

- of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;54:2269-76.
6. Wilkinson D, Murray J. Galantamine: a randomised, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;16:852-7.
 7. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2001;71:589-95.
 8. Olin J, Schneider L. Galantamine for Alzheimer's disease [Cochrane review]. In: The Cochrane Library; Issue 4, 2001. Oxford: Update Software.
 9. Wilcock G, Howe I, Coles H, Liliensfeld S, Truyen L, Zhu Y, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;20:777-89.

Competing interests: The authors are employed within Johnson & Johnson Pharmaceutical Services. Reminyl, a brand of galantamine, was developed by the research and development arm of Johnson & Johnson and is marketed around the world by various operating companies of Johnson & Johnson.

DOI:10.1053/cmaj.1031912

Although generally interesting, the meta-analysis by Krista Lancôt and associates¹ of the efficacy and safety of cholinesterase inhibitors in the treatment of Alzheimer's disease simply demonstrates what is observed in day-to-day clinical practice: a slight improvement or stabilization of the disease (as indicated by neuropsychological evaluation) and various gastrointestinal side effects. The meta-analysis showed a slightly greater benefit with donepezil than with the other drugs — again, just what is observed in daily clinical practice.

Unfortunately, the extensive support that some of the authors received from the pharmaceutical industry, as outlined in the competing interests statement,¹ might taint readers' perception of the authors' autonomy and independent interpretation of their findings. It is of course important to disclose potential competing interests, yet it is very difficult for readers to evaluate their influence on a study's conclusions. Furthermore, it might be useful if meta-analyses were to also include the competing interests of the authors of the papers included in the analysis. For example, the Japanese study² that showed a substantial treatment effect with donepezil — ascribed in the meta-analysis¹ to specific gene frequencies in the Japanese population — might have been influenced by the competing interests of its authors. As more and more clinical research is

funded by companies with a financial interest in the outcomes, there may be greater pressure on researchers to assess and report their financial interests.

Celio Levyman
Neurologist
São Paulo, Brazil

References

1. Lancôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ* 2003;169(6):557-64.
2. Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, et al. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. *Dement Geriatr Cogn Disord* 2000;11:299-313.

Competing interests: None declared.

DOI:10.1053/cmaj.1031685

[Three of the authors respond:]

The authors of these 2 letters raise several issues regarding our meta-analysis of the pivotal trials for 3 cholinesterase inhibitors used in the treatment of Alzheimer's disease.¹

Shane Kavanagh and Patricia Kabathova argue that the meta-analysis treats galantamine unfairly. In support of this claim, they point out that the majority of the galantamine trials included in the analysis did not use recommended doses. We explicitly recognized this and adjusted the meta-analysis of efficacy accordingly. They also suggest that meta-analyses focus on common treatment durations. However, there is no such thing as a "common treatment duration" in this context. In fact, the range of treatment duration is even greater than 12 weeks to 1 year, which Kavanagh and Kabathova refer to as "wide variation." We chose to be explicit about the treatment durations that were included and handled the differences by means of a subanalysis, assessing heterogeneity and providing confidence intervals.

In addition, Kavanagh and Kabathova suggest that more weight be given to the ADAS-cog assessment than to global clinical judgement. In keeping with the approach of health regulatory agencies such as the US Food and Drug

Administration,² we provided the numbers needed to treat (NNT) and confidence intervals for both cognitive outcomes (the ADAS-cog scores) and global clinical impression. The emphasis on global outcomes was consistent with the stated goal of the analysis.

Kavanagh and Kabathova, Celio Levyman and other authors,³ all comment on the issue of comparability between the 3 drugs. However, in our meta-analysis we cautioned that individual cholinesterase inhibitors cannot be directly compared until well-designed, properly blinded, head-to-head trials are conducted. Although Levyman shares his own clinical experience of a slightly greater benefit with donepezil, Kavanagh and Kabathova cite new evidence supporting the similarity in safety profiles between galantamine and other cholinesterase inhibitors. The study they selected as an example of a head-to-head trial⁴ was 1 of 3 published to date and was not available when we prepared our meta-analysis. All 3 studies⁴⁻⁶ had relatively small numbers of subjects, and none was completely double-blinded. In each case, the results presented favoured the sponsor's drug. The similarities or differences among various cholinesterase inhibitors in terms of efficacy and safety remain to be established.

