

tion in North America, and whether a net public health benefit was expected from reintroduction of this amphetamine product.

Why are the scientific data that form the basis of regulatory decisions in Canada considered proprietary? The New Drug Committee should have met in public, its reports and transcripts should have been posted on the Web, and other scientists, health care professionals and members of the public should have been allowed to make submissions. The committee's report provides a glimpse of the thinking behind regulatory decision-making. A glimpse is not enough: full participation and access to information are needed.

#### Pierre Biron

Honorary Professor  
Department of Pharmacology  
Faculty of Medicine  
Université de Montréal  
Montréal, Que.

#### Barbara Mintzes

Postdoctoral Fellow  
Department of Anaesthesiology,  
Pharmacology and Therapeutics  
University of British Columbia  
Vancouver, BC

#### Joel Lexchin

Associate Professor  
School of Health Policy and  
Management  
York University  
Toronto, Ont.

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## Questioning the evidence

I am writing about a recent article in the CMA Leadership Series on Elder Care, distributed with the Nov. 8, 2005, issue of *CMAJ*.<sup>1</sup>

As one who has been studying the

research and marketing related to Alzheimer's disease (AD) treatments for nearly a decade, I found the article disturbing. The discussion on the benefits of the AD drugs are nearly opposite to what the best evidence says.

The writer states that "In numerous randomized clinical trials (RCTs), cholinesterase inhibitors (ChEIs) have consistently been shown to improve or delay the decline of cognitive functioning, delay the emergence of challenging behaviours and slow the loss of activities of daily living. In RCTs, benefits have been shown to last over a period of up to 2 years, with data from open-label trials suggesting a longer benefit."<sup>1</sup>

However, the company-sponsored trials upon which this statement relies are problematic and overstate the case for the role of these drugs in managing AD. The latest meta-analyses find that the effects of ChEIs are marginal to non-existent.<sup>2</sup>

I found the discussion of side effects almost laughable: "Before initiating treatment, physicians should discuss reasonable expectations with the patient and their caregiver. Patients should be warned of possible side effects, noting that they are often mild and fleeting."<sup>1</sup>

When I have read the monographs of the key AD drugs, the effects such as nausea, vomiting, anorexia and stomach upset are as high as 30%. In fact some commentators have joked that these drugs are more effective as weight-loss pills than altering the rate of cognitive decline. Here is an example of some of the side effects related to an AD drug, rivastigmine (taken from the product monograph):

Exelon's use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6 to 12 mg/day developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase ... than in the maintenance phase ... Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo.<sup>3</sup>

I don't know any physician who would dismiss these effects as "mild and fleeting."

I would echo the words of one researcher, Jason Karlawish, who remarked on a flawed study on donepezil with: "Would it be churlish to wonder out loud how this paper is different from an advertisement?"<sup>4</sup> I have to admit I am on the verge of losing a lot of respect for the *CMAJ* unless it stops distributing this kind of clearly biased and non-evidence-based fluff. I cannot see how it is in the best interests of physicians to have such articles published under the banner of *CMAJ*.

#### Alan Cassels

Pharmaceutical Policy Researcher  
School of Health Information Science  
University of Victoria  
Victoria, BC

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#### [The author responds:]

Mr. Cassels raises 2 major objections relating to comments I made about the treatment of AD with ChEIs.<sup>1</sup> His first objection refers to the quality of the evidence supporting the use of these medications. The second objection relates to the tolerability of these drugs, specifically, addressing the issue of gastrointestinal side effects.

With regards to the evidence supporting the use of ChEIs, to date there are 22 RCTs with ChEIs published in leading peer-reviewed journals, including the *New England Journal of Medicine*, the *Journal of the American Medical Association*, the *Lancet*, *Neurology* and *JAGS*, that have consistently shown a modest benefit for patients with AD. All these trials were carried out under

Good Clinical Practice and International Conference of Harmonization guidelines.<sup>2</sup> Based on a systemic review of these trials, the Canadian Consensus Conference on Dementia guidelines<sup>1</sup> unequivocally recommended that all patients with mild to moderate AD be offered a trial of one of these drugs. Mr. Cassels argues that a recently published systematic review by Kaduszkiewicz in *BMJ* is “best evidence” and, in his view, this review not only negates the evidence from the aforementioned published clinical drug trials but also 4 previously published meta-analyses of ChEIs<sup>4-7</sup> and the Cochrane reviews,<sup>8-10</sup> all of which have concluded that ChEIs offer a modest benefit to patients with AD in the domains of cognition, behaviour, function and caregiver burden. In September 2005 the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) published a systematic review of this class of drugs claiming a modest impact on functional performance and global outcomes.<sup>11</sup> Lastly, in a recent survey conducted in the UK in 2295 patients with AD treated with ChEIs and the caregivers, 1569 (68%) of people who had been treated with at least one of the ChEIs stated that the treatment had worked. The 10 most frequently reported benefits included being more aware and more active, calmer, taking more interest in things, improved conversation, better quality of life and increased confidence, in addition to the improvements usually evaluated in clinical trials.<sup>12</sup> No study is without its flaws, but to write off all of the evidence supporting the use of ChEIs in the treatment of AD based on one critical review seems unreasonable. The Health Protection Branch of Health Canada has weighed the evidence and approved the use of these drugs for the treatment of mild to moderate AD, and most provincial and private drug benefit programs provide financial coverage for their use.

ChEIs are considered to be safe and well tolerated. The CCOHTA report concluded that these drugs have not shown an increased risk of serious adverse events or death. With regard to side effects, Mr. Cassels bases his comments on one of the drug’s (rivastigmine) product monograph, citing a high inci-

dence of gastrointestinal side effects and compares the drugs to “weight loss pills.” Gastrointestinal side effects are known to occur in this class of drugs, but their prevalence as reported in product monographs is based on data from clinical drug trials, which is greater than what is seen in clinical practice. This is for two reasons: first, in clinical drug trials a side effect is reported regardless of its frequency and severity; second, dosages are increased using forced titration schedules. In clinical practice, physicians can reduce the impact of side effects through slower titration and dose adjustments. Also, they can address the patient’s treatment expectations and potential side effects by providing education and support. Having personally treated hundreds of patients with these drugs, nausea, vomiting and weight loss have been infrequent complaints that have rarely necessitated discontinuation of treatment, and when treatment is stopped these side effects generally resolve quickly.

Mr. Cassels’ comments echo a number of recent critical reviews of ChEIs, including the preliminary report from the UK’s National Institute of Clinical Excellence and the University of British Columbia’s Therapeutics Initiative. These reports question the cost effectiveness of treating patients with ChEIs, claiming that the drugs, at best, have a modest effect and do not delay milestones such as time to institutionalization. As your readers know, AD is a progressive neurodegenerative disease for which there is no cure. It affects over 300 000 Canadians, robbing them of their self, stripping the, of their independence, leading them to institutionalization and death. In doing so, AD places a huge burden on patients, their caregivers and society at large. Taking this into consideration, treatments that offer even modest benefits can have an important impact on the quality of life of patients and caregivers affected by this disease.

**Ron Keren**  
Clinical Director  
University Health Network  
Memory Clinic  
Toronto Western Hospital  
Toronto, Ont.

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