the early identification of potential problems with adherence among patients with AD because of cognitive or physical limitations. A key question is when to change from self-management to having another person assume responsibility for medication administration.[28]

Effective strategies to enhance adherence and persistence will likely incorporate multiple components, including education.[27,28,30] A recent Japanese study suggested improvements may arise from a pharmacist-led consultation service directed at providing information to patients and families about the disease coupled with what are realistic expectations with pharmacotherapy.[92] While maximizing tolerability and ease of use (including consideration of the patient's daily preferences) will likely be helpful, our review indicates that the quality of communication and frequency of interaction between physician and patient and (or) their caregiver are important modifiable determinants of both persistence and adherence.

Future Research Priorities

There is a clear need for large-scale prospective studies exploring the impact of the patient's cognitive and functional status (as well as declines in these measures over time) on treatment nonadherence and discontinuation, as well as the potential moderating effects of caregiver involvement in medication management. Studies of the potential beneficial effects, as well as barriers to use, of various medication reminder and management systems (for example, calendars, computer and telehealth interventions, assistive devices, and pharmacist-led services) on treatment adherence and persistence among vulnerable patients with AD (for example, with greater cognitive impairment and [or] few social resources) are also warranted.[28]

Further examination of selected sociodemographic characteristics may significantly advance our understanding of adherence behaviour in patients with AD. Differences in cultural beliefs regarding aging, dementia, and the benefits and risks of treatment, as well as ethnoracial differences in health status,[63] may represent particularly important drivers of AD medication use, adherence, and persistence.[28,30,100,101] Within Canada, a particular priority is the need for a more thorough understanding of the growing burden of dementia among First Nations populations and the impact of commonly held cultural beliefs, expectations, and illness comprehension on appropriate diagnosis and treatment.[102,103]

It is also unclear to what extent older adults with AD who discontinue therapy restart therapy at a later date and, if so, why. Patients who discontinued statin therapy have been found to be more likely to restart treatment after a period of nonadherence following a visit with the original prescribing physician.[90] Similarly, preliminary findings from 2 ChEI studies suggest that between one-third[46] and one-half[34] of patients with AD who discontinue within 6 to 12 months

of initiating therapy may restart (primarily with the same agent) within the following year.

Finally, the long-term benefits of greater persistence and adherence with dementia pharmacotherapy, including the impact on cost-effectiveness and quality of life, require greater clarification.

Conclusions

Most observational studies indicate that 50% or more of patients discontinue ChEI therapy within 1 year of initiation. This compares with the considerably lower withdrawal rates (ranging from 18% to 33%, during 24 to 52 weeks), reported in the published randomized and open-label trials of donepezil.[8,14,104] Insights from ongoing work in this area may inform policy decisions, assist both patients and providers in the appropriate use of these agents, and shape the agenda for future research.

Acknowledgements

No funding was provided for this research.

Dr Seitz has served on an advisory board for Eli Lilly and Dr Herrmann has received research support and (or) speaker's honoraria from Lundbeck, Janssen-Ortho, and Pfizer.

The Canadian Psychiatric Association proudly supports the In Review series by providing an honorarium to the authors.

