

# Funding the future of health research

The decision by the Canadian Institutes of Health Research (CIHR) to close 2 senior investigator programs to new applicants has sounded an alarm within the medical research community. From the perspective of academe (see commentary by Eliot Phillipson (page 568),<sup>1</sup> this spanner in the works threatens not merely to slow the machinery of health research in Canada, but to wreck it. CIHR president Alan Bernstein (see page 567)<sup>2</sup> justifies the decision by arguing that the current CIHR budget is spread too thinly and that there are other funding sources for senior investigators, notably the \$1-billion Canada Research Chair (CRC) program launched in 2000.

The CIHR's decision will not affect training grants or start-up career funding, but it will force many established investigators to look elsewhere for salary support. No one disputes that salary support is necessary to allow investigators to dedicate most of their time to research. What is less clear is whether the CRC program can meet the need created by the CIHR cuts. In our News section, Allison Gandey reports on this controversy and tracks some of the financial constraints (see page 592),<sup>3</sup> but it is difficult to get a comprehensive picture of the state of health research funding in this country. Such a picture would include grants to universities from provincial ministries of education, which go toward bricks and mortar, equipment, libraries and, importantly, salary support for professors who both teach and do research. Most of this salary support is reserved for basic science faculty, not clinician scientists who are judged, incorrectly, to be self-supporting through their clinical incomes. A comprehensive picture would also include funding by private foundations (usually for research into a specific disease or condition), industry (for product research) and a partnership forged between industry and the CIHR for pharmaceutical research.

The CIHR decision to get out of the business of funding established career investigators must be viewed against this blurry mosaic of alternative funding sources.

It is unfortunate that the decision was made just 3 months before the application deadline. Prospective applicants to the fall competition worry that the loss of salary will jeopardize their current projects — along with their career prospects. Worse, this precipitate decision sends a

message to all health scientists that support for research in this country is fragile. The incoming generation of clinical scientists may well reconsider their career options.

The CIHR fix part of the justification (and blame) for their decision on “an impending change in political leadership [that] may delay the timing of the next federal budget. [The] CIHR must assume ... that its budget in [fiscal year] 2004–05 will be the same as in [fiscal year] 2003–04.”<sup>4</sup> Without a clear indication from the rudderless Liberal government on funding for next year, the CIHR anticipate having \$70 million in uncommitted funds next year — \$100 million less than last year. This was sufficient incentive to cut the already vulnerable senior career awards loose.

We urge the governing council of the CIHR to reconsider its decision as soon as possible. And we urge Health Minister Anne McLellan — whose government, to its credit, has allocated unprecedented funds to research — to act now to assure the CIHR will receive an anticipated and much-needed budget increment for 2003–04. In this way the government can confirm its commitment to support excellence in health research, minor bumps in the federal political landscape notwithstanding.

Given the paucity of coherent information on career funding for health research, a prudent move for the CIHR would be to establish an expert group involving government, universities, research institutes, industry and foundations to determine exactly what funding support for career investigators is available, whether it is sufficient, and whether it is sustainable long term. Is there enough funding to support the critical mass of career investigators needed for robust progress in health research? Or isn't there? We need to know before we allow more of our best and brightest to fall by the wayside next year. — *CMAJ*

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## Financer l'avenir de la recherche sur la santé

La décision qu'ont prise les Instituts de recherche en santé du Canada (IRSC) de n'accepter aucun nouveau candidat pour les 2 programmes destinés aux chercheurs chevronnés a sonné l'alarme dans les milieux de la recherche médicale. Pour le monde universitaire (voir le commentaire d'Eliot Phillipson [page 568]<sup>1</sup>), ce bâton dans les roues menace non seulement de ralentir l'appareil de la recherche en santé au Canada, mais de l'enrayer. Le président des IRSC, Alan Bernstein (voir page 567)<sup>2</sup>, justifie la décision en soutenant que le budget actuel des IRSC ne comporte plus aucune marge de manœuvre et qu'il existe d'autres sources de financement pour les chercheurs d'expérience, notamment le programme des chaires de recherche du Canada (CRC) d'un milliard de dollars lancé en 2000.

La décision des IRSC n'aura pas d'effet sur les subventions de formation ou le financement de démarrage de carrière, mais elle obligera de nombreux chercheurs établis à chercher de l'aide salariale ailleurs. Personne ne conteste la nécessité de l'aide salariale pour permettre aux chercheurs de consacrer la majeure partie de leur temps à la recherche. Ce qui est moins clair, c'est si le programme CRC peut répondre au besoin créé par les compressions imposées par les IRSC. Dans notre section sur les actualités, Allison Gandey présente un reportage sur cette controverse et décrit certaines des contraintes financières (voir page 592)<sup>3</sup>. Il est toutefois difficile de brosser un tableau complet de l'état du financement de la recherche en santé au Canada. Un tel tableau inclurait les subventions que les universités reçoivent des ministères provinciaux de l'Éducation et qui servent aux travaux de construction, à l'achat d'équipement, aux bibliothèques et, ce qui est important, à l'aide salariale versée aux enseignants qui font aussi de la recherche. La majeure partie de cette aide salariale est réservée aux enseignants en sciences fondamentales et non aux scientifiques cliniciens que l'on juge à tort autosuffisants grâce à leur revenu de clinicien. Un tableau complet inclurait aussi le financement provenant de fondations privées (habituellement destiné à la recherche sur une maladie ou un problème précis), de l'industrie (pour la recherche sur un produit) et d'un partenariat établi entre l'industrie et les IRSC dans le cas de la recherche pharmaceutique.

Il faut envisager la décision des IRSC de cesser de financer les chercheurs de carrière établis devant la toile de fond que constitue cette mosaïque floue d'autres sources de financement.

Il est malheureux que la décision ait été prise 3 mois à peine avant la date limite de présentation des demandes. Les candidats éventuels au concours de l'automne craignent que la perte d'un salaire ne mette en danger leurs projets en cours — et leurs possibilités de carrière. Il y a encore

pire : cette décision précipitée fait passer à tous les scientifiques du secteur de la santé un message indiquant que l'appui à la recherche est fragile au Canada. Les scientifiques cliniciens de la prochaine génération peuvent très bien remettre en question leur choix de carrière.

Les IRSC justifient en partie leur décision en rejetant le blâme sur «un changement imminent à la tête du gouvernement [qui pourrait retarder] le dépôt du prochain budget fédéral. À cause de cette incertitude, les IRSC doivent tenir pour acquis ... que leur budget pour l'exercice 2004-2005 sera le même qu'en 2003-2004»<sup>4</sup>. Comme le gouvernement libéral sans gouvernail ne donne aucune indication claire du financement du prochain exercice, les IRSC prévoient disposer de 70 millions de dollars de fonds non engagés l'année prochaine — soit 100 millions de moins que l'année dernière. Cet écart a suffi pour inciter les instituts à éliminer le programme, déjà vulnérable, de bourses aux chercheurs chevronnés.

Nous exhortons le conseil d'administration des IRSC à revoir sa décision le plus tôt possible. Nous exhortons aussi la ministre de la Santé Anne McLellan — dont le gouvernement, il faut le reconnaître, a affecté des fonds sans précédent à la recherche — à agir maintenant pour garantir que les IRSC recevront, pour 2003-2004, une augmentation prévue et des plus nécessaires de leur budget. Le gouvernement pourra ainsi confirmer qu'il est déterminé à appuyer l'excellence en recherche sur la santé, en dépit de soubresauts mineurs dans le panorama politique fédéral.

Compte tenu de la rareté de renseignements cohérents sur le financement des carrières en recherche dans le domaine de la santé, il serait prudent pour les IRSC d'établir un groupe d'experts constitué de représentants des gouvernements, des universités, des instituts de recherche, de l'industrie et des fondations afin de déterminer exactement l'appui financier disponible pour les chercheurs de carrière, s'il suffit et s'il est durable à long terme. Y a-t-il suffisamment d'argent ou non pour appuyer la masse critique de chercheurs de carrière nécessaire afin de réaliser des progrès solides en recherche sur la santé? Nous devons le savoir avant de perdre l'année prochaine encore d'autres talents parmi les meilleurs et les plus brillants. — *JAMC*

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4. Les IRSC annoncent d'importantes modifications à leurs programmes en prévision du cycle de concours de l'automne 2003. Disponible à l'adresse : [www.cihr-irsc.gc.ca/news/cihr/2003/fall\\_2003\\_program\\_changes\\_f.shtml](http://www.cihr-irsc.gc.ca/news/cihr/2003/fall_2003_program_changes_f.shtml) (consulté le 25 août 2003).

## Treating Alzheimer's disease with cholinesterase inhibitors

Cholinesterase inhibitors are the mainstay of treatment for Alzheimer's disease and are recommended as such by the Canadian Consensus Conference on Dementia, however, it has been difficult to quantify the overall benefits and harms of these drugs. Lanctôt and colleagues review the efficacy and safety of the second-generation cholinesterase inhibitors donepezil, galantamine and rivastigmine that are currently marketed in Canada for the treatment of Alzheimer's disease. These drugs have been developed in an attempt to address the problems of short duration of action and lack of acetylcholinesterase specificity found in the original cholinesterase inhibitors. Using meta-analysis, the authors found that the number needed to treat to obtain a global response to cholinesterase inhibitors in a non-Asian population was 12, and 4 in a Japanese study. The number needed to harm 1 additional patient was found to be 12, although the authors note that the adverse events were largely gastrointestinal and that no drug-related deaths were reported. They conclude that the newer cholinesterase inhibitors are safe and that the current recommendations for the treatment of Alzheimer's disease are supported by the existing literature.

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Vincenzo Pietropaolo

## Reducing inappropriate prescribing in primary care

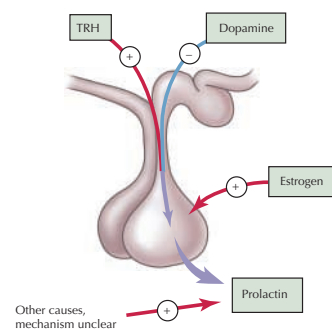
Efforts to treat multiple medical problems in elderly patients, although well intentioned, can nevertheless contribute to increasing morbidity and mortality in this population. Clinicians are aware that drug interactions can be harmful, however, the sheer number of drugs available makes keeping track of all of their potential interactions impossible. Tamblyn and colleagues show that the use of specialized computer software in the physician's office can help reduce inappropriate prescribing. Interestingly, physicians who used the software were reluctant to stop existing therapies despite being warned of potential problems, and prescriptions deemed to be inappropriate were not eliminated.

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## Hyperprolactinemia

Serri and colleagues present a comprehensive and practical review of hyperprolactinemia. They include a description of the normal physiology of prolactin secretion and provide concise points to help clinicians recognize and diagnose states of prolactin excess. The authors summarize the objectives of treatment, including the management of this condition during pregnancy. Dopamine agonists are the usual medical therapy, but surgical options exist. Indications for surgery and a description of its relative effectiveness are also presented.

Myra Rudakewich



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## Preventing violence against women

The Canadian Task Force on Preventive Health Care has reviewed the evidence regarding the potential benefits and harms of screening all women to detect abuse, interventions for abused women and treatment programs for men who abuse their partners. The Task Force concludes that based on the existing literature there is insufficient evidence to warrant routine screening. Four types of intervention for abused women were evaluated: shelters, post-shelter advocacy counselling, personal and vocational counselling, and prenatal counselling. The Task Force found evidence that women who had stayed 1 night in a shelter *and* had received a program of advocacy services reported less abuse and better quality of life over the ensuing 2 years than women who had only stayed in a shelter. Its review of the evidence for the value of programs that target male batterers yielded inconclusive results. Given the general lack of good evidence in this field, the Task Force concludes that there is a clear and pressing need for additional research to identify effective interventions to help women who suffer from domestic abuse.

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# Correspondance

## Who delivered Fredericton's babies?

As a Fredericton pediatrician, I join AMP Andy Scott in recognizing my longtime colleague, the late Bob Chalmers.<sup>1</sup> However, Dr. Bob was not "for over 10 years ... the only gynecologist in the city." Anna Loane, after practising obstetrics and gynecology at Women's College Hospital in Toronto for 3 years, opened her office in Fredericton in November 1951 and practised her specialty until her retirement in 1985. At the time Loane started practising here, Dr. Bob had left his general practice to do postgraduate training, returning in 1952 to open his practice in obstetrics and gynecology.

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## Medical students not mum on Iraq

Brad Mackay reports in *CMAJ* News on the muted response of Canadian physicians to the humanitarian catastrophe in Iraq.<sup>1</sup> However, "mum" hardly describes the activity that took place on Canadian medical school campuses, starting months before the US-led attack on Iraq began.

Medical students participated in and led rallies, vigils and discussions of the health consequences of the war in Iraq and have been a significant component of the unprecedented public opposition to this military intervention. Medical students across Canada initiated a petition voicing opposition to the detrimental health consequences of war in Iraq. This petition eventually reached every medical school in Canada and garnered over 650 signatories.<sup>2</sup>

Many Canadian physicians understandably feel ill-equipped to address the

health consequences of war. That is why we are encouraging medical schools to incorporate education about human rights and the health effects of war into medical undergraduate curricula. That is also why organizations like Physicians for Global Survival are so crucial in helping governments to reframe political, economic and military decisions in terms of projected health outcomes.

We continue to endeavour to use medicine as an avenue for peace, and we invite organizations such as the CMA to assess the health consequences of the war in Iraq and to take the position they deem appropriate, as would be done for any other health crisis.

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## SARS respiratory protection

Since preparation of my letter on respiratory protection against severe acute respiratory syndrome (SARS) for health care workers,<sup>1</sup> an additional important study has appeared. Ofner and associates<sup>2</sup> have reported on 9 of 11 health care workers in whom SARS developed even though they were following the infection-control precautions recommended in Canada at the time,<sup>3</sup> including use of an N95 respirator. However, the N95 respirator in use was a duckbill mask (PCM2000, Kimberly Clark Health Care, Roswell, Ga.),

which is not approved by the US National Institute for Occupational Safety and Health (NIOSH).<sup>2</sup> The use of N95 respirators, a recommendation adopted from tuberculosis (TB) protection guidelines, has been suggested by the US Centers for Disease Control and Prevention (CDC) for protection against SARS, although the CDC recommends that only NIOSH-approved respirators be used.<sup>4</sup> Of note, TB bacteria are much larger than the SARS virus, which indicates that a higher-efficiency respirator would be required for adequate protection against the virus.

Ofner and associates<sup>2</sup> reported that the health care workers in their study were not fit-tested, and at least one of the workers had a beard. In my earlier letter,<sup>1</sup> I suggested N100 respirators with ultra-low penetrating filters for the best protection. The respirator should also be elastomeric to allow a good fit on the face; notably, N100 elastomeric respirators can be cleaned and reused. Before a health-care worker uses a respirator, he or she should receive appropriate training, must be properly fit-tested, and should undergo a medical surveillance examination; these activities should be repeated yearly. In a previous study of asbestos workers,<sup>5</sup> I reported that many do not use their respirators properly, despite training. Thus, providing N100 respirators will be insufficient to prevent infection if health care workers use them improperly or compliance is less than 100%.

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Competing interests: None declared.

## Low-calcium diet

Elizabeth Sellers and associates<sup>1</sup> write about the adaptation of Inuit children to a low-calcium diet. Contemporary humans evolved in an equatorial environment, and there can be little doubt that populations living under radically different conditions have had to adapt in substantial ways. Nevertheless, 3 important errors in this article need clarification if we are to gain any insight into the character of the adaptation, at least with respect to calcium.

First, the magnitude of urinary calcium excretion, expressed in this paper as fractional micromoles per mole creatinine, is incorrect by 6 orders of magnitude. As reported by Sellers and associates,<sup>1</sup> the urine of these children would have contained less calcium than distilled water. This might be taken as an indication of the adaptation the authors are seeking to define, except that the values reported are considered either at or above age-specific normal values in all of the 10 children studied. Therefore, the units for this test result are incorrect.