Levyman rightly points out that while the competing interests of the authors of the meta-analysis were fully disclosed, the primary randomized controlled trials used in the meta-analysis might themselves have been subject to bias. The bias we fear is the presentation of results unreasonably or unjustifiably favouring those of the sponsor or disfavoring those of a competitor. Although we cannot control for such bias, we did obtain and present results that were not distorted from what is found in clinical practice, that did not unduly favour the drug of any given sponsor and that did not unduly favour those drugs as a group or class. Bias also influences which trials are published, with negative trials less likely to be published.⁵ We addressed this potential problem by using funnel plots.

Meta-analysts and, more important, clinicians practising evidence-based

medicine strongly rely on the data provided by high-quality, double-blind, randomized placebo-controlled trials. We thank Kavanagh, Kabathova and Levyman for reiterating the shortcomings in the literature to date, which led to the cautions described in our meta-analysis. Nevertheless, our conclusion, that cholinesterase inhibitors are effective as a class, and the quantification of NNT with the associated confidence intervals are supported by the data and our analysis.

Krista L. Lanctôt

Departments of Psychiatry
and Pharmacology

Nathan Herrmann

Department of Psychiatry

Thomas R. Einarson

Faculties of Pharmacy and Medicine
University of Toronto
Toronto, Ont.

References

1. Lanctôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety

- of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ* 2003;169(6):557-64.
2. Peripheral and central nervous system drugs advisory committee meeting; 1989 Jul 7. Rockville (MD): US Food and Drug Administration; 1989. p. 277.
3. Patient-Oriented Evidence that Matters. Donepezil is somewhat effective for Alzheimer's, probably better than galantamine [filler]. *BMJ* 2004;328(7431):0-g. Available at: bmj.bmjournals.com/cgi/content/full/328/7431/0-g (accessed 2004 Feb 11).
4. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;20:777-89.
5. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002;56:441-6.
6. Jones RW, Soinenen H, Hager K, Aarsland D, Passmore P, Murthy A, et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:58-67.

Competing interests: Dr. Lanctôt has received research honoraria and/or speaker's fees and/or travel assistance from Pfizer Canada Inc., Janssen-Ortho Inc. and Neotherapeutics. Dr. Herrmann has received speaker's honoraria and consulting fees from Pfizer Canada Inc., Janssen-Ortho Inc. and Novartis Pharmaceuticals, as well as research support from Janssen-Ortho Inc. None declared for Dr. Einarson.

DOI:10.1053/cmaj.1040150

Action on Canada's generic drug law

James Orbinski's informative commentary¹ on Bill C-56 was stirring. However, we also need suggestions for effective ways in which individuals can influence the powers that be; such strategies may have an important bearing on the form in which the legislation is passed.

It is mind-boggling that millions around the world continue to suffer and die from preventable causes while private interests help to stifle measures designed to deal with the problem. Mobilizing physicians who are concerned about the issue could go a long way toward making sure that Canada leads the way in breaking this catastrophic impasse.

Eila Abi-Jaoude

Fourth-year Medical Student
University of Manitoba
Winnipeg, Man.

Reference

1. Orbinski J. Access to medicines and global health: Will Canada lead or flounder? [editorial]. *CMAJ* 2004;170(2):224-6.

DOI:10.1053/cmaj.1040491

[The author responds:]

Medical students at, for example, McGill University and the University of Toronto have organized lectures, workshops, petitions, active lobbying and demonstrations in support of changes to Bill C-9 (formerly known as Bill C-56) that could make access to generic versions of patented medicines a reality in countries where the appropriate manufacturing capacity does not exist. In doing so, these students are active and full partners in a broad international coalition of church groups, national and international nongovernmental organizations, labour unions, medical associations and others concerned with access to health care at the global level. In my view, this is a powerful example of active citizenship and professional responsibility that challenges rather than acquiesces to the "powers that be."

The "right of first refusal" in the



HOW NUTRACEUTICAL RESEARCH IS SHAPING THE FUTURE OF YOUR PATIENTS' HEALTH

Evidence-based nutraceutical products for alternative and adjunctive therapies for disease prevention.



www.nfh.ca

Tel: 1.866.510.3123