References

1. World Health Organization (WHO) and Alzheimer's Disease International. Dementia: a public health priority. Geneva (CH): WHO; 2012.
2. Alzheimer Society of Canada. Rising tide: the impact of dementia on Canadian Society. Toronto (ON): Alzheimer Society of Canada; 2010.
3. Hogan DB, Bailey P, Black S, et al. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008;179:1019–1026.
4. Herrmann N, Gauthier S. Diagnosis and treatment of dementia: 6. Management of severe Alzheimer disease. CMAJ. 2008;179:1279–1287.
5. Herrmann N, Lanctôt KL, Hogan DB. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. Alzheimer Res Ther. 2013;5(Suppl 1):S5.
6. Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2007;22:806–812.
7. Winblad B, Wimo A, Engedal K, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21:353–363.
8. Doody RS, Geldmacher DS, Gordon B, et al, for the Donepezil Study Group. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer's disease. Arch Neurol. 2001;58:427–433.
9. Rogers SL, Doody RS, Pratt RD, et al. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study. Eur Neuropsychopharmacol. 2000;10:195–203.
10. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012;366:893–903.
11. Scarpini E, Bruno G, Zappalà G, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J Alzheimers Dis. 2011;26:211–220.
12. Seltzer B. Cholinesterase inhibitors in the clinical management of Alzheimer's disease: importance of early and persistent treatment. J Int Med Res. 2006;34:339–347.
13. Daiello LA, Ott BR, Lapane KL, et al. Effect of discontinuing cholinesterase inhibitor therapy on behavioral and mood symptoms in nursing home patients with dementia. Am J Geriatr Pharmacother. 2009;7:74–83.
14. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006;1:CD005593.
15. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006;2:CD003154.
16. Rolinski M, Fox C, Maidment I, et al. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev. 2012;3:CD006504.
17. Kaduszkiewicz H, Zimmerman T, Beck-Bornholdt H-P, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. Br Med J. 2005;331:321–327.
18. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148:379–397.
19. Knapp M, Iemmi V, Romeo R. Dementia care costs and outcomes: a systematic review. Int J Geriatr Psychiatry. 2013;28:551–561.
20. Bond M, Rogers G, Peters J, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No 111): a systematic review and economic model. Health Technol Assess. 2012;16:1–470.
21. Cappell J, Herrmann N, Cornish S, et al. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. CNS Drugs. 2010;24:909–927.
22. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. Lancet. 2004;363:2105–2115.
23. 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;23:178–184.
24. Lopez OL, Becker JT, Saxton J, et al. Alteration of a clinically meaningful outcome in the natural history of Alzheimer's disease by cholinesterase inhibitors. J Am Geriatr Soc. 2005;53:83–87.
25. 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;51:937–944.
26. Acri T, Gross R. Studies of medication adherence. In: Strom BL, Kimmel SE, Hennessy S, editors. Textbook of pharmacoepidemiology. 2nd ed. Hoboken (NJ): John Wiley & Sons, Ltd; 2013.
27. Campbell NL, Boustani MA, Skopelja EN, et al. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. Am J Geriatr Pharmacother. 2012;10:165–177.
28. Arlt S, Lindner R, Rösler A, et al. Adherence to medication in patients with dementia: predictors and strategies for improvement. Drugs Aging. 2008;25:1033–1047.
29. Small G, Dubois B. A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. Curr Med Res Opin. 2007;23:2705–2713.
30. Brady R, Weinman J. Adherence to cholinesterase inhibitors in Alzheimer's disease: a review. Dement Geriatr Cogn Disord. 2013;35:351–363.
31. Thiruchselvam T, Naglie G, Moineddin R, et al. Risk factors for medication nonadherence in older adults with cognitive impairment who live alone. Int J Geriatr Psychiatry. 2012;27:1275–1282.
32. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. Am J Geriatr Pharmacother. 2011;9:11–23.
33. Vik SA, Hogan DB, Patten SB, et al. Medication nonadherence and subsequent risk of hospitalization and mortality in older adults. Drugs Aging. 2006;23:345–356.