Second, the authors seem to have misinterpreted the data from the reference by Kuhnlein and colleagues<sup>2</sup> when they state "With a traditional diet, Inuit children in northern Canada ingest only 20 mg of elemental calcium per day." In the article concerned, traditional foods, providing 21 mg calcium daily (not the 20 mg cited), constituted only 17% of the total energy intake of the Inuit children studied. Had total energy intake come from traditional foods, total calcium intake would have

been at least 120 mg/day. That is still not very much, but it is not safe to extrapolate from such a small proportion of the diet, since deriving total energy from traditional foods might well have involved a change in food types. This is strongly suggested by the standard deviation around the 21-mg average reported by Kuhnlein and colleagues,<sup>2</sup> which was 400 mg. Thus, the intake data were severely skewed to the right, indicating that some of the children must have been getting 1000 mg calcium or more from traditional foods. Given these uncertainties, the article by Kuhnlein and colleagues<sup>2</sup> provides no useful information about the calcium content of diets based completely on traditional foods.

The third error relates to the uncritical assumption that any adaptation at all would suffice to build an adult skeleton with a daily intake as low as the 20-mg figure mentioned by Sellers and associates.<sup>1</sup> If all 20 mg could be absorbed and retained, and if dermal and excretory losses could be reduced to zero (both impossible conditions), total skeletal accumulation from birth to age 16 would produce a skeleton containing less than 120 g calcium. Thus, the premise that adaptation must be possible for such an intake is untenable. Whatever the basis for the error, the authors should have realized that any intake estimate as low as the one cited had to be incorrect.

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### [The authors respond:]

Our hospital laboratory customarily reports all concentration ratios with the same units for both numerator and denominator (i.e., moles per mole [mol/mol] or micromoles per micro-

mole [μmol/μmol]), and this was the case for both the results and the normative data for our study.<sup>1</sup> However, as Robert Heaney rightly points out, these values were inadvertently mislabelled and reported with units of micromoles per mole. Nonetheless, because the numbers for both the reported results and the reference values are correct (with units of moles per mole), neither the results, their interpretation nor our conclusions are affected by this error.

The study by Kuhnlein and colleagues<sup>2</sup> does indeed report 21 (standard deviation 400) mg as the calcium intake derived from the traditional portion of a mixed diet. During manuscript revision, this figure was accidentally substituted for the estimated total daily calcium intake, which by extrapolation to a fully traditional diet is on the order of 123 mg/day; this remains profoundly low compared with the recommended daily intake of 900 mg. In any case, as Heaney notes, the reported standard deviation precludes placing too great an emphasis on the precise numeric value. Hence, neither 20 mg nor 120 mg should be regarded as more than a round number illustrating the magnitude of the discrepancy, and neither the results nor the conclusions inferred from them are materially affected by reference to the extrapolated value. Moreover, given this uncertainty and the absence of any reports of bone mineral density for a population using a traditional diet alone, it may be premature to speculate as to the sufficiency of bone mineralization under these circumstances. Further studies in this area are clearly warranted.

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## Serotonin syndrome: not a benign toxidrome

Philippe Birmes and associates<sup>1</sup> suggest that serotonin syndrome is a less serious condition than neuroleptic malignant syndrome (NMS), but this has not been our experience.<sup>2-5</sup> In our prospective study of serotonin syndrome,<sup>4,5</sup> 6 of the 16 patients experienced disseminated intravascular coagulation (DIC), rhabdomyolysis and hypotension necessitating admission to the intensive care unit. Acute renal fail-

ure developed in 2 patients, and 1 patient died.

Table 2 in the article by Birmes and associates<sup>1</sup> does not capture the key differences between NMS and serotonin syndrome. Both conditions can be fulminant, and patients may present with delirium, hyperthermia, rhabdomyolysis, dilated pupils, tachycardia, diaphoresis, rigidity and blood pressure changes<sup>2-5</sup> (see Table 1 with this letter). The main difference lies in the clinical gestalt: typically a patient with serotonin syndrome is agitated, speaks incoherently and has prominent myoclonus, whereas a patient with NMS is immobile, mute and staring. Although rhabdomyolysis is a complication of both toxidromes, DIC, seizures, ventricular tachycardia

and severe hypotension are extremely rare in NMS.<sup>2</sup>

We agree with the mainstays of treatment suggested by Birmes and associates,<sup>1</sup> but we also advise monitoring of vital signs, platelet count, muscle enzymes and myoglobin twice daily for at least 72 hours. We have serious concerns about the use of chlorpromazine and propranolol for serotonin syndrome. Both drugs decrease blood pressure, which will exacerbate the hard-to-treat hypotension that can occur in serotonin syndrome; in addition, chlorpromazine may precipitate NMS. An absolute contraindication for the use of propranolol is a history of asthma, which is difficult to elicit if the patient is delirious. Finally, it is important to advise patients taking serotonergic agents about the risks of this potentially serious and fulminant syndrome.

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Competing interests: None declared.

## Smith-Magenis syndrome

Waleed Al Busairi and Fawzi Ali<sup>1</sup> describe a 15-year-old boy with mental retardation and a history of putting inedible objects into his mouth. The authors might want to investigate

**Table 1: Clinical characteristics, laboratory abnormalities, complications, and risk factors for neuroleptic malignant syndrome and serotonin syndrome<sup>2-5</sup>**

Characteristic	Neuroleptic malignant syndrome	Serotonin syndrome
Typical clinical presentation	Rigid, mute, staring, immobile	Agitated, incoherent speech, myoclonic twitching, bruising
Cognitive	Mild confusion to delirium; difficult to assess because of mutism	Mild confusion to delirium
Autonomic	Fever, tachycardia, diaphoresis, dilatation of pupils, blood pressure instability	Fever, tachycardia, diaphoresis, dilatation of pupils, blood pressure instability (hypertension in moderate cases, hypotension in severe cases)
Gastrointestinal	Constipation, ileus	Nausea, vomiting, diarrhea
Neurologic	Severe muscular rigidity (cogwheel), rigours, tremulousness	Hyperreflexia, myoclonus, tremulousness, clonus, fasciculations, ataxia, with or without rigidity
Psychiatric	Facial expression "fearful," underlying psychosis, premorbid mood disorder	Underlying mood or anxiety disorder; delirium may be misinterpreted as psychosis
Common laboratory abnormalities	Leukocytosis, elevation of muscle enzymes (CPK, ALT, AST, LDH), low serum iron	Leukocytosis, elevation of muscle enzymes (CPK, ALT, AST, LDH), thrombocytopenia
Complications	Aspiration pneumonia, renal failure, pulmonary embolus, contractures, postepisode muscle weakness	Falls, seizures, severe hypotension, ventricular tachycardia, disseminated intravascular coagulation, renal failure, coma (mortality rate unknown)
Risk factors	Antipsychotic drug use (all types), polypharmacy, rapid increase in neuroleptic dosage, concurrent use of lithium, dehydration, catatonia, agitation, benzodiazepine withdrawal during neuroleptic treatment	Use of serotonergic agents (all types), polypharmacy, concurrent use of lithium, MAOIs plus demerol (other risk factors unknown)

Note: CPK = creatine phosphokinase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactic dehydrogenase, MAOIs = monoamine oxidase inhibitors.

for Smith-Magenis syndrome if this has not previously been considered.

Smith-Magenis syndrome is associated with mental retardation, sleep disturbances, few facial dysmorphic features, self-injurious behaviour and putting objects into orifices. This trait of bodily insertions is known as polyembolokoilamania.<sup>2</sup> The definitive diagnosis is based on absence of the 17p11.2 region (a band on the short arm of chromosome 17), determined by cytogenetic examination (in more than 95% of cases<sup>2,3</sup>) or by fluorescence in situ hybridization (also known as FISH).

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#### [One of the authors responds:]

We did not consider Smith-Magenis syndrome for the patient described in our article.<sup>1</sup> This chromosomal microdeletion syndrome is associated with a clinically recognizable pattern of physical, developmental and behavioural features.<sup>2</sup> The facial appearance is characterized by broad, square shape, brachycephaly, prominent forehead, synophrys, up-slanting palpebral fissures, deep-set eyes, broad nasal bridge, midfacial hypoplasia and prognathism. The behavioural phenotype includes sleep dis-

turbance, attention deficit disorders, attention-seeking, aggression, self-injurious behaviour and stereotypes, especially the self-hug and lick-and-flip movements.

We suspect that Chitra Prasad raised the possibility of Smith-Magenis syndrome because the patient was mentally retarded and ingested foreign bodies. However, 2 important distinctions must be made. First, most people with Smith-Magenis syndrome have mild to moderate mental retardation, whereas this patient had severe to profound retardation. Second, the syndrome is associated with polyembolokoilamania, the insertion of objects into body orifices such as the rectum, vagina, urethra, nose and ear, rather than pica, in which ingestion is restricted to the oral route, as in the patient we described. Smith-Magenis syndrome is rare, occurring in 1 of 25 000 births, but pica affects some 20% of mentally retarded people.<sup>3</sup>

Other facts about this patient, not given in the article, made a diagnosis of Smith-Magenis syndrome unlikely. For example, the patient did not show the distinctive facial appearance or behavioural phenotype of this syndrome. Furthermore, virtually all cases of Smith-Magenis syndrome occur de novo, whereas the patient's family included

other mentally retarded siblings, which indicated an inherited abnormality.

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#### Correction

In a recent article on adaptation of Inuit children to a low-calcium diet,<sup>1</sup> the units for the urinary calcium to creatinine ratio were given incorrectly. The units in the text and the table should have been moles per mole (mol/mol). Note that the numeric values for both the study results and the normative values are correct as presented.

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# The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care

Robyn Tamblyn, Allen Huang, Robert Perreault, André Jacques, Denis Roy, James Hanley, Peter McLeod, Réjean Laprise

## Abstract

**Background:** Adverse drug-related events are common in the elderly, and inappropriate prescribing is a preventable risk factor. Our objective was to determine whether inappropriate prescribing could be reduced when primary care physicians had computer-based access to information on all prescriptions dispensed and automated alerts for potential prescribing problems.

**Methods:** We randomly assigned 107 primary care physicians with at least 100 patients aged 66 years and older (total 12 560) to a group receiving computerized decision-making support (CDS) or a control group. Physicians in the CDS group had access to information on current and past prescriptions through a dedicated computer link to the provincial seniors' drug-insurance program. When any of 159 clinically relevant prescribing problems were identified by the CDS software, the physician received an alert that identified the nature of the problem, possible consequences and alternative therapy. The rate of initiation and discontinuation of potentially inappropriate prescriptions was assessed over a 13-month period.

**Results:** In the 2 months before the study, 31.8% of the patients in the CDS group and 33.3% of those in the control group had at least 1 potentially inappropriate prescription. During the study the number of new potentially inappropriate prescriptions per 1000 visits was significantly lower (18%) in the CDS group than in the control group (relative rate [RR] 0.82, 95% confidence interval [CI] 0.69–0.98), but differences between the groups in the rate of discontinuation of potentially inappropriate prescriptions were significant only for therapeutic duplication by the study physician and another physician (RR 1.66, 95% CI 0.99–2.79) and drug interactions caused by prescriptions written by the study physician (RR 2.15, 95% CI 0.98–4.70).

**Interpretation:** Computer-based access to complete drug profiles and alerts about potential prescribing problems reduces the rate of initiation of potentially inappropriate prescriptions but has a more selective effect on the discontinuation of such prescriptions.

Drug-related adverse events are reported to be the sixth leading cause of death<sup>1,2</sup> and contribute to substantial morbidity, particularly in the elderly.<sup>2-9</sup> Inappropriate prescribing has been identified as a preventable cause of at least 20% of drug-related adverse events.<sup>10-16</sup> Elderly patients are at greatest risk of receiving inappropriate prescriptions.<sup>17</sup> Because primary care physicians write approximately 80% of prescriptions for people 65 years of age and older,<sup>18</sup> effective interventions to optimize prescribing in primary care are a priority.

Computerized decision-making support (CDS) for drug management may be an effective method of reducing inappropriate prescribing. Automated surveillance of a patient's drug and disease profile can alert a physician to potentially problematic prescriptions when treatment decisions are being made. There is evidence that CDS in hospital can reduce the incidence of drug-related adverse events,<sup>19-22</sup> improve the cost-effectiveness of drug selection<sup>23-27</sup> and optimize drug-dose calculations.<sup>28-32</sup>

Evaluation of CDS for prescription drug management in primary care settings has been limited.<sup>20</sup> One of the challenges in community-based practice is that there is no central pharmacy to track all drugs prescribed. This is a substantial problem because 40% of elderly patients use more than 1 pharmacy, and 70% have more than 1 prescribing physician.<sup>18</sup> In this study we assessed whether inappropriate prescribing would be reduced when primary care physicians had access to information on all prescriptions dispensed to their elderly patients.

## Methods

### Context

The study was conducted in Quebec, where a universal health insurance program provides complete coverage of medical and hospital services for all residents, as well as comprehensive drug insurance for the elderly. Beneficiary, medical-service and prescription-claims databases maintained by the Régie de l'assurance maladie du Québec (RAMQ)<sup>33</sup> and previously validated<sup>34</sup> were used to



assemble the eligible study population, provide information on prescriptions dispensed, and evaluate the use of both medical services and drugs before and after the implementation of CDS.

## Study design and participants

To test whether CDS would reduce inappropriate prescribing, we conducted a 13-month cluster-randomized controlled trial between January 1997 and February 1998. Sample size was estimated for the cluster trial<sup>35</sup> with a relative reduction in inappropriate prescribing of 30%, type 1 and 2 errors of 1% and 20% respectively and estimates of variation in rates among patients and among physicians.<sup>36</sup> The Collège des médecins du Québec used annual licensure-renewal data to identify eligible physicians: general practitioners 30 years of age or older who had practices in Montreal, spent at least 70% of the week in private fee-for-service practice and had a minimum of 100 elderly patients. Letters of invitation and information sessions were used to recruit physicians. To minimize the possibility of contamination, only 1 physician per group practice was included. Differences in characteristics and prescribing habits of participating and non-participating physicians were assessed with the use of non-identifiable data from the Collège and the RAMQ prescription-claims files.

Patients of participating physicians were eligible if they were 66 years of age or older, had been seen on 2 or more occasions by the study physician in the past year, and were living in the community at the start of the study. The RAMQ provided a list of eligible patients to each physician and a total count of patients per practice to the investigators. With the consent of the patient, personal information was provided to the RAMQ and the researchers.

## Randomization and blinding

Physicians were stratified by age (3 categories), sex, language (French, English), location of medical school of graduation (foreign, Canada or the United States) and number of elderly patients (less than 118, 118 or more).

Two months before CDS was implemented, after more than 90% of patients had been recruited, half of the physicians within each stratum were randomly assigned to the CDS group and the other half to the control group. Physicians and patients were not told the specific outcomes of the study but were aware of which group they had been assigned to.

## Basic intervention

Each physician was given a computer, a printer, health-record software and dial-up access to the Internet. The health-record software documented health problems and medications prescribed. For each patient, trained personnel developed a health-problem list by abstracting, coding and entering data from the primary care physician's chart, using a standardized form that documented the 26 health problems related to the targeted drug-disease contraindications, as well as other chronic health problems. Concordance in identification of key target problems between the chief abstractor and the abstraction team was 86.1% ( $\kappa = 0.56$ ) in independent audits of a systematic sample of 1138 charts.

## CDS group

Physicians in the CDS group obtained information on each patient by downloading updates of dispensed prescriptions from the RAMQ drug-insurance program. All retail pharmacies have a data link to the RAMQ for online prescription adjudication, which provided a daily update of all prescriptions dispensed for each patient. These data were integrated into the patient's health record and categorized as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly, a list established previously by expert consensus.<sup>37</sup> 26 problems were related to drug-disease contraindications, 23 to drug interactions, 17 to drug-age contraindications, 3 to duration of therapy and 90 to therapeutic duplication. The alerts appeared when the electronic chart was opened, when prescription-record updates were downloaded from the RAMQ, and when current health problems and prescriptions were recorded by the physician in the chart. Each alert message identified the nature of the problem and possible consequences and suggested alternative therapy in accordance with the expert consensus.

## Outcomes

The primary outcome measures were initiation and discontinuation rates of the 159 prescription-related problems. Records of prescriptions dispensed and medical visits (from the RAMQ prescription-claims and medical-service-claims files and from the abstracted office-chart data) were used to assess outcomes to ensure that the same measures were used for the 2 groups of physicians. Discontinuation rates were calculated for patients who had been given at least 1 inappropriate prescription in the 2 months before the study began. An inappropriate prescription was considered to have been discontinued by the study physician if it had not been refilled within 2 months after the prescription end date and if there had been a visit to the study physician before or during the month of the prescription end date. Initiation rates were calculated for the remaining patients from the prescriptions written by the study physician for 1 or more of the 159 prescription-related problems during the 13-month study period. The denominator for each rate, measured by medical-service claims, was the number of patient visits to the study physician during the study period; this number provided an accurate assessment of differences in opportunity to initiate or discontinue inappropriate prescriptions. Follow-up was terminated after an inappropriate prescription had been initiated or discontinued. Secondary outcomes were initiation and discontinuation rates by type of prescribing problem and discontinuation rates by source of prescription.

