



# CAGP

## Bulletin

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*Contributors:* Submissions are welcome, and should be directed to the editor. Submissions are preferred via E-mail, in Rich Text Format (RTF) or Hypertext Markup Language (HTML). Direct submissions via E-mail attachment to [myronuk@geripsych.com](mailto:myronuk@geripsych.com) with a note as to the proposed format for the item—letter to the editor, opinion column, or peer-reviewed original research.

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## *Editorial*

# **Evidence-Based Reviews of Clinical Questions for Geriatric Psychiatry**

ROB VAN REEKUM

**T**his volume of the CAGP Bulletin marks the start of a new feature of the Bulletin: Evidence-Based Reviews of Clinical Questions for Geriatric Psychiatry. These articles are developed from reviews conducted by the staff and learners of the Department of Psychiatry at Baycrest Centre for Geriatric Care in Toronto. We hope that these will be of value to the members of the Academy and that they will become a regular feature of the CAGP Bulletin.

Each question reviewed is derived from a clinical case, or a representative clinical scenario, seen by one of the Evidence-Based Medicine (EBM) reviewers. Based on the case, a question is generated that specifies the intervention (i.e., diagnostic test, therapeutic intervention, prognostic statement or causation argument), the target population, and the outcome of interest. Literature searches are then conducted, the specific databases and search terms utilized being noted as part of the review process documentation. Articles judged relevant to the question as formulated are then reviewed. The most important paper, generally the most methodologically rigorous study available, which addresses the question most directly, is identified for more detailed critical appraisal. This critical appraisal utilizes a structured format, as proposed by the Department of Epidemiology at McMaster University. The data are then synthesised into conclusions which are presented along with the reference, type of study, and study results which support them. These conclusions form the basis of EBM clinical and research recommendations which are identified by consensus of the members of the EBM group at Baycrest.

Please give us your feedback on this feature of the Bulletin by writing to us ([bulletin@cagp.ca](mailto:bulletin@cagp.ca)). Is this type of review useful? What would make it better? Do you have strong disagreements with our conclusions or recommendations? Did we miss some useful evidence? Do you have clinical questions you would like to have asked? We will include some of your comments in future volumes of the Bulletin.

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## President's Report

DAVID K. CONN

Mark your calendar! The Annual Scientific Meeting of our Academy will take place in Montreal on Thursday, November 15, immediately prior to the Annual Meeting of the CPA. I would like to thank this year's organizers: François Primeau, François Rousseau and (as always) Lilian Thorpe. The theme for this year's meeting is Service Delivery Models and the Organizing Committee is putting together an exciting program. This year all of the plenary sessions will be simultaneously translated into English and French and, as in previous years, workshops will be held in both English and French. In addition, this year we will have a poster session so please consider submitting posters which could include work in progress, etc. We look forward to seeing as many of you as possible in Montreal.

Secondly, I would like to thank Lonny Myronuk for his work as Editor of the *Bulletin*. It is a difficult task to conjure up enough material for each edition. Please remember that the *Bulletin* is intended to offer an opportunity

for all of us to exchange ideas and information. You are encouraged to submit anything that you feel would be of interest to fellow members. This could include news of developments in your region or program, summaries of conferences attended, brief academic reviews or simply letters to the editor.

Some months ago we distributed a survey to all members with regard to priorities and future directions for the Academy in the years to come. It is very important for the Board to receive your opinions, suggestions and ideas and, therefore, we are enclosing another copy of this survey. Please take a few minutes to think about the issues and send us your responses.

Finally, if you have any immediate suggestions for the Board, please feel free to e-mail or phone me.