34. Taipale H, Tanskanen A, Koponen M, et al. Antidementia drug use among community-dwelling individuals with Alzheimer's disease in Finland: a nationwide register-based study. Int Clin Psychopharmacol. 2014;29:216–223.
35. Haider B, Schmidt R, Schweiger C, et al. Medication adherence in patients with dementia: an Austrian cohort study. Alzheimer Dis Assoc Disord. 2014;28:128–133.
36. Gardette V, Lapeyre-Mestre M, Piau A, et al. A 2-year prospective cohort study of antidementia drug non-persistency in mild-to-moderate Alzheimer's disease in Europe: predictors of discontinuation and switch in the ICTUS study. CNS Drugs. 2014;28:157–170.
37. Saleh S, Kirk A, Morgan DG, et al. Less education predicts anticholinesterase discontinuation in dementia patients. Can J Neurol Sci. 2013;40:684–690.
38. Brewer L, Bennett K, McGreevy C, et al. A population-based study of dosing and persistence with anti-dementia medications. Eur J Clin Pharmacol. 2013;69:1467–1475.
39. Olazaran J, Navarro E, Rojo JM. Persistence of cholinesterase inhibitor treatment in dementia: insights from a naturalistic study. Dement Geriatr Cogn Dis Extra. 2013;3:48–59.
40. Le Couteur DG, Robinson M, Leverton A, et al. Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease. Australas J Ageing. 2012;31:164–169.
41. van den Bussche H, Kaduszkiewicz H, Koller D, et al. Antidementia drug prescription sources and patterns after the diagnosis of dementia in Germany: results of a claims data-based 1-year follow-up. Int Clin Psychopharmacol. 2011;26:225–231.
42. Mansour D, Wong R, Kuskowski M, et al. Discontinuation of acetylcholinesterase inhibitor treatment in the nursing home. Am J Geriatr Pharmacother. 2011;9:345–350.
43. Kröger E, van Marum R, Souverein P, et al. Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: a retrospective cohort study. Drugs Aging. 2010;27:663–675.
44. Amuah JE, Hogan DB, Eliasziw M, et al. Persistence with cholinesterase inhibitor therapy in a population-based cohort of patients with Alzheimer's disease. Pharmacoepidemiol Drug Saf. 2010;19:670–679.
45. Pariente A, Pinet M, Moride Y, et al. Factors associated with persistence of cholinesterase inhibitor treatments in the elderly. Pharmacoepidemiol Drug Saf. 2010;19:680–686.
46. Gadzhanova S, Roughead L, Mackson J. Anticholinesterase duration in the Australian veteran population. Aust N Z J Psychiatry. 2010;44:469–474.
47. Gardette V, Andrieu S, Lapeyre-Mestre M, et al. Predictive factors of discontinuation and switch of cholinesterase inhibitors in community-dwelling patients with Alzheimer's disease: a 2-year prospective, multicentre, cohort study. CNS Drugs. 2010;24:431–442.
48. Herrmann N, Binder C, Dalziel W, et al. Persistence with cholinesterase inhibitor therapy for dementia: an observational administrative health database study. Drugs Aging. 2009;26:403–407.
49. Umegaki H, Itoh A, Suzuki Y, et al. Discontinuation of donepezil for the treatment of Alzheimer's disease in geriatric practice. Int Psychogeriatr. 2008;20:800–806.
50. Massoud F, Dorais M, Charbonneau C, et al. Drug utilization review of cholinesterase inhibitors in Quebec. Can J Neurol Sci. 2008;35:508–509.
51. Abughosh SM, Kogut SJ. Comparison of persistence rates of acetylcholine-esterase inhibitors in a state Medicaid program. Patient Prefer Adherence. 2008;2:79–85.
52. Mucha L, Shaohung S, Cuffel B, et al. Comparison of cholinesterase inhibitor utilization patterns and associated health care costs in Alzheimer's disease. J Manag Care Pharm. 2008;14:451–461.
53. Sun Y, Lai M-S, Lu C-J, et al. How long can patients with mild or moderate Alzheimer's dementia maintain both the cognition and the therapy of cholinesterase inhibitors: a national population-based study. Eur J Neurol. 2008;15:278–283.
54. Herrmann N, Gill SS, Bell CM, et al. A population-based study of cholinesterase inhibitor use for dementia. J Am Geriatr Soc. 2007;55:1517–1523.