## Analysis

Descriptive statistics were used to summarize the characteristics of the physicians and patients in the 2 groups. The association between the weekly frequency of prescription downloads and the number of weeks of computer problems was estimated with Pearson correlation. Poisson regression, within the framework of a generalized estimating equation, was used to determine if there were differences between the 2 groups of physicians in the rates of initiation and discontinuation of inappropriate prescriptions, based on an intention-to-treat

analysis.<sup>38,39</sup> The patient was the unit of analysis. Physicians were identified as the clustering factor within which rates were examined, and an exchangeable correlation structure was used to take into account the dependence of observations for patients of the same physician. Empirical standard errors were used to take into account the overdispersion in estimated rates.

## Results

Of the 440 eligible physicians, 127 (28.9%) agreed to participate, and the first 107 were included in the study (Fig. 1). Participating physicians were slightly younger than those who did not participate (mean age 46.5 v. 49.4 years). However, participating and nonparticipating physicians were similar in the average number of prescriptions per elderly patient (35.6 v. 33.8) and the prevalence of inappropriate prescribing (18.9% v. 18.8%) in the 18 months before the study start date. There were no differences in characteristics between the CDS and control groups (Table 1).

Of the 20 109 eligible patients, 12 560 (62.4%) agreed to participate. Those in the CDS group were more likely than those in the control group to be men, to have made fewer visits to their primary care physician and to have received fewer prescriptions from their primary care physician (Table 1).

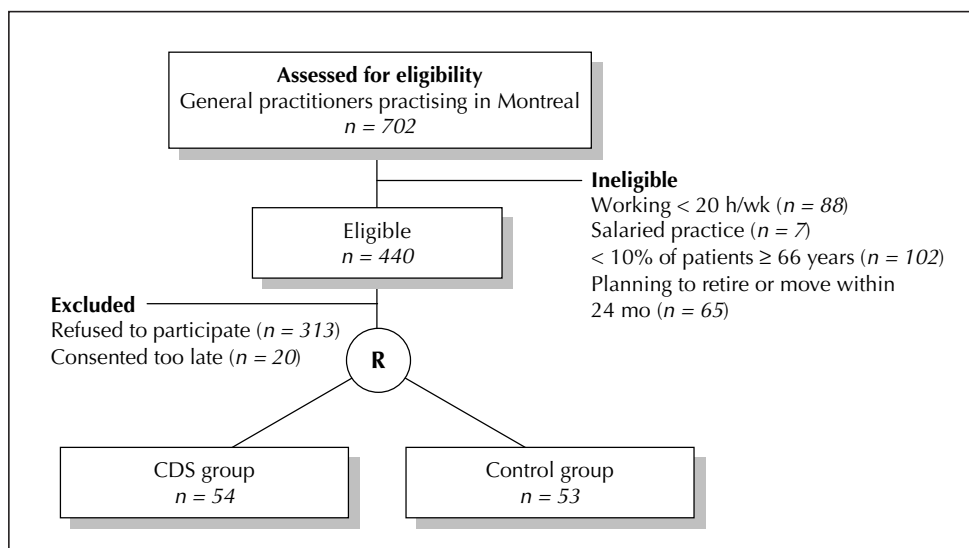
At the beginning of the study, there was at least 1 prescribing problem for 33.3% of the patients in the control group and 31.8% of those in the CDS group (Table 2). For 20.4% and 18.8%, respectively, the problems were attributable to a study physician, for 3.3% and 3.2% they were attributable to a study physician plus another physician,

and for 8.3% and 9.1% they were attributable to another physician. In both groups, drug–disease contraindications were the most common prescribing problems, followed by drug–age contraindications and excessive duration of therapy (Table 2).

Two unforeseen factors influenced the effectiveness of the CDS. First, copayments for prescription drugs were increased when the study began, which resulted in a 9% reduction in prescription drug use by the elderly.<sup>40</sup> Second, 22% of the physicians experienced frequent hardware or software failure in the early months of the study; the proportion declined to 4% by month 6. Physicians in the CDS group downloaded prescription information in 81% of the study weeks; however, those who had more computer problems downloaded information less often ( $r = -0.31$ ).

During the study, the rate of initiation of an inappropriate prescription was significantly lower (18%) in the CDS group than in the control group (Table 3). This trend was evident for drug–disease contraindications, drug–age contraindications, excessive duration of therapy and therapeutic duplication and was significant for drug–age contraindications and excessive duration of therapy.

CDS had no significant impact on the discontinuation of pre-existing inappropriate prescriptions (Table 4). Although more patients in the CDS group than in the control group had all inappropriate prescriptions discontinued (47.5% v. 44.5%; or 35.5 v. 32.1 per 1000 visits; relative rate [RR] 1.14; 95% confidence interval [CI] 0.98–1.33), the 14% difference was not statistically significant. The only substantially higher discontinuation rate



**Fig. 1: Selection and assignment of study population.** List of Montreal general practitioners provided by the Collège des médecins du Québec. Random assignment was within strata defined by physician age (34–44, 45–48, 49–68 years), language (French, English), sex, number of elderly patients (< 118, ≥ 118) and location of medical school of graduation (foreign, Canada or the United States). CDS = computerized decision-making support.

for a specific prescribing problem was for drug interactions: 68.6 v. 51.5 per 1000 visits in the CDS and control groups respectively.

Physicians in the CDS group were able to identify excessive duration of therapy, therapeutic duplication and drug interaction resulting from more than one source of prescribing for the same patient. Most of the therapeutic duplications and drug interactions occurred because prescriptions were written by both the study physician and another physician or another physician alone (Table 5). Discontinuation rates in the CDS group were systematically higher for problems created by the combination of

prescriptions from study physicians and other physicians than for the other types of prescription problems. An exception was with drug interactions: the relative difference in discontinuation rates between CDS and control physicians was highest for problematic prescriptions written by the study physician, followed by problematic prescriptions written by both the study physician and another physician.

Adjusting for patient characteristics (Table 1) did not modify differences in initiation and discontinuation rates between the CDS and control groups. However, a physician's previous computer experience influenced the effectiveness of CDS. Among experienced computer users the

**Table 1: Characteristics of physicians and patients in study of effectiveness of computerized decision-making support (CDS) in reducing inappropriate prescribing**

Variable	Practice group	
	CDS	Control
<b>Physician characteristics</b>		
No.	54	53
Mean age (and SD), yr	48.0 (6.7)	46.2 (5.6)
Sex, % (and no.)		
Male	81.5 (44)	83.0 (44)
Female	18.5 (10)	17.0 (9)
First language, % (and no.)		
French	74.1 (40)	73.6 (39)
English	25.9 (14)	26.4 (14)
Medical school of graduation, % (and no.)		
Foreign	22.2 (12)	22.6 (12)
North American	77.8 (42)	77.4 (41)
Computer experience,* % (and no.)		
Beginner	40.7 (22)	41.5 (22)
Experienced	59.3 (32)	58.5 (31)
<b>Practice characteristics</b>		
Eligible elderly patients, mean no. (and SD)	214.3 (101.7)	214.5 (114.5)
Eligible patients participating in study, mean % (and SD)	64.6 (16.6)	65.6 (15.7)
<b>Characteristics of participating patients</b>		
No.	6284	6276
Sex, % (and no.)		
Male	38.8 (2439)	35.8 (2248)
Female	61.2 (3845)	64.2 (4028)
Mean age (and SD), yr	75.4 (6.3)	75.3 (6.2)
Mean values per patient (and SD) in 18 mo before study		
Total no. of physician visits	20.7 (19.5)	21.2 (20.5)
No. of visits to primary care physician	7.7 (5.3)	8.3 (5.5)
% of visits to primary care physician	49.5 (26.4)	51.4 (25.5)
Total no. of prescriptions	51.0 (43.1)	53.3 (40.7)
No. of prescriptions from primary care physician	30.3 (32.4)	32.4 (31.8)
No. of prescribing physicians	3.3 (2.3)	3.3 (2.2)
No. of pharmacies	1.8 (1.1)	1.8 (1.2)

Note: SD = standard deviation.

\*Physicians were considered beginners if they had no experience using a computer for word-processing, Internet activity, literature searches, or any other recreational or work-related activity. Physicians who had used computers for any of the aforementioned activities were considered to be experienced.

**Table 2: Prevalence of potentially inappropriate prescribing in the 2-month period before the study**

Prescribing problem	% (and no.) of participating patients with prescribing problems; practice group			
	Overall		Attributable only to study physician	
	CDS (n = 6284)	Control (n = 6276)	CDS (n = 6284)	Control (n = 6276)
<b>Any of 159 clinically relevant problems</b>	31.8 (1996)	33.3 (2092)	18.8 (1180)	20.4 (1282)
Mean no. of problems per patient (and SD)	1.36 (0.64)	1.38 (0.65)	1.25 (0.53)	1.28 (0.55)
<b>Drug–disease contraindication</b>	17.2 (1080)	16.7 (1047)	10.5 (659)	10.1 (637)
NSAID–hypertension	6.5 (410)	6.1 (383)	4.6 (292)	4.2 (264)
NSAID–peptic ulcer disease	3.2 (198)	3.6 (229)	2.0 (128)	2.4 (153)
<b>Drug–age contraindication</b>	11.3 (711)	14.2 (891)	8.0 (505)	11.1 (699)
Long-half-life benzodiazepine	5.3 (331)	6.7 (422)	4.0 (252)	5.2 (327)
Active-metabolite TCA	3.6 (226)	4.0 (252)	2.5 (157)	3.0 (191)
<b>Excessive duration of therapy</b>	8.2 (515)	8.7 (547)	5.9 (371)	6.4 (401)
Benzodiazepine > 90 d	5.2 (330)	6.1 (382)	3.8 (242)	4.5 (284)
NSAID > 60 d	3.2 (204)	3.2 (198)	2.2 (142)	2.2 (139)
<b>Therapeutic duplication</b>	3.8 (238)	4.1 (255)	1.0 (60)	1.0 (63)
Salicylate	0.7 (42)	0.9 (55)	0.1 (7)	0.2 (11)
<b>Drug interaction</b>	2.6 (166)	2.4 (149)	0.7 (46)	0.8 (49)

Note: NSAID = nonsteroidal anti-inflammatory drug, TCA = tricyclic antidepressant.

**Table 3: Potentially inappropriate prescribing started by the study physicians during the 13-month study period**

Prescribing problem and practice group	No. of patients at risk*	No. of visits at which inappropriate prescribing could have started†	No. of patients given an inappropriate prescription	No. of inappropriate prescriptions started per 1000 visits	Relative rate‡ (and 95% CI)
<b>Any</b>					
CDS	4767	17 246	755	43.8	0.82 (0.69–0.98)
Control	4603	17 430	909	52.2	Reference
<b>Drug–disease contraindication</b>					
CDS	5520	23 869	396	16.6	0.89 (0.72–1.10)
Control	5469	25 597	470	18.4	Reference
<b>Drug–age contraindication</b>					
CDS	5727	26 423	283	10.7	0.77 (0.59–1.00)
Control	5516	27 307	375	13.7	Reference
<b>Excessive duration of therapy</b>					
CDS	5791	27 056	361	13.3	0.78 (0.61–0.99)
Control	5768	29 199	499	17.1	Reference
<b>Therapeutic duplication</b>					
CDS	6193	29 170	179	6.1	0.87 (0.69–1.11)
Control	6188	31 846	217	6.8	Reference
<b>Drug interaction</b>					
CDS	6221	30 847	49	1.6	1.12 (0.68–1.87)
Control	6212	33 906	51	1.5	Reference

Note: CI = confidence interval.

\*No. of participating patients in the study physician's practice who had no prescribing problem in the 2-month period before the start of the study who visited the study physician during the study period.

†No. of ambulatory visits to the study physician before the dispensing date of a potentially inappropriate prescription or during the study period for patients for whom no potentially inappropriate prescriptions were started.

‡Relative rates were estimated by means of Poisson regression within a generalized estimation equation framework. The patient was the unit of analysis. Physicians were identified as the clustering factor within which rates were examined, and an exchangeable correlation structure was used to take into account the dependence of observations for patients of the same physician.



rate of initiation of inappropriate prescriptions was 30% lower in the CDS group than in the control group (RR 0.70, 95% CI 0.55–0.89). Among the computer beginners the rate of initiation of inappropriate prescriptions was virtually identical in the 2 groups (RR 1.03, 95% CI 0.82–1.29). The same trend was evident for discontinuation rates (RR for experienced users 1.17 and for beginners 0.93), but this apparent modification of the effectiveness of CDS by computer experience was not significant (interaction term: study group\*computer experience,  $p = 0.32$ ).

## Interpretation

This study illustrated the magnitude of the challenge of coordinating health care for elderly patients in an urban setting. Primary care physicians provided only half of all medical services to their elderly patients, who, on average, received prescriptions from at least 3 other physicians and filled those prescriptions at several pharmacies. We addressed the problem of incomplete information on current drug use by using existing prescription-claims information to provide a complete drug profile for each patient. This was a lower-cost solution than using pharmacy-information networks<sup>41,42</sup> or smart cards.<sup>43</sup>

The study also addressed one of the chief criticisms of software screening for drug interactions: clinical relevance.<sup>44</sup> We limited alerts to interactions judged by a consensus panel to produce clinically important adverse effects, and we expanded surveillance to include clinically relevant drug–disease contraindications, drug–age contraindications, excessive duration of therapy and therapeutic duplication.<sup>37</sup> The alert system was limited, however, by the absence of treatment indications (needed to assess prescription appropriateness) and the absence of weight, height and data on renal function (needed to assess dosage appropriateness). Further, because lower levels of evidence are used to identify potentially problematic prescriptions, the effect of reducing inappropriate prescribing on health outcome remains unknown.

The selectively greater impact of CDS on the initiation of inappropriate prescriptions than on the discontinuation of existing ones could be the result of inaccurate measurement of discontinuation or type 1 errors from multiple comparisons. However, the same pattern was observed in a drug review trial,<sup>45</sup> in which physicians were reluctant to stop drug therapy, even when they agreed with the consulting pharmacist's recommendation, because of concerns for patient resistance or discomfort in discontinuing ther-

**Table 4: Potentially inappropriate prescribing discontinued by the study physicians during the 13-month study period**

Prescribing problem and practice group	No. of patients with inappropriate prescriptions before start of study*	No. of visits at which inappropriate prescriptions could have been discontinued†	No. of patients for whom inappropriate prescriptions were discontinued	No. of discontinuations of inappropriate prescriptions per 1000 visits	Relative rate (and 95% CI)
<b>Any</b>					
CDS	1578	14 043	1002	71.4	1.06 (0.89–1.26)
Control	1670	15 586	1045	67.4	Reference
<b>Drug–disease contraindication</b>					
CDS	933	8 818	552	62.6	1.08 (0.85–1.36)
Control	881	9 024	522	57.9	Reference
<b>Drug–age contraindication</b>					
CDS	636	8 101	330	40.7	0.94 (0.79–1.13)
Control	812	9 351	401	42.9	Reference
<b>Excessive duration of therapy</b>					
CDS	506	6 075	196	32.3	1.00 (0.77–1.29)
Control	548	6 372	208	32.6	Reference
<b>Therapeutic duplication</b>					
CDS	150	461	146	317.1	0.94 (0.59–1.51)
Control	176	509	170	334.0	Reference
<b>Drug interaction</b>					
CDS	148	1 546	106	68.6	1.33 (0.90–1.95)
Control	134	1 729	89	51.5	Reference

\*No. of patients with an inappropriate prescription in the 2 months before the start of the study who visited the study physician during the study period. During the study period 418 (20.9%) of the 1996 patients in the CDS group and 422 (20.2%) of the 2092 in the control group with an inappropriate prescription preceding the study had that prescription discontinued before the first visit to the study physician, died or entered long-term care.

†No. of ambulatory visits to the study physician before and including the month in which the inappropriate prescription was discontinued or during the study period for patients for whom no inappropriate prescription was discontinued.