*David K. Conn*

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## *Pharmacologia* **ChEIs: Good for Whatever Ails Ya?**

NATHAN HERRMANN

Cholinesterase Inhibitors (ChEIs) have revolutionized the treatment of Alzheimer's disease (AD)! Whether you are a passionate proponent or opponent of this statement, ChEIs have unquestionably opened a therapeutic window previously unavailable to clinicians. While we may quibble over their cost/benefit ratio, well-designed double-blind, placebo-controlled studies have clearly documented their modest but significant efficacy at improving cognitive impairment and, more recently, improving function, behaviour and decreasing caregiver burden. Cholinergic deficits were first noted in AD over 20 years ago in pioneering studies that documented loss of cholinergic neurons in the basal forebrain, leading to marked reductions in choline acetyltransferase. While many therapeutic interventions aimed at the cholinergic system have been studied, it is only the ChEIs that appear to have both efficacy and tolerability. As their name suggests, ChEIs act by inhibiting the enzyme responsible for the breakdown of acetylcholine in the synaptic cleft. This inhibition leads to increased acetylcholine at muscarinic and nicotinic receptors, and recent evidence suggests that their effects might be much more profound and could include activation of nicotinic receptors, neurotropic effects, neuroprotective effects, regulation of beta amyloid production, etc.

Cholinergic neurons and their projections are widespread throughout the brain. Limbic areas including the amygdala and hippocampus have the highest density of cholinergic axons. The nucleus basalis of Meynert is the cell group that provides the major cholinergic innervation for the cerebral cortex and amygdala. It has been

suggested that the nucleus basalis and its afferents may play a major role in emotionally relevant brain function. It is, therefore, not surprising that acetylcholine plays an important role in many neuropsychiatric disorders besides AD. This article will, therefore, focus on reports and studies that have examined the use of ChEIs in conditions other than AD.

Sticking for the moment with dementia, there are now several reports and studies that have examined the use of ChEIs in dementia with Lewy bodies (DLB)(1-4) and vascular dementia (VaD). There are four published case series that have documented that donepezil and rivastigmine can have dramatic effects on both cognition and behaviour in patients with DLB. Behavioral improvements have included effects on hallucinations, delusions, apathy, and agitation. McKeith has recently published a double-blind, randomized, placebo-controlled study of 120 patients with DLB treated with rivastigmine(5). Significant benefits in behavior and cognition were noted. Considering how sensitive these patients are to antipsychotics, even atypical agents, it is likely that following the publication of this study, the treatment of first choice for patients with DLB will be a ChEI. There is at least one case series documenting the use of donepezil in patients diagnosed clinically with VaD(6). This study suggested that there was improvement in cognition, function and behavior, with caregivers particularly noting improved alertness and initiative. The role of ChEIs in the treatment of VaD should be clarified in the near future as several double-blind placebo-controlled studies with a variety of agents are currently well underway.

Down's Syndrome patients who live long enough develop the characteristic amyloid plaques and neurofibrillary tangles of AD. Neuronal loss in the nucleus basalis of Meynert has also been documented in Down's Syndrome patients. It is, therefore, not surprising that ChEIs have been suggested for this patient population. There are, however, only two small case series which have

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reported results(7, 8). While some patients appear to benefit both cognitively and behaviorally, one report raised concerns about worsening of behavior (agitation and aggression) and urinary incontinence(8). Clearly, controlled studies should be considered for this indication.

The link between anticholinergic medications and delirium is well documented. Unfortunately, there is only a single case report of a patient who actually had mild cognitive impairment diagnosed as Alzheimer's disease prior to the development of the delirium that was treated successfully with donepezil(9). This would appear to be another important indication for further research.

There are reports on the use of ChEIs in a variety of other neuropsychiatric disorders including Multiple Sclerosis, traumatic brain injury, Huntington's disease, and Tourette's disease. An open study of donepezil in 17 patients with Multiple Sclerosis noted significant improvements in attention, memory, executive function, and several aspects of behavior(10). In one series of 22 patients treated with donepezil following traumatic brain injury, there was a statistically significant improvement in full-scale IQ as well as clinician-based ratings(11). A small series of 2 patients treated successfully with donepezil for memory deficits following closed head injury has also been published(12).