55. Suh D-C, Thomas SK, Valiyeva E, et al. Drug persistency of two cholinesterase inhibitors: rivastigmine versus donepezil in elderly patients with Alzheimer's disease. Drugs Aging. 2005;22:695–707.
56. Mauskopf JA, Paramore C, Lee WC, et al. Drug persistency patterns for patients treated with rivastigmine or donepezil in usual care settings. J Manag Care Pharm. 2005;11:231–239.
57. Singh G, Thomas SK, Arcona SK, et al. Treatment persistency with rivastigmine and donepezil in a large state Medicaid program. J Am Geriatr Soc. 2005;53:1269–1270.
58. Dybicz SB, Keohane DJ, Erwin WG, et al. Patterns of cholinesterase inhibitor use in the nursing home setting: a retrospective analysis. Am J Geriatr Pharmacother. 2006;4:154–160.
59. Kogut SJ, El-Maouche D, Abughosh SM. Decreased persistence to cholinesterase inhibitor therapy with concomitant use of drugs that can impair cognition. Pharmacotherapy. 2005;25:1729–1735.
60. Roe CM, Anderson MJ, Spivack B. How many patients complete an adequate trial of donepezil? Alzheimer Dis Assoc Disord. 2002;16:49–51.
61. Blais L, Kettani FZ, Perreault S, et al. Adherence to cholinesterase inhibitors in patients with Alzheimer's disease. J Am Geriatr Soc. 2009;57(2):366–368.
62. Borah B, Sacco P, Zarotsky V. Predictors of adherence among Alzheimer's disease patients receiving oral therapy. Curr Med Res Opin. 2010;26:1957–1965.
63. Poon I, Lal LS, Ford ME, et al. Racial/ethnic disparities in medication use among veterans with hypertension and dementia: a national cohort study. Ann Pharmacother. 2009;43:185–193.
64. Tian H, Abouzaid S, Chen W, et al. Patient adherence to transdermal rivastigmine after switching from oral donepezil: a retrospective claims database study. Alzheimer Dis Assoc Disord. 2013;27:182–186.
65. Lopez-Pousa S, Arranz FJ. Characteristics of patients with Alzheimer's disease who switch to rivastigmine transdermal patches in routine clinical practice. Patient Prefer Adherence. 2013;7:47–54.
66. Schwalbe O, Scheerans C, Freiberg I, et al. Compliance assessment of ambulatory Alzheimer patients to aid therapeutic decisions by healthcare professionals. BMC Health Serv Res. 2010;10:232.
67. Zhu CW, Livote EE, Kahle-Wrobleski K, et al. Longitudinal medication usage in Alzheimer disease patients. Alzheimer Dis Assoc Disord. 2010;24:354–359.
68. Schneider LS, Insel PS, Weiner MW, for the Alzheimer's Disease Neuroimaging Initiative. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol. 2011;68:58–66.
69. Maxwell CJ, Vu M, Hogan DB, et al. Patterns of dementia pharmacotherapy in a population-based cohort of home care clients. Drugs Aging. 2013;30:569–585.
70. Gill SS, Bronskill SE, Mamdani M, et al. Representation of patients with dementia in clinical trials of donepezil. Can J Clin Pharmacol. 2004;11:e274–e285.
71. Belle SH, Zhang S, Czaja SJ, et al. Use of cognitive enhancement medication in persons with Alzheimer disease who have a family caregiver: results from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) project. Am J Geriatr Psychiatry. 2004;12:250–257.
72. Seitz DP, Gruneir A, Conn DK, et al. Cholinesterase inhibitor use in US nursing homes: results from the National Nursing Home Survey. J Am Geriatr Soc. 2009;57:2269–2274.
73. Haywood WM, Mukaetova-Ladinska EB. Sex influences on cholinesterase inhibitor treatment in elderly individuals with Alzheimer's disease. Am J Geriatr Pharmacother. 2006;4:273–286.
74. Höer A, Gothe H, Khan ZM, et al. Persistence and adherence with antihypertensive drug therapy in a German sickness fund population. J Hum Hypertens. 2007;21:744–746.
75. Erkens JA, Panneman MM, Klungel OH, et al. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. Pharmacoepidemiol Drug Saf. 2005;14:795–803.
76. Hernandez S, McClendon MJ, Zhou X-H, et al. Pharmacological treatment of Alzheimer's disease: effect of race and demographic variables. J Alzheimers Dis. 2010;19:665–672.