Table 5: Discontinuation rates for prescribing problems that can be created by multiple prescribing physicians

Problem and study group (and no. of patients receiving inappropriate prescriptions)	Inappropriate prescribing by study physician alone				Inappropriate prescribing by study physician and another physician				Inappropriate drug prescribed by another physician alone			
	% (and no.) of all prescribing problems	No. of discontinuations per 1000 visits	Relative rate (and 95% CI)		% (and no.) of all prescribing problems	No. of discontinuations per 1000 visits	Relative rate (and 95% CI)		% (and no.) of all prescribing problems	No. of discontinuations per 1000 visits	Relative rate (and 95% CI)	
<b>Excessive duration of therapy</b>												
CDS (506)	63.6 (322)	63.7	1.06 (0.8–1.5)		13.4 (68)	16.3	1.43 (0.7–3.1)		22.9 (116)	46.4	1.09 (0.63–1.89)	
Control (548)	65.5 (359)	59.7	Reference		13.0 (71)	11.4	Reference		21.5 (118)	42.3	Reference	
<b>Therapeutic duplication</b>												
CDS (148)	21.6 (32)	388.1	0.78 (0.3–2.2)		35.8 (53)	519.6	1.66 (0.99–2.79)		42.5 (63)	662.5	1.10 (0.65–1.85)	
Control (174)	17.8 (31)	495.7	Reference		40.2 (70)	312.1	Reference		42.0 (73)	585.6	Reference	
<b>Drug interaction</b>												
CDS (148)	29.7 (44)	165.1	2.15 (0.98–4.70)		36.5 (54)	74.6	1.33 (0.74–2.54)		33.8 (50)	81.8	0.75 (0.35–1.59)	
Control (133)	35.3 (47)	76.5	Reference		36.8 (49)	56.1	Reference		27.8 (37)	122.0	Reference	

apy prescribed by another physician. Physicians in the CDS group expressed similar concerns, particularly in relation to drugs prescribed by other physicians. As with a Dutch study,<sup>46</sup> we found that the perception of responsibility for patients' treatment varied among the physicians. This lack of clarity in responsibility likely had an impact on the action taken when physicians identified problematic prescriptions.

Poor technical performance is a known deterrent to the use of computer-based systems.<sup>47–49</sup> Hardware and software failures reduced the frequency of computer use and likely the potential benefits of the CDS. An extensive infrastructure was required to resolve numerous technical problems with the computers and local patient databases. This “heavy client model” is not a viable solution for community-based computer networks. Handheld “personal digital assistants” and wireless technologies, coupled with architectures that provide centralized services for applications and data,<sup>50</sup> will provide community-based physicians with less labour-intensive technologic solutions in patient care.

Future research should assess the role of more robust information technologies in primary care, as well as the impact of inappropriate prescriptions on health outcomes.

This article has been peer reviewed.

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# Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis

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## Abstract

**Background:** Cholinesterase inhibitors (ChEIs) are the only drugs marketed for the treatment of Alzheimer's disease. Despite numerous randomized controlled trials, the efficacy and safety of this group of medications has not been quantified. Our objective was to quantitatively summarize data on the efficacy and safety of ChEIs in Alzheimer's disease in a format useful to clinicians.

**Methods:** We performed a meta-analysis of randomized, double-blind, placebo-controlled, parallel-group trials of currently marketed ChEIs (donepezil, rivastigmine and galantamine), used in therapeutic doses for at least 12 weeks, from which a cognitive outcome was reported. Studies were identified through 3 electronic databases searched to May 2002, pharmaceutical companies and journals. We extracted the proportions of subjects who responded, experienced adverse events, discontinued treatment for any reason or discontinued treatment because of adverse events.

**Results:** In the 16 identified trials that met the inclusion criteria, 5159 patients were treated with a ChEI and 2795 received a placebo. The pooled mean proportion of global responders to ChEI treatment in excess of that for placebo treatment was 9% (95% confidence interval [95% CI] 6%–12%). The rates of adverse events, dropout for any reason and dropout because of adverse events were also higher among the patients receiving ChEI treatment than among those receiving placebo, the excess proportions being 8% (95% CI 5%–11%), 8% (95% CI 5%–11%) and 7% (95% CI 3%–10%), respectively. The numbers needed to treat for 1 additional patient to benefit were 7 (95% CI 6–9) for stabilization or better, 12 (95% CI 9–16) for minimal improvement or better and 42 (95% CI 26–114) for marked improvement; the number needed to treat for 1 additional patient to experience an adverse event was 12 (95% CI 10–18).

**Interpretation:** Treatment with ChEIs results in a modest but significant therapeutic effect and modestly but significantly higher rates of adverse events and discontinuation of treatment. The numbers needed to treat to benefit 1 additional patient are small.

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Alzheimer's disease (AD) is an irreversible, progressive disorder characterized by neuronal deterioration that results in loss of cognitive functions, such as memory, communication skills, judgement and reasoning. AD is diagnosed on the basis of the development of multiple cognitive deficits (impairments of both memory and cogni-

tion at a minimum) and significant impairment of social and occupational functioning, with gradual onset, continuing decline and lack of alternative explanations (e.g., delirium, other central nervous system or psychiatric conditions, systemic diseases).<sup>1</sup> According to the Canadian Study of Health and Aging, 1 in 20 Canadians over age 65 has AD.<sup>2</sup> Thus, in 2001 an estimated 238 000 Canadians over 65 had AD,<sup>2</sup> and 60 000 new cases were expected per year.<sup>3</sup>

The Canadian Consensus Conference on Dementia<sup>4-6</sup> and others<sup>7</sup> recommend cholinesterase inhibitors (ChEIs) for standard symptomatic treatment of AD. Currently 3 “second-generation” ChEIs — donepezil, galantamine and rivastigmine — are marketed in Canada for treating the cognitive symptoms of mild to moderate AD. The “first-generation” ChEIs (tacrine, velnacrine and physostigmine) had a short duration of action and lacked specificity for acetylcholinesterase.<sup>8</sup>

A number of randomized controlled trials have evaluated the efficacy and tolerability of the second-generation ChEIs,<sup>9-25</sup> reporting that 18%<sup>20</sup> to 48%<sup>14</sup> of treated patients improved in global measures. Aside from the wide range, response was defined with a cognitive scale that is difficult to translate into clinically meaningful information. The benefit offered by ChEIs, though statistically significant, were described as moderate at best.<sup>8,26-28</sup>

Meta-analysis is a statistical technique often used to quantitatively incorporate outcomes of different studies.<sup>29</sup> Although the data from trials of individual second-generation ChEIs such as donepezil and galantamine<sup>30</sup> have been combined, there is no report in the literature of a meta-analysis of data for all 3 medications. One analysis determined the numbers needed to treat for donepezil and rivastigmine;<sup>31</sup> however, only 5 studies were included, tolerability was not addressed, and trials of galantamine were not yet available. A more recent meta-analysis addressed behavioural and functional outcomes only, included irrelevant ChEIs and did not calculate numbers needed to treat.<sup>32</sup>

The primary care physician is expected to communicate realistic information concerning treatment options and expectations to patients with AD and their families.<sup>5</sup> Therefore, we performed a meta-analysis of second-generation ChEIs to quantify the therapeutic effect of these medications, estimate tolerability and calculate the number needed to treat to benefit 1 additional patient.



## Methods

The population to be studied was adults with AD diagnosed on the basis of standardized criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition,<sup>1</sup> or the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.<sup>33</sup> Treatment included therapeutic doses for at least 12 weeks (the minimum period needed to see a treatment effect) of any of the available second-generation ChEIs. Cognitive outcomes must have been measured, on any validated scale. We accepted only original reports (not secondary publications of previously reported data) of randomized, double-blind, placebo-controlled, parallel-group clinical trials.

We searched the English-language literature, using MEDLINE and EMBASE, from January 1980 to May 2002, since the earliest publication concerning clinical use of a second-generation ChEI appeared in the 1990s.<sup>34</sup> Key words were cholinesterase inhibitor AND Alzheimer, and the limits were randomized controlled trials, English and human. Searches were also conducted for individual ChEIs (key words donepezil, E2020 or Aricept; rivastigmine, ENA 713 or Exelon; galantamine or galanthamine; AND Alzheimer). The Cochrane databases were searched from inception. Recent review articles and published reports of clinical trials were manually cross-referenced, as were all references and bibliographies from retrieved articles.

"Differential" photocopying was used to blind raters as to authors and their location and as to date and journal of publication to reduce potential bias. First, 2 raters reviewed the Methods section of all articles identified. Articles meeting the inclusion criteria were then rated on quality by 2 raters using the Jadad scale,<sup>35</sup> which is simple to use and has been validated.<sup>35-37</sup> Disagreements regarding inclusion and quality were settled through consensus discussion.

From the Results section of the included articles 3 raters extracted the numbers of patients in the following categories: responding or not responding to treatment, reporting any adverse event, discontinuing treatment ("dropping out") for any reason and dropping out because of adverse events. Discrepancies were managed through consensus discussion among all the reviewers.

Data relating to responders were extracted with the use of 2 definitions. *Global responders* were defined as subjects rated as "improved" (i.e., excluding "unchanged" but including "minimal improvement" and better) on a global assessment scale (Clinical Global Impression of Change [CGIC]<sup>38</sup> or Clinician Interview-Based Impression of change plus caregiver input [CIBIC+]<sup>39</sup>); the intent-to-treat (ITT) population was the denominator for proportions. This meta-analysis focused on global improvement since it is an important outcome and a regulatory requirement that includes treatment effects not captured on strictly cognitive scales, and it measures clinically relevant change.<sup>28,40</sup> *Cognitive responders* were defined as subjects with a 4-point or greater improvement on the Alzheimer's Disease Assessment Scale-cognitive portion (ADAS-cog);<sup>41</sup> the ITT population was the denominator for proportions. This is the standard definition of responder, as first defined by the US Food and Drug Administration.<sup>42</sup> The denominators for the proportions of subjects reporting any adverse event, dropping out for any reason or dropping out because of adverse events were also the ITT population. Manufacturers were contacted for data missing from the published reports.

For the main analyses, we identified the numbers of responders and nonresponders in each of the 2 groups within each study, calculated response rates for the treated patients ( $R_t$ ) and placebo

recipients ( $R_p$ ), then calculated an effect size for each study: the difference in response rates ( $D_i = R_t - R_p$ ).

Outcomes ( $D_i$  values) were pooled across the studies with the random-effects meta-analytic model developed by Cochran,<sup>43,44</sup> which essentially weights each study's effect size by its sample size and by the between-study variance. This model yields a pooled mean point estimate and a 95% confidence interval (95% CI). Thus, it generally creates wider confidence intervals than other methods.<sup>45</sup> However, because it incorporates between-study differences, it tends to mitigate discrepant results when there is a great deal of variation. Such variation is to be expected because of the wide variations found in this disease and in its response to treatment.

This procedure was followed for global response, cognitive response and other outcomes of interest, which included adverse events, dropout for any reason and dropout because of adverse events. For this research, adverse events were defined as any adverse event that emerged during treatment, as reported by the original authors.

To evaluate publication bias, we generated a funnel plot comparing effect size with sample size<sup>46</sup> and evaluated the results with the Begg and Mazumdar adjusted rank correlation test.<sup>47</sup>

The number needed to treat (NNT) and the number needed to harm (NNH) were calculated according to the method of Cook and Sackett.<sup>48</sup> The NNT is the reciprocal of the risk difference when the outcome is positive, and the NNH is the reciprocal of the risk difference when the outcome is negative. NNTs were based on the proportion of global responders and NNHs on the proportion of patients reporting adverse events. For studies in which the difference between treatment groups is not statistically significant, CIs may cross zero and, as such, are difficult to characterize; we used the method described by Altman<sup>49</sup> to overcome this difficulty.

We performed subanalyses to assess the impact of ethnicity (Asian v. predominantly white patients), dose, drug, duration of treatment and CGIC definition. Compared with white patients, the Japanese require lower doses of many psychotherapeutic medications<sup>50</sup> and may have a higher rate of response to ChEI therapy.<sup>14</sup> Dosages were grouped according to common prescribing practice or analysis of the literature, or both, as follows: subtherapeutic (donepezil, 1 to 3 mg/d; galantamine, 8 mg/d), low (donepezil, 5 mg/d; rivastigmine, 3 to 6 mg/d), high (donepezil, 10 mg/d; galantamine, 16 to 24 mg/d; rivastigmine, 9 to 12 mg/d) or above that recommended (galantamine, 32 mg/d); low-dose and high-dose groups were compared. Studies were grouped by duration of treatment, with shorter term defined as 12 to 14 weeks and longer term as 24 to 52 weeks. The ChEIs were also grouped by definition of CGIC. The CGIC scale indicates degrees of change from baseline as follows: 1, marked improvement; 2, moderate improvement; 3, minor improvement; and 4, no change. Thus, CGIC<sub>1-4</sub> includes no change and CGIC<sub>1-2</sub> is the strictest definition.

## Results

Of the 40 articles identified in the literature searches, 24<sup>25,34,51-72</sup> were excluded for the following reasons: the article was not an original report of a clinical trial ( $n = 6$ ); the trial was not randomized ( $n = 3$ ), not double-blind ( $n = 5$ ), not of parallel (crossover) design ( $n = 5$ ) or not placebo-controlled ( $n = 5$ ); treatment lasted less than 12 weeks ( $n =$

4); there was no measurement of cognitive outcome ( $n = 3$ ); and subjects did not have AD ( $n = 7$ ). The remaining 16 studies met the inclusion criteria<sup>9-24</sup> (Table 1). All 16 studies had a Jadad quality score greater than 3; the median score was 5. These studies examined ChEI therapy in 5159 subjects and placebo treatment in 2795 subjects.

## Efficacy

The proportion of global responders could be extracted from 9 studies,<sup>10-12,14,18,20,21,23,24</sup> involving 4468 subjects of either predominantly white (8 studies) or Japanese (1 study) patients. Heterogeneity among the studies was statistically

significant ( $\chi^2 = 23.8$ ,  $p = 0.002$ ); the study by Homma and colleagues<sup>14</sup> was by far the greatest contributor to the heterogeneity and was the only study done exclusively on Japanese patients. Thus, a subanalysis was performed on the white-patient-based studies, which involved 4205 subjects and were not heterogeneous (Table 2).

The pooled mean proportion of global responders to ChEI treatment in excess of that for placebo treatment in the 8 studies was 9% (95% CI 6%–12%) (Table 2). Fig. 1 shows the contribution of individual studies. A funnel plot indicated no relationship between sample size and effect size.

The proportion of cognitive responders could be extracted from 5 studies,<sup>10,18,21,23,24</sup> involving 2419 subjects. The

**Table 1: Included double-blind, randomized, placebo-controlled trials of therapy with cholinesterase inhibitors (ChEIs) for mild to moderate Alzheimer's disease\***

First author, publication year	ChEI studied; doses; duration of treatment	No. of subjects randomly assigned, total (ChEI, placebo), no. of subjects completing study	Scales(s) used to assess response†	Jadad quality score‡
Rogers, <sup>9</sup> 1996	Donepezil; 1, 3, 5 mg/d; 12 wk	161 (121, 40), 141	ADAS-cog, CGIC, MMSE	4
Rogers, <sup>11</sup> 1998a	Donepezil; 5, 10 mg/d; 12 wk	468 (315, 153), 412	ADAS-cog, CDR-SB, CIBIC+, MMSE, QoL	4
Rogers, <sup>10</sup> 1998b	Donepezil; 5, 10 mg/d; 24 wk	473 (311, 162), 368	ADAS-cog, CDR-SB, CIBIC+, MMSE, QoL	5
Burns, <sup>12</sup> 1999	Donepezil; 5, 10 mg/d; 24 wk	818 (544, 274), 631	ADAS-cog, CDR-SB, CIBIC+, IDDD	4
Winblad, <sup>13</sup> 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 52 wk	286 (142, 144), 192	ADL, GBS, GDS, MMSE, NPI	5
Homma, <sup>14</sup> 2000	Donepezil; 5 mg/d; 24 wk	263 (134, 129), 228	ADAS-Jcog, CDR-SB, CMCS, J-CGIC, MENFIS	4
Mohs, <sup>15</sup> 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 54 wk	431 (217, 214), 111	ADFACS, CDR-SB, MMSE	5
Feldman, <sup>16</sup> 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 24 wk	290 (144, 146), 247	CIBIC+, DAD, FRS, MMSE, NPI, SIB	5
Agid, <sup>17</sup> 1998	Rivastigmine; 4, 6 mg/d; 13 wk	402 (269, 133), 357	CGIC	5
Rösler, <sup>18</sup> 1999	Rivastigmine; 1–4, 6–12 mg/d; 26 wk	725 (486, 239), 581	ADAS-cog, CIBIC+, GDS, MMSE, PDS	5
Corey-Bloom, <sup>19</sup> 1998	Rivastigmine; 1–4, 6–12 mg/d; 26 wk	699 (464, 235), 545	ADAS-cog, CIBIC+, GDS, MMSE	5
Raskind, <sup>20</sup> 2000	Galantamine; 24, 32 mg/d; 6 mo	636 (423, 213), 438	ADAS-cog, CIBIC+, DAD, MMSE	5
Wilcock, <sup>21</sup> 2000	Galantamine; 24, 32 mg/d; 6 mo	653 (438, 215), 525	ADAS-cog, CIBIC+, DAD	5
Tariot, <sup>22</sup> 2000	Galantamine; 8, 16, 24 mg/d; 5 mo	978 (692, 286), 779	ADAS-cog, ADCS/ADL, CIBIC+, NPI	5
Rockwood, <sup>24</sup> 2001	Galantamine; 24, 32 mg/d; 3 mo	386 (261, 125), 288	ADAS-cog, CIBIC+, DAD, NPI	5
Wilkinson, <sup>23</sup> 2001	Galantamine; 18, 24, 36 mg/d; 3 mo	285 (198, 87), 206	ADAS-cog, CGIC, PDS	5

\*Except in the study of Feldman and coworkers, who studied treatment of moderate to severe dementia.

†ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADAS-Jcog = Alzheimer's Disease Assessment Scale–cognitive subscale, Japanese version; ADCS/ADL = AD Cooperative Study Activities of Daily Living; ADFACS = AD Functional Assessment and Change Scale; ADL = Activities of Daily Living; CDR-SB = Clinical Dementia Rating–Sum of the Boxes; CGIC = Clinical Global Impression of Change; CIBIC+ = Clinician's Interview-Based Impression of change plus caregiver input; CMCS = Caregiver-rated Modified Crichton Scale; DAD = Disability Assessment for Dementia; FRS = Functional Rating Scale; GBS = Gottfries–Brane–Steen; GDS = Global Deterioration Scale; IDDD = Modified Interview for Deterioration in Daily Living Activities in Dementia; J-CGIC = Japanese version of CGIC; MENFIS = Mental Function Impairment Scale; MMSE = Mini-Mental Status Examination; NPI = Neuropsychiatric Inventory; PDS = Progressive Deterioration Scale; QoL = Quality of Life; SIB = Severe Impairment Battery.

pooled mean proportion of cognitive responders to ChEI treatment in excess of that for placebo treatment was 10% (95% CI 4%–17%) (Table 2). The studies were heterogeneous in this analysis, but when the study by Rösler and associates,<sup>18</sup> which compared high- and low-dose rivastigmine and found a low proportion of ChEI responders (19%), was excluded, the studies were not heterogeneous ( $\chi^2 = 4.2$ ,  $p = 0.24$ ); pooling the data from the remaining 4 studies showed a therapeutic effect of 14% (95% CI 8%–18%). There was no obvious reason in the way the Rösler study was designed or conducted for a lower rate of response; furthermore, the global response was not different from that in the other studies. Thus, the heterogeneity remains unexplained.

Safety

The proportion of subjects in whom any adverse event emerged during treatment could be extracted from 14 stud-

ies.<sup>9,10,12–18,20–24</sup> Compared with those receiving placebo, significantly more subjects receiving ChEI treatment had adverse events (8%), dropped out (8%) and dropped out because of adverse events (7%) (Table 2). There was significant heterogeneity among the studies in all 3 analyses, perhaps because of different titration schedules, protocol differences or simply random variation.

Numbers needed to treat/harm

The number of patients who needed to be treated with a ChEI compared with placebo in order that 1 additional patient demonstrate a global response was found to be 12 (95% CI 9–16) when the studies of non-Asian patients were analyzed and 4 (95% CI 3–6) in the Japanese study. For cognitive response the NNT was 10 (95% CI 8–15). The number needed to harm 1 additional patient (cause adverse events) was 12 (95% CI 10–18).

Table 2: Summary of comparative outcomes, according to data extracted from the included studies and pooled

Outcome	No. of subjects, total (ChEI, placebo)	Mean difference in proportions, % (and 95% CI)	Heterogeneity: $\chi^2$ (and $p$ value)	No. needed to treat/harm (and 95% CI)
Global response*	4205 (2804, 1401)	9 (6, 12)	12.2 (0.10)	12 (9, 16)
Cognitive response†	2419 (1606, 813)	10 (4, 17)	12.7 (0.01)	10 (8, 15)
Adverse events	6784 (4381, 2403)	8 (5, 12)	26.8 (0.01)	12 (10, 18)
Dropout	7691 (5022, 2669)	8 (5, 11)	40.4 (< 0.001)	13 (11, 17)
Dropout due to adverse events	7952 (5154, 2798)	7 (3, 10)	104.3 (< 0.001)	16 (13, 19)

\*Minimal or greater improvement on a standardized global scale, such as the CIBIS+ or the CGIC, in a predominantly Caucasian population.  
†Improvement of 4 or more points on the ADAS-cog.

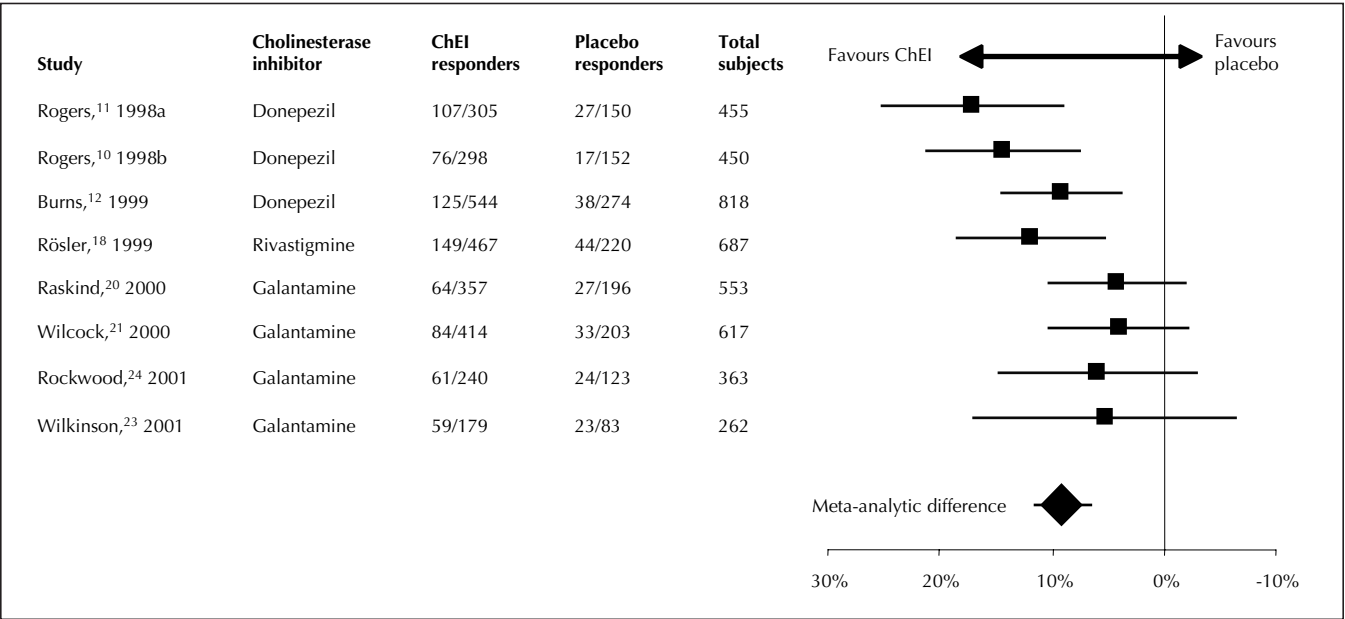


Fig. 1: Global response to treatment with cholinesterase inhibitors (ChEIs) in 8 randomized, double-blind, placebo-controlled, parallel-group trials. The graph indicates the proportions of global responders to ChEI treatment in excess of the proportions responding to placebo for each of the studies and overall, when the data were pooled, with 95% confidence intervals.

## Analysis by drug

For donepezil (3 studies; 1147 subjects treated with the ChEI and 576 treated with placebo) and galantamine (4 studies; 1190 and 605 subjects, respectively) the excess pooled mean proportions of global responders were 13% (95% CI 8%–17%) and 5% (95% CI 1%–8%), respectively. The NNTs were 8 (95% CI 6–12) and 22 (95% CI 12–157), respectively. The treatment effect was significant for both drugs. The single study of rivastigmine indicated an excess proportion of 12% (95% CI 5%–19%).

Dropout rates in excess of those for placebo were lowest for donepezil (3%; 95% CI 1%–6%), followed by rivastigmine (9%; 95% CI 5%–12%) and then galantamine (14%; 95% CI 8%–21%;  $\chi^2 = 17.6$ ,  $p = 0.001$  for heterogeneity). This trend was repeated for adverse events, the excess rates being donepezil 6% (95% CI 2%–9%), rivastigmine 8% (95% CI 1%–10%) and galantamine 12% (95% CI 7%–18%;  $\chi^2 = 12.1$ ,  $p = 0.01$ ), and for dropouts due to adverse events, the excess rates being donepezil 2% (95% CI -1%–4%;  $\chi^2 = 14.0$ ,  $p = 0.05$ ), rivastigmine 9% (95% CI 6%–12%) and galantamine 14% (95% CI 5%–22%). Only the results for galantamine consistently showed heterogeneity, possibly owing to the use of higher-than-recommended doses in some studies.

## Analysis by dose

For global responders, meta-analysis revealed comparable results for low and high ChEI doses, with an excess proportion of 8% for low doses (95% CI 5%–12%; 7 studies, in which 1348 subjects were treated with a ChEI and 1140 with placebo) and 11% for high doses (95% CI 7%–15%; 10 studies, with 1816 and 1739 subjects, respectively), both significantly better than the results with placebo ( $p < 0.001$ ). However, the studies with high ChEI doses showed unexplained heterogeneity ( $\chi^2 = 22.1$ ,  $p < 0.01$ ).

## Analysis by duration of treatment

The excess proportion of global responders was similar after short-term ChEI treatment (11%; 95% CI 5%–16%; 3 studies, in which 724 subjects were treated with a ChEI and 356 with placebo;  $\chi^2 = 19.3$ ,  $p < 0.001$ ) and long-term ChEI treatment (9%; 95% CI 5%–12%; 5 studies, with 2080 and 1045 subjects, respectively;  $\chi^2 = 7.4$ ,  $p = 0.12$ ), although only the long-term trials showed no heterogeneity.

## Analysis by CGIC definition

When the ChEIs were grouped by increasing degree of global improvement, the excess proportions of responsive subjects were 15% for stability or improvement ( $p < 0.001$ , 95% CI 11%–18%; 7 studies, in which 2076 subjects were treated with a ChEI and 1052 with placebo), 9% for any

improvement ( $p < 0.001$ ; Table 2) and 2% for greater than minimal improvement ( $p = 0.04$ , 95% CI 1%–4%; 3 studies, with 1001 and 522 subjects, respectively). There was no significant heterogeneity. The corresponding NNTs were 7 (95% CI 6–9), 12 (95% CI 9–16) and 42 (95% CI 26–114).

## Interpretation

This meta-analysis confirmed that AD patients treated with ChEIs demonstrate statistically significant global improvement compared with those treated with placebo, supporting current guidelines advocating treatment.<sup>4–7</sup> At 9%, the therapeutic benefit is consistent with the modest benefits described in previous qualitative reviews.<sup>8,26–28</sup> The NNT of 12 for 1 additional patient to demonstrate a global response is similar to NNTs previously calculated for AD.<sup>31</sup> By comparison, reported NNTs are 3 for antipsychotics in schizophrenia,<sup>73,74</sup> 4 for antidepressants for depression in medical illness<sup>75</sup> and 29 to 86 (5-year NNT) for antihypertensives to prevent 1 major event (myocardial infarction, stroke or death).<sup>76</sup>

The definition of treatment response had an important impact. Although minimal improvement or better was the definition in the main analysis, many authors use stabilization as the definition in studies lasting 6 months or more.<sup>16,19,20</sup> Our results confirm that ChEI treatment is associated with significantly better global improvement than placebo treatment for all 3 definitions of response (stabilization or better, minimal improvement or better, marked improvement).

Tolerability of ChEIs is an important consideration when evaluating their place in therapy. The proportion of patients in whom adverse events emerged during treatment was only 8% higher in those receiving ChEIs than in those receiving placebo, which shows that these medications are well tolerated. The adverse events were mostly gastrointestinal, and no related deaths were reported. The rates of dropout and dropout due to adverse events were higher with ChEIs than with placebo (8% and 7%, respectively). The rates seen in clinical practice should be lower when dosage is tailored to the individual.

The study of Homma and colleagues<sup>14</sup> detected a very large treatment effect (28%) in a Japanese population receiving low-dose donepezil, which suggests ethnic differences. A lower frequency of the  $\epsilon 4$  gene of apolipoprotein E<sup>77</sup> and differences in major enzymes that metabolize ChEIs, such as cytochrome P450 2D6,<sup>78</sup> in the Japanese may explain this finding. Although no conclusion can be reached on the basis of a single study, our findings support earlier descriptions of purported differences.<sup>14</sup>

Subanalyses of the data for individual ChEIs indicated similar efficacy but differences in tolerability. The excess proportions of subjects who dropped out for any reason and who dropped out because of adverse events were lowest for donepezil and highest for galantamine. A similar



trend was found for overall proportions reporting adverse events. These results must be interpreted with caution, as they were derived from a small number of trials for each medication and were based on a comparison of independent placebo-controlled trials; that is, they were not analyses of head-to-head trials (single trials with random allocation to different ChEIs). When comparing efficacy one must bear in mind that the interrater reliability of global assessment scales may be less well established than that for cognitive measures,<sup>40</sup> and the scales used for global assessment may have different psychometric properties. Differences in tolerability may reflect differences in aspects of study design such as rate of titration or use of galantamine in a dose that is not recommended clinically (32 mg/d), which may not translate to the clinical setting, where doses are determined for the individual.

Although the second-generation ChEIs share the ability to inhibit acetylcholinesterase, their pharmacologic variations may distinguish them. Donepezil inhibits acetylcholinesterase but not butyrylcholinesterase;<sup>79</sup> the latter is thought to be a component of neuritic plaques and tangles,<sup>80,81</sup> the pathological hallmarks of AD. Rivastigmine has central selectivity<sup>82</sup> and inhibits both acetylcholinesterase and butyrylcholinesterase.<sup>83</sup> Galantamine is unique in that it provides allosteric modulation of nicotinic receptors,<sup>84-86</sup> a characteristic postulated to confer disease-modifying benefits.<sup>86</sup> Preliminary head-to-head trials indicate a slightly greater response to donepezil than to galantamine<sup>87</sup> and similar efficacy for donepezil and rivastigmine.<sup>88</sup> Those trials also indicate better tolerability of donepezil than of both galantamine<sup>87</sup> and rivastigmine.<sup>88</sup> Unfortunately, important issues such as open-label design, dose of the comparator and titration rate may account for those results. Nevertheless, our findings were consistent with the findings of those trials.

Our subanalyses indicated similar response to all 3 drugs when studies were grouped by dose or by duration of treatment. Lack of a dose effect could reflect near-maximal cholinesterase inhibition or be the product of an ITT analysis. In such an analysis, if more patients on high doses drop out of the study before responding, the treatment effect will be diluted.<sup>89</sup> In addition, since in AD there is deterioration over time, when the last observation for a subject who dropped out is carried forward, the apparent benefit may be false. The lack of an effect of duration of treatment may reflect the fact that these studies were carried out within a relatively narrow time frame (3 to 12 months). Small numbers and heterogeneity limit the ability to draw meaningful conclusions from these subanalyses.