In an interesting study which reported on the use of donepezil for the treatment of psychotropic induced memory loss(13), 22 patients were treated prospectively with 5 to 10 mg. per day. Almost all patients reported subjective improvement in memory as well as reductions in dry mouth and constipation. Seventeen of these patients were on tricyclic antidepressants or bupropion. While bupropion is not reported to have anticholinergic effects *in vitro*, the authors note that clinically many patients on bupropion complain of anticholinergic-type symptoms. They speculate that there may be indirect effects via monoaminergic interactions with the cholinergic system. Another unexpected finding in this study was that 2 bipolar patients became manic within hours of starting the donepezil. The relationship between cholinergic dysfunction and affective disorders has been hypothesized, though generally these hypotheses would suggest that increased cholinergic function would lead to an increase in depressive symptomatology. In fact, based upon these hypotheses, there is another case series which documents the use of donepezil for treatment-resistant bipolar patients(14). In this study of 11 patients, 6 demonstrated marked improvements and most patients experienced amelioration of symptoms within 2 weeks of initiation of therapy.

Finally, there are reports on the use of ChEIs in patients with schizophrenia, attention deficit disorder, and REM sleep abnormalities. In schizophrenic patients, ChEIs may improve cognition, negative symptoms and even tardive dyskinesia.

I would find it hard to believe that ChEIs would become first-line treatments for all the indications described above. On the other hand, given the ubiquitous nature of the cholinergic system and the proposed relationship between cholinergic dysfunction and many of these entities, it is possible that ChEIs will find a role in the treatment of illnesses beyond AD and DLB. These are truly psychotropic compounds and their role in psychiatry remains to be clarified. Stay tuned. ...

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***Announcement***  
**First Annual**  
**Lilly - CAGP Fellowship in Geriatric Psychiatry**

The Canadian Academy of Geriatric Psychiatry, in collaboration with Eli Lilly Canada, is offering \$40,000 for a one-year fellowship in geriatric psychiatry. The first of these annual fellowships starts in July 2001. The fellowship funding is to be utilized to protect time for the recipient to develop and complete an academic project in the area of research, education or program development, with the goal of further developing his or her expertise in geriatric psychiatry and contributing to the field. It will also be used to fund the fellow's travel to the two CAGP annual scientific meetings at the beginning of, and completion of, his or her fellowship.

***\$40,000.00 for a  
one-year Fellowship  
in geriatric  
Psychiatry***

Fellowship applicants must be Canadian citizens, have completed their psychiatric residency training and be eligible for, or have received, their FRCPC. The fellowship training must occur at one of the 16 medical schools in Canada that has a psychiatry training program.

Applications for the 2001 Fellowship closed February 27, 2001. The successful applicant was notified Tuesday, April 3, 2001, and the recipient will be acknowledged in a

subsequent issue of the *CAGP Bulletin*.

For further information regarding the Lilly-CAGP Fellowship in Geriatric Psychiatry and the application process, please contact:

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## *Millennium Project* **Mental Health & Long Term Care**

SHELLY HABER

The Millennium Project had its second meeting in October 2000 in Victoria. The purpose of the Project is "to improve mental health of the elderly in long term care through education, advocacy and collaboration." At the October meeting the committee supported a number of important initiatives.

### **NATIONAL CONSENSUS FORUM**

A two-day Consensus building Forum is being planned for Spring of 2002. The Forum is a collaborative initiative with other provider and consumer stakeholders including:

- Canadian Pharmacists Association
- College of Family Physicians of Canada
- Health Canada
- Canadian Geriatrics Society
- Canadian Alzheimer Association
- Canadian Mental Health Association
- Canadian Nurses Association
- Canadian Association for Community Care
- Canadian Association of Retired Persons

Collaboration with these stakeholders highlights the importance of the issues and sets the stage for innovative opportunities.

The first meeting with the stakeholders working group was held in January 2001. The participants all support the Project and are willing to help make the Con-

sensus forum a success. Some early positive suggestions include:

- an emphasis on outcomes that include a detailed action plan and a commitment to the implementation of multi-stakeholder initiatives; and
- where possible, all participants identify innovative strategies that can be shared.