77. Gilligan AM, Malone DC, Warholak TL, et al. Racial and ethnic disparities in Alzheimer's disease pharmacotherapy exposure: an analysis across four state Medicaid populations. Am J Geriatr Pharmacother. 2012;10:303–312.
78. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–497.
79. Goldman PD, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. JAMA. 2007;298:61–69.
80. Piette JD, Heisler M, Wagner TH. Medication characteristics beyond cost alone influence decisions to underuse pharmacotherapy in response to financial pressures. J Clin Epidemiol. 2006;59:739–746.
81. Pariente A, Fourrier-Réglat A, Ducruet T, et al. Antipsychotic use and myocardial infarction in older patients with treated dementia. Arch Intern Med. 2012;172:648–653.
82. Hernandez RK, Farwell W, Cantor MD, et al. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England Healthcare System. J Am Geriatr Soc. 2009;57:1997–2003.
83. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors. A population-based cohort study. Arch Intern Med. 2009;169:867–873.
84. Carnahan RM, Lund BC, Perry PJ, et al. The concurrent use of anticholinergics and cholinesterase inhibitors: rare event or common practice? J Am Geriatr Soc. 2004;52:2082–2087.
85. Adler G, Mueller B, Articus K. The transdermal formulation of rivastigmine improves caregiver burden and treatment adherence of patients with Alzheimer's disease under daily practice conditions. Int J Clin Pract. 2014;68:465–470.
86. Boada M, Arranz FJ. Transdermal is better than oral: observational research of the satisfaction of caregivers of patients with Alzheimer's disease treated with rivastigmine. Dement Geriatr Cogn Disord. 2013;35:23–33.
87. Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease—rivastigmine patch versus capsule. Int J Geriatr Psychiatry. 2007;22:456–467.
88. Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. Int J Geriatr Psychiatry. 2007;22:485–491.
89. Hogan DB, Goldlist B, Naglie G, et al. Comparison studies of cholinesterase inhibitors for Alzheimer's disease. Lancet Neurol. 2004;3:622–626.
90. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long term medication adherence. A study of the dynamics of statin use. Arch Intern Med. 2007;167:847–852.
91. Dhalla IA, Anderson GM, Mamdani MM, et al. Inappropriate prescribing before and after nursing home admission. J Am Geriatr Soc. 2002;50:995–1000.
92. Watanabe N, Yamamura K, Suzuki Y, et al. Pharmacist-based donepezil outpatient consultation service to improve medication persistence. Patient Prefer Adherence. 2012;6:605–611.
93. Barro-Belaygues N, van Kan GA, Rolland Y, et al. Patterns of dementia treatment use in assisted living facilities: a cross-sectional study of 1975 demented residents. J Am Med Dir Assoc. 2011;12:648–654.
94. Cherubini A, Ruggiero C, Dell'Aquila G, et al. Underrecognition and undertreatment of dementia in Italian nursing homes. J Am Med Dir Assoc. 2012;13:759.e7–e13. doi: 10.1016/j.jamda.2012.05.015. Epub 2012 Jun 23.
95. Hogan DB. Long-term efficacy and toxicity of cholinesterase inhibitors in the treatment of Alzheimer's disease. Can J Psychiatry. 2014;59(12):618–623.
96. Ritchie CW, Zhinchin G. Low dose, high dose, or no dose: better prescribing of cholinesterase inhibitors for Alzheimer's disease. Int Psychogeriatr. 2013;25:511–515.
97. Massoud F. Persistence with cholinesterase inhibitor treatment in Alzheimer disease. Can J Neurol Sci. 2013;40:623–624.
98. Parsons C, Hughes CM, Passmore AP, et al. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying? Drugs Aging. 2010;27:435–449.
99. Park-Wyllie LY, Mamdani MM, Li P, et al. Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study. PLoS Med. 2009;6:e1000157.
100. Gray HL, Jimenez DE, Cucciare MA, et al. Ethnic differences in beliefs regarding Alzheimer disease among dementia family caregivers. Am J Geriatr Psychiatry. 2009;17:925–933.
101. Roberts JS, Connell CM, Cisewski D, et el. Differences between African Americans and whites in their perceptions of Alzheimer disease. Alzheimer Dis Assoc Disord. 2003;17:19–26.
102. Jacklin KM, Walker JD, Shawande M. The emergence of dementia as a health concern among First Nations populations in Alberta, Canada. Can J Public Health. 2013;104:e39–e44.
103. Finkelstein SA, Forbes DA, Richmond CAM. Formal dementia care among First Nations in Southwestern Ontario. Can J Aging. 2012;31:257–270.
104. Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology. 2001;57:489–495.