Meta-analyses may suffer from publication bias, since studies with a statistically positive result are more likely to be published than those with a negative result, resulting in an overestimate of treatment efficacy. In this study, there was no significant relationship between effect size and sample size. However, there may be negative studies with small samples that were not published. In addition, since the

overall ChEI differences over placebo were not heterogeneous, the studies were summarized by single NNT and NNH estimates, with 95% CIs. Since the control rates in the included studies were heterogeneous, a range of NNTs and NNHs may exist for specific patient groups.<sup>90</sup>

Overall, the results of this meta-analysis indicate that ChEI therapy in AD is efficacious compared with placebo therapy. In addition, few patients need to be treated to achieve global improvement in 1 more patient and even fewer to achieve stabilization. For future studies, defining treatment response to ChEIs on the basis of clinically important outcomes, such as delay to institutionalization, maintenance of activities of daily living and reduced caregiver burden,<sup>40</sup> will clarify the benefits of these medications.

This article has been peer reviewed.

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# Canadian Institutes of Health Research budgetary dilemma: unprecedented growth and program reductions

Alan Bernstein

§ See related articles pages 533, 568 and 592

**Editor's note:** For the first time in its 3-year history, the Canadian Institutes of Health Research cannot count on an increase in its overall budget and may thus have to make do with existing funds. As a result, only about \$70 million in uncommitted funds will be available next year. Cuts to programs have been announced, including termination of the Investigator and Senior Investigator Awards. We asked Dr. Alan Bernstein and Dr. Eliot Phillipson to comment.

In this short commentary, I want to accomplish 4 objectives: review the progress that the Canadian Institutes of Health Research (CIHR) has made in realizing the bold mandate we have been given, explain why CIHR is facing possible short-term funding constraints, describe the reasoning that led to the cancellation of CIHR's senior awards programs, and outline CIHR's strategy in response to the current situation.

First, some observations and facts: In 3 short years, we have made significant progress in transforming and re-energizing health research in Canada. The 13 health research institutes are in place, innovative new research and training programs have been launched, our mandate to include all disciplinary approaches to health is well in hand, and new partnerships have been made that have resulted in almost a doubling of partners' contributions. For example, the Strategic Training Initiative in Health Research includes 17 partners that CIHR's 13 institutes brought on board, as well as many more partnerships built by the 84 health research training centres. In short, we are on the way to becoming a strategic research organization and community built on a strong foundation of excellence.

CIHR's grants and awards budget has increased from \$275 million (in the last year of the Medical Research Council of Canada [MRC]) to \$580 million in the current fiscal year. The number of grants funded, of all types, has increased from 2962 to 4256 over the same period, and the value of operating grants awarded in the open competitions each year has increased from \$80 000 to \$105 000. Whereas the greatest increase in dollars invested has been in biomedical sciences (close to \$150 million), the increased investment, relative to the last year of the MRC, has been greatest for health services research (\$16 million, that is, a 16-fold increase) and for research on population health

(\$6 million, that is, a 6-fold increase). Investment in clinical research has increased over 2-fold from about \$43 million in 1999 to \$90 million in 2002, and the average value of a CIHR-funded clinical trial has jumped from \$107 000 to \$275 000 over the same period. Health researchers from all disciplines have benefited from the increased support available from CIHR.

Most of the CIHR budget is locked into long-term commitments such as 3–5-year grants and awards. CIHR has received substantial budget increases over the past 4 years, augmenting the amount of funding available each fiscal year to support new grants and awards, which otherwise would be derived only from the redistribution of funds from grants that have ended. When budget growth stops, the uncommitted funds available to support new grants and awards will shrink to the much smaller amount derived from ending grants. This is the situation CIHR may face at the beginning of fiscal year 2004/05, particularly because the transition in government makes uncertain the timing of any federal budget. Given the risk of a sharp reduction in available funds in 2004/05, relative to the past 3 years, CIHR decided to warn the health research community in advance that it had to introduce strategies to reduce the impact of a decrease in uncommitted funds by suspending some competitions to avoid wasting the time of both applicants and reviewers. This problem is not a result of the formation of the CIHR, the launch of our strategic research initiatives or the amount of the increase to our budget this past year. It occurs because CIHR is financed by the federal government through "lapsing annual appropriations," which means that we know our budget only 1 year at a time, and carrying over of funds from 1 year to the next is not allowed. CIHR could have avoided the current situation if it had not invested all the increases it has received in long-term grants and awards, for example, by allowing some funds to lapse each year, or by funding a large number of grants and awards for only 1 year. Either of these strategies would have been unpopular with the research community, and, equally importantly, would not be the way to realize the vision of CIHR to improve the health of Canadians through excellence in research.

Decisions to suspend programs in the face of financial exigency are difficult and painful. CIHR's scientific direc-



tors and governing council discussed the situation extensively and agreed that our priorities have to be support for the open grants program and the provision of some, although reduced, funding to the 13 institutes to allow them to continue to support research in accordance with their recently developed strategic plans. Lower priority must go to areas of research support where there are other federal sources of funding.

Since CIHR was established, other federal initiatives have improved the environment for health research, and CIHR must therefore redefine its niche. In particular, the Canada Research Chairs (CRC) program will support 700 health researchers at career stages corresponding primarily to the CIHR Investigator and Senior/Distinguished Investigator Awards, of which there are only 158 in total. However, the CRC program does not support large numbers of researchers at the very earliest stages of their independent careers, namely, those eligible for the New Investigator Awards, and this remains an important niche for CIHR. Success rates in all our awards competitions have been falling steadily and, with a reduced budget available for these awards programs next year, success rates would probably decrease below 10%.

We remain committed to supporting the careers of health researchers, particularly through strategic investment in areas where research capacity must be increased. For example, the New Emerging Teams Grants include funding for the recruitment of new researchers to a team. A task force on clinical research will recommend improved career support for those who combine research with clinical practice in the health professions. Some of our institutes have supported career transition awards, allowing established investigators to refocus their research interests. Governing council has asked CIHR staff to examine the idea of release-time stipends for

holders of CIHR grants who have significant responsibilities beyond their commitment to research. We will continue to celebrate the achievements of outstanding health researchers through enhancements to the Michael Smith Prize.

The solution to the problems faced by CIHR, and the entire research community, is not limited to increases in CIHR's budget so it can fulfill its mandate. Ideally, we would also have some increased financial flexibility, particularly the ability to carry over a small portion of our annual government appropriation from year to year in order to avoid the cycles of feast and famine that compromise the continuity of high-quality health research. We will continue to present our case to decision-makers in Ottawa and look forward to receiving the support of health researchers everywhere. Following extensive consultation, CIHR is moving ahead with a blueprint for the next stage of its evolution.<sup>1</sup> The success of *Blueprint* depends on the constructive engagement of all of CIHR's stakeholders. As in our first 3 years when the research community and other stakeholders responded positively to the creation of CIHR, we have the opportunity to build a truly outstanding, inclusive, strategic and responsive health research enterprise in Canada.

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Competing interests: None declared.

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# Preserving our intellectual capital: the Canadian Institutes of Health Research funding crisis

Eliot A. Phillipson

§ See related articles pages 533, 567 and 592

Launched just 3 years ago, the Canadian Institutes of Health Research (CIHR) has already been established as a success story in which the health care community can take great pride. In embarking on a strategic planning exercise involving "wide-ranging consultations with a variety of partners and the research community,"<sup>1</sup> the CIHR appears intent on building on that success. A background document designed to guide the planning process

notes that "a robust, energetic and broad-based cadre of accomplished researchers, armed with the best tools, state-of-the-art facilities, and outstanding trainees, is the best strategy to ensure that Canada has the capacity and expertise to mobilize in order to address important health issues."<sup>1</sup>

Given such an assertion, it is difficult to understand why CIHR has also announced an immediate program change that will have profound implications for Canada's

“cadre of accomplished researchers.” The change in question is the termination of the CIHR Investigator and Senior Investigator Awards, the only CIHR program that provides salary support for mid-career and senior health care investigators. The decision to terminate this program means that, although current awards will continue until their normal expiration date, no new applications will be accepted. Investigators currently in the fifth (and final) year of a CIHR career award (granted by CIHR’s predecessor, the Medical Research Council of Canada) will have no CIHR salary support program to which they can apply in September, and hence no possibility of CIHR salary support as of July 2004.

The timing of this decision by CIHR — just 2 months before the next application deadline, and in advance of its strategic planning exercise — is not only unfair, it is baffling. The rationale given for cutting this particular program — namely, that the CIHR career awards can be substantially replaced by the Canada Research Chairs (CRC) program — is not credible. The numbers do not add up. The CRC program, announced in the federal budget of 2000, created 2000 research chairs rolled out at a rate of 400 per year, ending in 2005. Not all of these chairs are for health care research; the program also supports research in the natural sciences and engineering, and in the social sciences and humanities. Half of the CRCs are “tier 2” chairs earmarked for new investigators in the first 5 to 7 years of their research careers. Therefore, by the time their current awards expire, the vast majority of researchers who currently hold 5-year CIHR career awards will be eligible only for the “tier 1” CRCs reserved for experienced researchers. However, the number of available tier 1 CRCs will be insufficient to replace even a reasonable number of expiring CIHR career awards.

For example, the Faculty of Medicine at the University of Toronto has been allocated about 25 CRCs per year. Only 12 of these are tier 1 awards. Since tier 1 CRCs are 7-year awards, no additional chairs will become available until the first cohort of awards expires in 2008. In the meantime, 20 CIHR career awards in the Faculty of Medicine will expire each year. By 2008, there could potentially be a backlog of over 100 established investigators competing for the 12 available tier 1 CRCs.

Furthermore, the CRC program is supposed to facilitate the repatriation of Canadian investigators working abroad and recruit outstanding international investigators to research positions in Canada. If this objective is to be honoured, there will be even fewer than 12 tier 1 CRCs available in 2008 for the backlog of over 100 investigators. The same figures would apply in subsequent years.

The decision to terminate the Investigator and Senior Investigator Awards has sent a chilling message to young in-

vestigators that will undermine their confidence in the long-term prospects for a research career in Canada. Indeed, the abrupt withdrawal of the career support program weakens the morale of the research community and diminishes the positive impact of the CIHR, the CRC program, the Canada Foundation for Innovation and other recent federal research funding initiatives. If it is not reversed or mitigated quickly, the decision will cause young research trainees and junior faculty members to reconsider their options and to look toward the abundant opportunities available for our “best and brightest” to take up attractive research positions in the United States. In contrast to CIHR, the US National Institutes of Health not only supports an extensive program of career support awards at the junior and mid-career levels, but also allows a portion of the investigator’s salary to be built into the budget of research operating grants.

The termination of the CIHR career support program strikes at our most precious resource: our intellectual capital. Whereas a reduction in the size of research operating grants may slow the research machine, the loss of intellectual capital will wreck the machinery and weaken whatever strategic plan CIHR develops for the future.

It is critical that CIHR move quickly to control the damage resulting from termination of its Investigator and Senior Investigator Awards program. Two possibilities are to reinstate the program or to move to a funding model that allows the investigators’ salaries to be covered by their operating grants. For the immediate future, either option would require that funds be redirected from other CIHR programs. Beyond this temporary solution, however, CIHR will require an increase in its budget and, to achieve this goal, will need the active support of the health research and health care communities. In this regard, medical researchers and clinicians alike have a responsibility to remind government that to jeopardize the adequacy of research funding is to jeopardize not only our intellectual capital, but ultimately the health and quality of life of Canadians.

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Competing interests: None declared.

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# Violence against women: integrating the evidence into clinical practice

Harriet L. MacMillan, C. Nadine Wathen

§ See related article page 582

Violence against women is common and is associated with major physical and psychological impairment.<sup>1,2</sup> Along with recognition of woman abuse as a serious public health problem<sup>3,4</sup> has come the call for clinicians to find ways to identify and help their abused female patients.

However, before advising physicians to screen routinely for woman abuse, we must first establish that screening does more good than harm. Two key elements must be considered: does the screening identify the target condition (in this case exposure to or risk of violence in women) and does the subsequent “treatment” intervention, be it some form of counselling or referral to local services, lead to a favourable outcome (i.e., reduction of violence)?

The first question is easily answered. Several screening instruments with acceptable psychometric properties are available to detect violence against women, including brief forms for use in primary and emergency care settings and for pregnant women.

For the second question, there is a lack of good evidence to guide clinical decision-making, and no studies have linked screening to treatment intervention in a way that allows us to determine whether routine screening for violence against women does more good than harm.<sup>5</sup>

The broad range of programs that are being recommended to reduce violence against women, including primary care counselling, referral to shelters and referral to personal and vocational counselling, have not been sufficiently evaluated to determine their effectiveness in reducing violence.<sup>6</sup> In terms of batterer treatment, the only high-quality study using a randomized controlled design<sup>7</sup> found no difference in abuse outcomes between the treatment groups (group sessions for men alone, sessions with their partners or rigorous monitoring) and the control group. Because this study was conducted with a sample of United States Navy couples, the results cannot necessarily be applied to the general population. In contrast, several other studies of lesser quality have suggested that such interventions for batterers are effective. The evidence remains conflicting.

The only program for which there is some evidence of effectiveness in reducing violence, a structured program of advocacy services, is specific to women who are leaving a woman abuse shelter.<sup>8</sup> The study evaluating the program did not address the issue of screening (as women in the

study were not screened) nor the question of whether going to a shelter itself is beneficial in reducing subsequent abuse; indeed at least one study<sup>9</sup> has suggested that women seeking immediate safety in shelters may be exposed to reprisal violence once they leave the shelter. In sum, if violence against women is identified through primary care screening, no intervention to which women can be referred has been shown to be effective in reducing that violence.

For these reasons, and because the potential harms of screening and treatment have also not been sufficiently evaluated, the Canadian Task Force on Preventive Health Care (CTFPHC) has concluded that there is insufficient evidence to recommend for or against routine screening for violence against women and for referral to counselling or to shelters (see page 582).<sup>10</sup> This differs from several existing guidelines,<sup>11-14</sup> but not from more recent evidence-based examinations of this issue.<sup>15</sup>

Given the insufficient evidence for screening for abuse, should primary care practitioners ask women about exposure to or risk of violence? The answer to this difficult question depends on many factors unique to each clinical encounter. These include what services might be available in the community as well as the woman's specific situation, including the severity of abuse, her immediate concerns regarding her own safety and that of her children, and her own assessment of the benefits and risks of disclosing abuse — for example, whether she currently feels able to seek help or whether she fears reprisal violence from her abuser if she decides to do so. The clinician should maintain a degree of awareness about the issue of family violence and be sensitive to clinical signs and symptoms associated with abuse (for excellent summaries of such manifestations see Ferris and colleagues<sup>3</sup> and Campbell<sup>16</sup>).

It is also necessary to distinguish between *routine universal screening* of all women, which “implies a standardized assessment of patients, regardless of their reasons for seeking medical attention”<sup>17</sup> (p. 551), and *diagnostic assessment* (medical or psychiatric), which involves asking patients presenting with specific signs or symptoms about abuse. Despite the lack of evidence to support routine screening, the CTFPHC concluded that the prevalence of and significant impairment associated with violence against women make it important for clinicians to maintain a high index of suspicion when assessing patients.

Furthermore, not asking women about exposure to violence during certain diagnostic assessments (e.g., investigation of chronic pain) may lead to misdiagnosis and a path of inappropriate investigations or treatments that will not address the underlying problem.<sup>17</sup> For a discussion of approaches to asking about woman abuse and subsequent management, we recommend *A Handbook Dealing with Woman Abuse and the Canadian Criminal Justice System: Guidelines for Physicians*.<sup>3</sup> Details about indicators of risk for violence against women can be found in Table 1 of the systematic review detailing the evidence base for the CTFPHC's recommendations.<sup>5</sup>

Until we can determine whether the potential benefits of routine screening for woman abuse outweigh the potential harms, the best course of action for primary health care providers is to be alert for the signs and symptoms of abuse, and to question women about this issue if it might be related to a clinical problem. Fortunately, studies funded by the National Center for Injury Prevention and Control, the Agency for Healthcare Research and Quality, the US Centers for Disease Control and Prevention, the Canadian Institutes of Health Research and the Ontario Women's Health Council are underway to provide evidence to answer this question.