Funding for the project will be sought from private industry partners and Health Canada's "Population Health Fund".

### **WEBSITE**

The Millennium Committee supported the renewal of the CAGP Website. The Website will be used to disseminate educational resources and information.

### **EDUCATIONAL RESOURCES**

An educational subcommittee of the Millennium Project has been asked to identify ways and means of collecting educational resources that can be disseminated to CAGP members and other relevant stakeholders. Two specific activities have been recommended. A survey will be sent to all members asking them to identify teaching modules (CDs, slide presentations, videos, etc). The survey will also ask for the coordinates of local or provincial agencies that may assist in identifying valuable teaching resources. All members are asked to respond to the survey.

A second activity is to define a comprehensive and current list of resource materials such as books, articles, journals that can be made available to the membership through the Website.

## REGIONAL INITIATIVES

WE NEED YOUR INPUT! In order to make this project a success we are looking for individuals who are interested in participating in the development of local/regional/provincial initiatives. Various types of committee support can be provided to any CAGP members who would like to participate in a regional initiative to enhance mental health care to clients of long term care settings. If you are interested please contact either one of the CAGP Millennium Project members (listed below) or Shelly Haber at (416) 781-2886 or e-mail at [s.haber@sympatico.ca](mailto:s.haber@sympatico.ca).

### The CAGP Millennium Project Members

If you have any questions about this Project please do not hesitate to contact one of the members:

David Conn, Co-Chair  
 Ken LeClair, Co-Chair  
 Lilian Thorpe  
 Evelyn Keller  
 Ian Ferguson  
 Maria Geiser  
 Cathy Shea  
 Susan Lief  
 Elizabeth Drance  
 Isabel Martins  
 Serge Gagné

## Membership Report

SUSAN LIEFF

The mailing for membership renewal will be out shortly. Consider the 3 year renewal option to avoid your membership lapsing by getting lost in your "to do" pile. The introduction to our membership criteria is being revised to ensure clarity for new applicants. Once this has been completed, we will be actively recruiting new members with the assistance of our affiliated organizations such as the CPA. Your comments and suggestions are welcome.

Please welcome to membership the following colleagues:

### Full members

Melissa Andrew  
 Sharon Levine  
 Christine Caravan  
 Hussam Bawa

### Affiliate member

Cindy Grief

*New Feature*  
**Evidence Based Reviews  
of Clinical Questions for Geriatric Psychiatry**

ROB VAN REEKUM & VICKI STERGIPOULOS

*This is the first of a series of evidence-based medicine (EBM) reviews that are planned for the CAGP Bulletin. The format being used here follows that utilized at the Baycrest Centre for Geriatric Care in Toronto. The language is pithy and direct, by design. The purpose is not to develop and present an argument; each study's authors will have done this in the writing being surveyed. What are presented here are the points that the original authors have succeeded in making with their arguments, in the EBM reviewers' estimation.*

*For this introductory installment, editorial annotations have been added to help explain the format. Editorial comments, like these ones, are set in italic typeface. -Ed.*

<b>Study Type</b>	<b>Conclusions</b>
RCT <sup>1</sup>	Metrifonate may be efficacious in the treatment of hallucinations in AD.
RCT <sup>2</sup>	Metrifonate may be efficacious in the treatment of hallucinations in AD in a dose dependent manner.
RCT <sup>3</sup>	Low dose Metrifonate may be efficacious in the treatment of hallucinations in Alzheimer's Disease.
RCT <sup>5</sup>	Other cholinesterase inhibitors and muscarinic agents may be efficacious in the treatment of hallucinations in Alzheimer's Disease.
N=1 double blind placebo control <sup>8</sup>	
Case series <sup>4</sup>	Cholinesterase inhibitors may be efficacious in the treatment of hallucinations related to diseases other than Alzheimer's Disease.
Case study <sup>6</sup>	
Case report <sup>7</sup>	
Case report <sup>9</sup>	

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**CLINICAL CASE:**

An 80 year old female with longstanding Parkinson's Disease and associated dementia is being treated with levodopa/carbidopa (Sinemet) and develops visual hallucinations. *This clinical vignette provides a specific instance of a class of problem that can be encountered in geriatric psychiatry practise. A question is then formulated with which to approach the literature.*

**CLINICAL QUESTION:**

"Are cholinesterase inhibitors efficacious in the treatment of hallucinations in dementia?"