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# Diagnosis and management of hyperprolactinemia

Omar Serri, Constance L. Chik, Ehud Ur, Shereen Ezzat

## Abstract

PROLACTIN IS A PITUITARY HORMONE that plays a pivotal role in a variety of reproductive functions. Hyperprolactinemia is a common condition that can result from a number of causes, including medication use and hypothyroidism as well as pituitary disorders. Depending on the cause and consequences of the hyperprolactinemia, selected patients require treatment. The underlying cause, sex, age and reproductive status must be considered. We describe the diagnostic approach and management of hyperprolactinemia in various clinical settings, with emphasis on newer diagnostic strategies and the role of various therapeutic options, including treatment with selective dopamine agonists.

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Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. It is an essential factor for normal production of breast milk following childbirth. Furthermore, prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and follicle-stimulating hormone. An excess of prolactin, or hyperprolactinemia, is a commonly encountered clinical condition.<sup>1</sup> Management of this condition depends heavily on the cause and on the effects it has on the patient. In this review we summarize advances in our understanding of the clinical significance of hyperprolactinemia and its pathogenetic mechanisms, including the influence of concomitant medication use. Emphasis will be placed on newer diagnostic strategies and the role of various therapeutic options, including treatment with selective dopamine agonists, in various clinical settings.

## Epidemiologic features

An excess of prolactin above a reference laboratory's upper limits, or "biochemical hyperprolactinemia," can be identified in up to 10% of the population.<sup>1</sup> Women with oligomenorrhea, amenorrhea, galactorrhea or infertility, and men with hypogonadism, impotence or infertility must have serum prolactin levels measured.

The occurrence of clinically apparent hyperprolactinemia depends on the study population. The prevalence has been reported to range from 0.4% in an unselected healthy adult population in Japan to 5% among clients at a family planning clinic.<sup>1</sup> The rate is even higher among patients with specific symptoms that may be attributable to hyperprolactinemia: it is estimated at 9% among women with amen-

orrhea, 25% among women with galactorrhea and as high as 70% among women with amenorrhea and galactorrhea.<sup>1</sup> The prevalence is about 5% among men who present with impotence or infertility.<sup>1</sup>

## Regulation of prolactin secretion

Like most anterior pituitary hormones, prolactin is under dual regulation by hypothalamic hormones delivered through the hypothalamic-pituitary portal circulation (Fig. 1). Under most conditions the predominant signal is inhibitory, preventing prolactin release, and is mediated by the neurotransmitter dopamine. The stimulatory signal is mediated by the hypothalamic hormone thyrotropin-releasing hormone. The balance between the 2 signals determines the amount of prolactin released from the anterior pituitary gland.<sup>2</sup> Furthermore, the amount cleared by the kidneys influences the concentration of prolactin in the blood.<sup>2,3</sup>

### Box 1: Clinical presentations of hyperprolactinemia

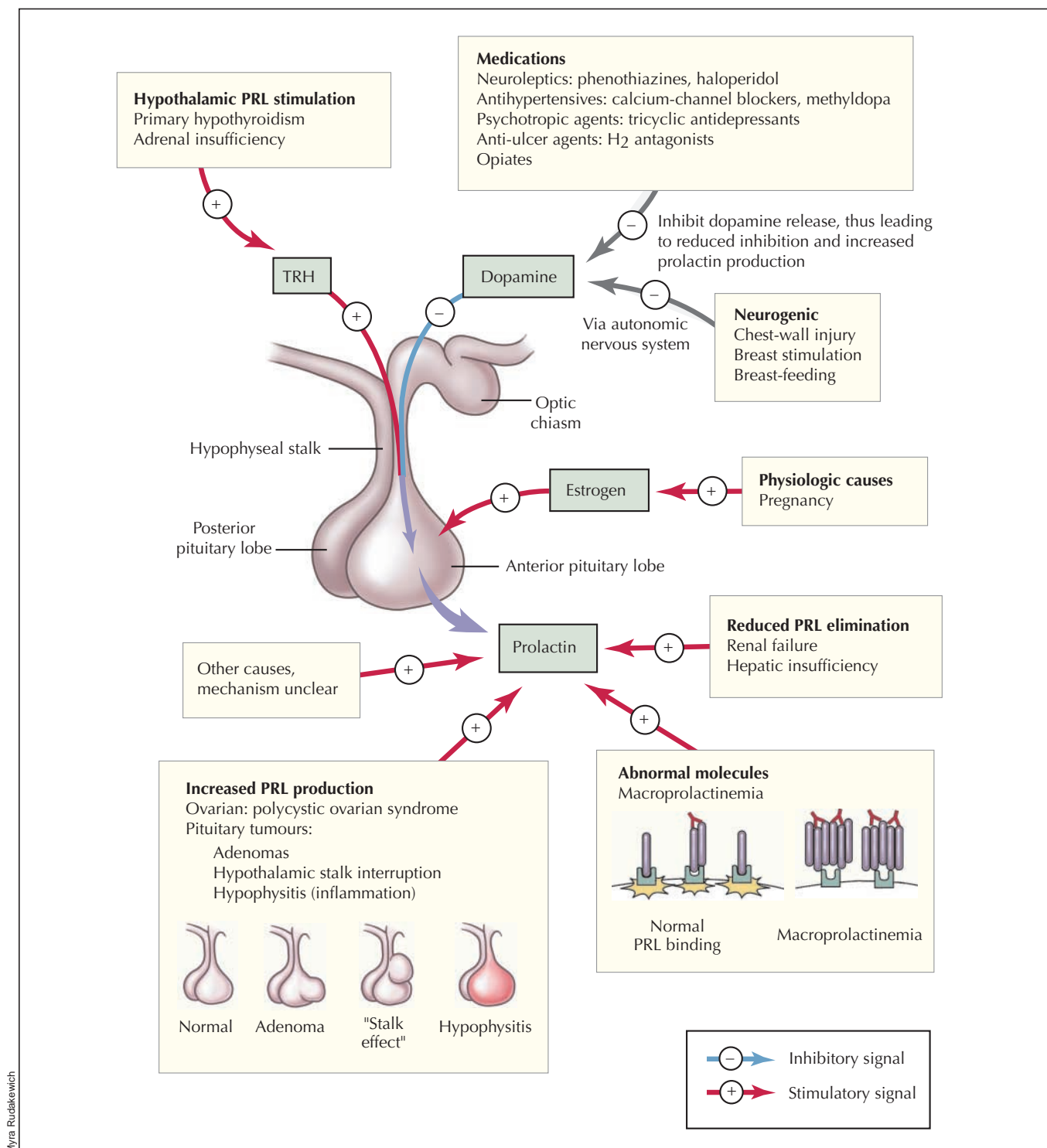
#### Premenopausal women

- Marked prolactin excess (> 100 µg/L [normally < 25 µg/L]) is commonly associated with hypogonadism,\* galactorrhea and amenorrhea
- Moderate prolactin excess (51–75 µg/L) is associated with oligomenorrhea
- Mild prolactin excess (31–50 µg/L) is associated with short luteal phase, decreased libido and infertility
- Increased body weight may be associated with prolactin-secreting pituitary tumour<sup>5</sup>
- Osteopenia is present mainly in people with associated hypogonadism
- Degree of bone loss is related to duration and severity of hypogonadism\*<sup>6</sup>

#### Men

- Hyperprolactinemia presents with decreased libido, impotence, decreased sperm production, infertility, gynecomastia and, rarely, galactorrhea
- Impotence is unresponsive to testosterone treatment and is associated with decreased muscle mass, body hair and osteoporosis<sup>7</sup>

\*The degree of hypogonadism is generally proportionate to the degree of prolactin elevation



**Fig. 1: Causes of hyperprolactinemia.** Prolactin (PRL) is under dual control from the hypothalamus, where dopamine serves as an inhibitory signal, preventing PRL secretion, and thyrotropin-releasing hormone (TRH), under some conditions, stimulates increased PRL production and release. Increased anterior pituitary hormone production can occur from a PRL-producing adenoma or from inflammation (hypophysitis). However, conditions that result in impaired dopamine delivery or enhanced TRH signalling, or both, will also result in increased PRL release. In general, medications result in increased PRL production through their anti-dopaminergic properties. Chest-wall injury and breast stimulation serve as peripheral triggers of autonomic control, which impinge on central neurogenic pathways that attenuate dopamine release into the hypophyseal portal circulation. In some conditions, such as renal or hepatic insufficiency, PRL is cleared less rapidly from the systemic circulation, which results in increased blood levels of PRL.

**Box 2: Objectives of treatment of hyperprolactinemia**

- Restoration and maintenance of normal gonadal function
  - Restoration of normal fertility
  - Prevention of osteoporosis
- If a pituitary tumour is present:
- Correction of visual or neurological abnormalities
  - Reduction or removal of tumour mass
  - Preservation of normal pituitary function
  - Prevention of progression of pituitary or hypothalamic disease

**Causes of hyperprolactinemia**

The differential diagnosis and causes of pathological hyperprolactinemia are summarized in Fig. 1. The presence of a secondary cause and fluctuating degrees of hyperprolactinemia should raise the suspicion of a nontumorous cause. Consideration of such secondary contributions can obviate the need for unnecessary testing and inappropriate treatment.

**Macroprolactinemia**

Asymptomatic patients with intact gonadal and reproductive function and moderately elevated prolactin levels may have macroprolactinemia.<sup>3</sup> This term should not be confused with macroprolactinoma, which refers to a large pituitary tumour greater than 10 mm in diameter. Macroprolactinemia refers to a polymeric form of prolactin in which several prolactin molecules form a polymer that is recognized by immunologically based serum assays. In general, macroprolactin results from the binding of prolactin to IgG antibodies. The large prolactin polymer is unable to interact with the prolactin receptor. Little, if any, biological effect of prolactin excess is noted. If macroprolactinemia is suspected, the laboratory should be notified, and the specimen can be subjected to polyethylene glycol precipitation before assessment.<sup>3</sup> If macroprolactinemia accounts for most of the prolactin excess, no specific treatment is needed.

**Hypothyroidism**

The hyperprolactinemia of hypothyroidism is related to several mechanisms. In response to the hypothyroid state, a compensatory increase in the discharge of central hypothalamic thyrotropin-releasing hormone results in increased

stimulation of prolactin secretion.<sup>2</sup> Furthermore, prolactin elimination from the systemic circulation is reduced, which contributes to increased prolactin concentrations.<sup>2</sup> Primary hypothyroidism can be associated with diffuse pituitary enlargement, which will reverse with appropriate thyroid hormone replacement therapy.<sup>2</sup>

**Pituitary tumours**

Pituitary tumours are common neoplasms that exhibit a wide range of biological behaviour, as evidenced by hormonal and proliferative activities.<sup>2</sup> Among pituitary adenomas, prolactin-producing pituitary tumours are the most common type. About one-third of all pituitary tumours are not associated with hypersecretory syndromes but, rather, present with symptoms of an intracranial mass, such as headaches, nausea, vomiting or visual field disturbances. Because of suprasellar extension, pituitary tumours may interrupt dopamine delivery from the hypothalamus to the pituitary, resulting in loss of inhibition of prolactin release, or the "stalk effect." In contrast, tumours that produce growth hormone (GH) may also secrete prolactin in nearly 25% of cases.<sup>2</sup> This is a common source of misdiagnosis, as the features of prolactin excess may capture attention while the more subtle features of GH excess go unnoticed. In both cases the distinction is important. Surgery is indicated for a nonfunctional pituitary adenoma that is large enough to cause the stalk effect. For tumours that are secreting both GH and prolactin, therapy with GH-inhibitory agents is the preferred treatment in most cases. Finally, an autoimmune condition of the pituitary with lymphocytic infiltration can lead to hyperprolactinemia.<sup>4</sup> This form of lymphocytic hypophysitis is typically noted in the postpartum phase in women of childbearing age. Surgery is rarely indicated, and spontaneous resolution is common.<sup>4</sup>

**Box 3: Medical therapeutic options for the management of hyperprolactinemia**

- Dopamine agonists are currently the first therapeutic option (Table 1)
- Dopamine agonists have proven efficacy in reducing prolactin levels, restoring ovulation in premenopausal women and restoring gonadal function in men<sup>7,9</sup>
- Prolactin levels may remain above normal in about 20% of cases of macroprolactinoma and about 10% of cases of microprolactinoma despite dopamine agonist therapy<sup>9</sup>
- Bromocriptine has been used the longest.
- Cabergoline has greater affinity and selectivity for pituitary dopamine D<sub>2</sub> receptors and longer duration of action.<sup>9-11</sup> It is indicated in cases of bromocriptine resistance or intolerance
- Quinagolide is an alternative dopamine agonist<sup>10</sup> but with limited access

## Clinical presentations

The clinical manifestations of prolactin excess (Box 1) can be divided into 2 main categories: those that are mediated by prolactin excess directly and those representing the consequences of the resulting hypogonadism.

## Diagnosis

The evaluation is aimed at excluding physiologic, pharmacologic or other secondary causes of hyperprolactinemia (Fig. 1). In the absence of such causes, imaging (preferably MRI) of the pituitary fossa is recommended to establish whether a prolactin-secreting pituitary tumour or other lesion is present. CT scanning may not be sensitive enough to identify small lesions or large lesions that are isodense with surrounding structures. Whereas serum prolactin lev-

els between 20 and 200  $\mu\text{g/L}$  can be found in patients with hyperprolactinemia due to any cause, prolactin levels above 200  $\mu\text{g/L}$  usually indicate the presence of a lactotroph adenoma. In general, there is a relatively linear relation between the degree of prolactin elevation and the size of a true prolactinoma. If a patient with only a mildly elevated serum prolactin level has a pituitary macroadenoma, the diagnosis is more likely to be a non-prolactin-producing pituitary adenoma or other sellar mass causing the stalk effect. The approach to the diagnosis of hyperprolactinemia is summarized in Fig. 2.

## Natural history

Several series of patients with prolactin-secreting microadenomas observed for long periods without treatment have shown that the risk of progression to macro-



Fig. 2: Approach to diagnosis of hyperprolactinemia.



adenoma over 10 years is small (about 7%).<sup>8</sup> In some cases, prolactin levels returned to normal in patients who did not receive treatment or who received treatment intermittently with dopamine agonists. Women with prolactin-secreting microadenomas who became pregnant during this interval had a higher rate of remission than women who did not become pregnant (35% v. 14%).

## Management

The objective of hyperprolactinemia treatment is to correct the biochemical consequences of the hormonal excess (Box 2). When present, the compressive features of a large (macro) tumour must also be alleviated and the tumour prevented from regrowing. The approach to the management of hyperprolactinemia is summarized in Fig. 3.

## Medical therapy

Medical therapy has traditionally involved agonists of the physiologic inhibitor of prolactin, dopamine (Box 3, Table 1). Although initially it was thought that patients would require dopamine agonist therapy all their lives, the current use of these agents has evolved into a dynamic process depending on the patient's needs and circumstances.

## Surgical therapy

Surgical removal of tumours associated with prolactin excess requires careful consideration of treatment objectives (Box 4). It is indicated in patients with nonfunctional pituitary adenomas or other nonlactotroph adenomas associated with hyperprolactinemia and in patients in whom medical therapy has been unsuccessful or poorly tolerated.