**LITERATURE SEARCH:**

Database: Medline

Terms: psychosis, hallucinations, cholinesterase inhibitors

**CLINICAL IMPLICATIONS:**

Metrifonate and possibly other acetylcholinesterase inhibitors may be efficacious in the treatment of hallucinations in Alzheimer's disease and possibly in dementias of other causes.

**RESEARCH IMPLICATIONS:**

Further randomized controlled treatment trials of pro-cholinergic agents in clinical populations with hallucinations appear warranted.

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**Evidence: Study Results**

Least square mean change differed between active and placebo group for NPI hallucination scale (-0.50 p=0.002)

Least square mean change differed between 60/80 mg dose and placebo group but not between 40/50 mg dose and placebo groups for NPI hallucinations scale (0.29 p=0.004) and ADAS noncognitive hallucinations scale (0.21 p=0.001)

Least square mean change between active (50 mg/day) and placebo groups were not statistically significant for the delusions and hallucinations subscores on the NPI and ADAS non-cognitive scale.

Dose dependent reduction in delusions (p=0.001) and hallucinations (p< 0.0012) in Alzheimer's Disease.

Physostigmine was associated with a decrease in global psychosis scale from 7.0 to 4.2.

In 8 of 9 patients with Lewy Body Disease, frequency, duration and content of hallucinations decreased with donepezil.

Visual hallucinations improved in a previously treatment resistant patient with Lewy Body Disease given donepezil 10mg/day.

Psychosis resolved with Risperidone and donepezil (5 mg OD) in a patient with Lewy Body Disease.

Visual hallucinations of unclear etiology disappeared with donepezil.

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## CRITICAL ASSESSMENT OF ARTICLE

### Article:

Kaufer et al. Beyond the Cholinergic Hypothesis: The Effect of Metrifonate and Other Cholinesterase Inhibitors on Neuropsychiatric Symptoms in Alzheimer's Disease.<sup>1</sup>

### 1. What is the research question in this study?

What is efficacy of acetylcholinesterase inhibitors for the treatment of hallucinations?

### 2. Was the design architecture appropriate?

Yes, but patients were assigned 2:1 active treatment:placebo. Behaviour of groups was similar at baseline as assessed by the Neuropsychiatric Inventory (NPI).

### 3. Were all relevant health outcomes reported?

No. Only the impact on mood and behaviour (per the NPI) was assessed. The NPI is reliable and valid and the outcome was assessed blind.

### 4. Were the study patients (population) recognizably similar to your own?

Uncertain. Eligibility criteria were well defined (AD as per NINCDS-ADRDA, MMSE 10-26, HIS<4) but baseline characteristics and recruitment sites not described. Note: this was a multi-centre trial.

### 5. Were both clinical/administrative and statistical significance considered?

Uncertain. The differences for hallucinations, depression, apathy, and total NPI score were all statistically significant. The clinical significance is difficult to assess as the data are presented as least-square mean differences.

### 6. Is the manoeuvre (health intervention) feasible in your setting?

No. Metrifonate is not currently available. It is unclear if contamination or co-intervention occurred. Compliance was not measured.

### 7. Were all patients who entered the study accounted for in its conclusion?

No. The subjects in the randomized sample (N=135 placebo + 273 active treatment) were not all considered "valid" for the intent to treat analysis (N=133 placebo + 260 active treatment), but it is not clear why they were invalid.