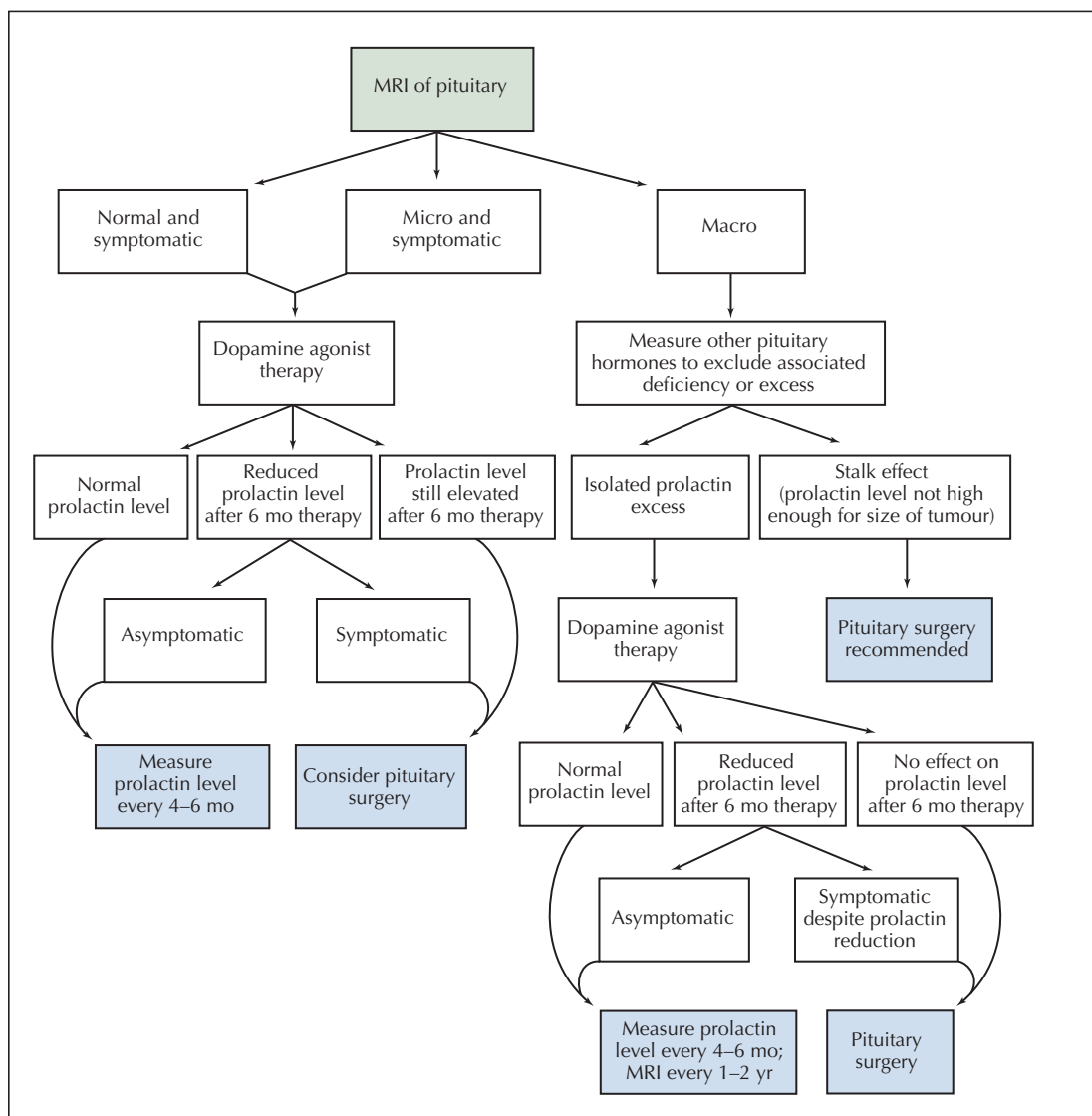


Fig. 3: Approach to management of hyperprolactinemia.

The best results with transsphenoidal resection of the prolactinoma are limited to centres that have the greatest experience. In one study, the apparent surgical cure rate for prolactinomas, although good in the short term, decreased on re-evaluation during long-term follow-up.<sup>12</sup> Hyperprolactinemia recurred within 5 years after surgery in about 50% of patients with microprolactinomas who were initially thought to be cured.<sup>12</sup> In other series, the rate of recurrence of hyperprolactinemia following initial cure by surgery ranged from 20% to 40%.<sup>13</sup> However, recurrence of hyperprolactinemia after surgery is not necessarily a permanent feature and does not inevitably indicate operative failure.<sup>13,14</sup> Re-evaluation of long-term results indicates a success rate of about 75% for surgical removal of microprolactinoma. However, the results of surgery for macroprolactinoma are poor, with a long-term success rate of only 26%.<sup>13</sup>

### Management of hyperprolactinemia in pregnancy

The collaboration of various specialists, including an obstetrician, is required for the careful planning of pregnancy in women with hyperprolactinemia (Box 5). Ideally, this should occur before conception, to permit a full assessment of the risks and benefits of dopamine agonist therapy during pregnancy.

## Monitoring and follow-up

Biochemical and clinical improvements in response to dopamine agonist therapy are readily apparent in most patients. In addition, tumour shrinkage can be expected in about 80% of macroadenomas.<sup>17</sup> However, a major drawback of medical therapy is the potential need for lifelong treatment. Discontinuation of bromocriptine therapy has been shown to lead to recurrence of hyperprolactinemia in most patients and to tumour regrowth if treatment duration has been less than 2 years.<sup>18</sup> Passos and associates<sup>18</sup> reported maintenance of normal prolactin levels and absence of adenoma re-expansion after withdrawal of dopamine agonist therapy in 6.6% to 37.5% of patients. Recurrence usually occurs within months after drug withdrawal. These authors also reported reduced and normal prolactin levels after pregnancy in women who had

prolactinomas treated with dopamine agonists. Menopause has also been suggested as a factor that increases the probability of maintaining normoprolactinemia after dopamine agonist therapy is stopped.<sup>18</sup> Unless there is evidence of growth of a prolactinoma or related symptoms, such as headache, there is no indication to continue dopamine agonist therapy after menopause.<sup>18</sup> There are no significant differences in age, sex, initial dopamine agonist dose or length of treatment between those with continued normopro-

#### Box 4: Indications for pituitary surgery in patients with hyperprolactinemia

- Surgery is indicated in cases of resistance or intolerance to optimal medical therapy
- Surgery should be considered in patients with intrasellar tumour for whom long-term drug treatment is not acceptable
- Surgical decompression may be required for tumours pressing on the optic chiasm
- Surgery should be avoided in cases of extrasellar (without optic chiasm compression) expanding tumours because of the low success rate

**Table 1: Advantages, disadvantages and cost of various dopamine agonist agents available in Canada**

Agent	Main advantages	Disadvantages	Typical dose	Monthly cost, \$
Bromocriptine	Longest track record	High frequency of gastrointestinal upset and sedation	2.5 mg/d	112.97
Cabergoline	High efficacy; low frequency of adverse events; indicated in cases of bromocriptine resistance or intolerance	Experience during pregnancy relatively limited	0.5 mg/wk	139.50
Quinagolide	Pituitary selectivity; indicated in cases of bromocriptine resistance or intolerance	Daily use; limited access	0.075 mg/d	129.90
Pergolide	Occasionally beneficial in resistant cases	High frequency of adverse events	0.25 mg/d	127.19

### Box 5: Management of hyperprolactinemia in pregnancy

- There is no evidence of increased teratogenicity associated with bromocriptine or cabergoline use during pregnancy<sup>15,16</sup>
- Similarly, there is no evidence of increased risk of abortion or multiple pregnancies with dopamine agonist use
- If the tumour size before pregnancy is < 10 mm, dopamine agonist therapy is stopped during pregnancy because the risk of tumour expansion is low<sup>15</sup>
- If the tumour size before pregnancy is ≥ 10 mm before pregnancy, bromocriptine use is advised during pregnancy to avoid significant tumour expansion<sup>15</sup>
- All patients should be evaluated every 2 months during pregnancy
- Formal visual field testing is indicated in patients with symptoms or a history of macroadenoma
- If visual field defects develop despite dopamine agonist treatment, early delivery or pituitary surgery should be considered<sup>15</sup>

lactinemia and those with recurrence of hyperprolactinemia.<sup>18</sup> We suggest that the dopamine agonist dose be decreased after 2 or 3 years of normal prolactin levels and that therapy be stopped if the prolactin levels remain unchanged after 1 year at the reduced dose. The dose can be reduced by half over the course of 3 months while prolactin levels are measured monthly. After complete discontinuation of treatment, regular monitoring of clinical symptoms and prolactin levels is recommended. Given the propensity for early recurrence, prolactin levels should be measured monthly for the first 3 months and every 6 months thereafter.

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# Prevention of violence against women

## *Recommendation statement from the Canadian Task Force on Preventive Health Care*

C. Nadine Wathen, Harriet L. MacMillan, with the Canadian Task Force on Preventive Health Care

§ See related article page 570

### Recommendations

- There is insufficient evidence to recommend for or against routine universal screening for violence against either pregnant or nonpregnant women (grade I recommendation); however, clinicians should be alert to signs and symptoms of potential abuse and may wish to ask about exposure to abuse during diagnostic evaluation of these patients.
- There is insufficient evidence to recommend any of the following primary care interventions to prevent violence against pregnant or nonpregnant women, although decisions to do so may be made by the clinician and patient on other grounds:
  - primary care counselling (grade I recommendation)
  - referral to shelters (grade I recommendation)
  - referral to personal and vocational counselling (grade I recommendation).
- There is fair evidence (level 1) to refer women who have spent at least 1 night in a shelter to a structured program of advocacy services (grade B recommendation). A structured, multi-phased post-shelter advocacy service is described by Sullivan and Bybee;<sup>1</sup> to our knowledge, no such programs currently exist in Canada.
- There is insufficient evidence to recommend for or against screening men as potential perpetrators of violence against their intimate partner (grade I recommendation).
- There is conflicting evidence regarding the effectiveness of batterer interventions (with or without partner participation) in reducing the rate of further intimate partner violence (grade C recommendation).

In Canada, the annual prevalence of violence against women is about 8% among nonpregnant<sup>2</sup> and 6% to 8% among pregnant women.<sup>3,4</sup> For the purpose of our review<sup>5</sup> and recommendations, violence against women is defined as physical and psychological abuse of women by their male partners, including sexual abuse and abuse during pregnancy. Of women who are abused, 25% suffer episodes of beating, 20% of choking and 20% of sexual assault; 40% suffer injury, and 15% receive medical care as a result of partner violence. Separate from physical violence, 19% of women suffer emotional abuse and controlling behaviour, including financial abuse or control.<sup>2</sup> Emotional forms of

abuse are highly correlated with physical violence: 5-year rates of violence are 10 times greater among those in emotionally abusive situations than among those who do not report emotional abuse.<sup>2</sup> Women exposed to partner violence are at increased risk of injury and death as well as a range of physical, emotional and social problems.<sup>6</sup> Abuse during pregnancy is associated with impairment in both the mother and child, including low birth weight.<sup>7</sup>

### Manoeuvres

The following interventions were evaluated:

- Screening of all women, including pregnant women, in the primary

care setting to detect intimate partner violence

- Interventions for women who are abused
- Treatment programs for men who abuse their partners

### Potential benefits

- Decrease in the incidence of physical, sexual or emotional abuse by men against their female partners
- Increase in women's use of safety behaviours, social support, community resources, etc., following intervention

### Potential harms

- Reprisal violence by men against women seeking intervention
- Failure to detect abuse (either by not screening or through false-negative results of screening)

[See "Evidence and clinical summary"<sup>8-23</sup> section on the next page.]

### Recommendations by others

In 1996, the US Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against the use of specific screening tools to detect domestic violence, although it suggested that clinicians be alert to signs of abuse and use selective screening questions if indicated.<sup>24</sup> The American Medical Association's Council on Scientific Affairs recommends routine screening in primary care settings and a structured approach to documentation and referral to appropriate community resources.<sup>25</sup> The Society of Obstetricians and Gynaecologists of Canada (SOGC) advocates a high degree of clinical suspicion and outlines



## Evidence and clinical summary

- Several screening instruments with acceptable psychometric properties have been developed,<sup>8-15</sup> including brief forms<sup>16-18</sup> for primary<sup>16</sup> and emergency<sup>17</sup> care settings and forms for pregnant women.<sup>19</sup> However, at present there is insufficient evidence to evaluate whether screening is effective in reducing violence against women or associated negative outcomes. In addition, data about the potential harms of screening are lacking. This finding is similar to that of another recent systematic review.<sup>20</sup>
- Four types of interventions for abused women were evaluated within the category of potential referrals by primary care physicians: shelters, post-shelter advocacy counselling, personal and vocational counselling, and prenatal counselling. No evidence of suitable quality exists to assess the effectiveness of shelters to decrease the incidence of violence. Among women who had spent at least 1 night in a shelter, there was fair evidence that those who received a program of advocacy services reported less repeat abuse and better quality of life in the following 2 years than women who did not receive such services.<sup>1</sup>
- Programs that target male batterers—alone or with their partners—represent the largest group of interventions. Of 10 studies and 1 review of these programs, only 1 randomized controlled trial was considered of good quality.<sup>21</sup> This trial (the San Diego Navy Experiment) showed that 3 programs for batterers, their female partners or both (a weekly men's group, a conjoint group with men and their female partners and monitoring with individual counselling sessions) showed no reduction in abuse compared with a control group. Despite the excellent internal validity of this trial, the extent to which these findings are applicable to the general population is unclear, as the study group consisted of US Navy couples. The other studies in this category were all rated "poor" in terms of methodological quality.
- There is a clear and pressing need for additional research employing rigorous designs to test the effect of domestic violence interventions on important clinical outcomes.
- *A Handbook Dealing with Woman Abuse and the Canadian Criminal Justice System: Guidelines for Physicians* is an excellent resource and provides an overview of the clinical manifestations of physical<sup>22</sup> and psychological<sup>23</sup> abuse.

key physical and psychological presenting symptoms.<sup>26</sup> Although not directly encouraging routine screening, the SOGC provides a brief set of screening questions to be used as part of history-taking. The American College of Obstetricians and Gynecologists takes a similar approach.<sup>27</sup> Both groups also provide guidance regarding counselling (including safety planning), referral and follow-up. A similar case-finding approach is also advocated by the American Academy of Pediatrics.<sup>28</sup>

Nadine Wathen was coauthor of the systematic evidence review, drafted the current article and made subsequent revisions. Harriet MacMillan was co-author of the systematic evidence review, critically revised the current article and reviewed subsequent revisions. The Canadian Task Force on Preventive Health Care critically reviewed the evidence and developed the recommendations according to its methodology and consensus development process.

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# Preventing pregnancy: a fresh look at the IUD

**Background and epidemiology:** According to US data, 49% of pregnancies are unintended.<sup>1</sup> The typical American woman achieves her desired family size by age 31 and then spends the next 20 years until menopause trying to avoid pregnancy. In Canada the induced abortion rate is about 32 per 100 live births.<sup>2</sup> This means that at least 1 in 4 pregnancies is unintended and unwanted.

For women in long-term monogamous relationships the IUD offers an excellent contraceptive option. Worldwide, over 100 million women have used the IUD, yet in Canada less than 1.5% of women aged 15–45 use it. Unfortunately, negative publicity about a particular IUD — the Dalkon Shield — in the 1970s raised many questions about the safety of all IUDs. In addition, myths predominate over evidence, such as the misperceptions that IUDs increase the risk of ectopic pregnancy and the long-term risk of pelvic inflammatory disease (PID).<sup>3</sup> A major task is to provide correct information to women and health care professionals and to increase the availability and use of this effective method of contraception.

Many IUD models exist. In Canada, 2 basic models are available: a copper-releasing device (Nova-T or Flexi-T) and a levonorgestrel-releasing intrauterine system (Mirena). Both elicit foreign-body reactions. The copper inhibits sperm transport and mobility.<sup>4</sup> The levonorgestrel changes cervical mucus, endometrial morphology and ovarian function.<sup>5</sup> In a large randomized trial, the copper IUD was found to have a failure rate of 1.26 per 100 woman-years and was associated with a rate of ectopic pregnancy of 0.25 per 100 woman-years; the corresponding rates for the levonorgestrel system were 0.09 and 0.02 per 100 woman-years.<sup>6</sup> These failure rates are better than actual-use failure rates for oral contraceptives.<sup>7</sup>

Moreover, the IUD is an inexpensive, low-maintenance and reversible method of contraception. It can stay in

place for 3–5 years. After 3 years, both the copper device (\$90) and the Mirena system (\$385) work out to be cheaper than 39 cycles of oral contraceptive (\$18/cycle).

**Clinical management:** An IUD can be a good option for many women, particularly those who are breast-feeding or who cannot use estrogen-based methods because of cigarette smoking or hypertension. The Mirena system offers particular advantages for women with heavy menstrual flow. But IUDs are not for everyone. Common side effects are bleeding and dysmenorrhea; the 5-year cumulative termination rate because of bleeding problems is up to 20% for the copper IUD and up to 14% for the levonorgestrel system.<sup>6</sup> Certain complications (e.g., PID, expulsions, pregnancy-related complications) make screening critical for identifying women at risk of IUD-associated complications. The small risk of PID<sup>8</sup> is attributable to a transient risk at time of insertion<sup>9</sup> and to exposure to STDs subsequent to insertion.<sup>3,8,9</sup> Strict screening for STD risk before insertion, sepsis during insertion and leaving the IUD in place for its lifespan can reduce the risk of PID.<sup>7</sup> Between 2% and 10% of IUD users spontaneously expel their IUD within the first year; risk factors include nulliparity, heavy periods or severe dysmenorrhea.<sup>9</sup> In the rare event of a woman becoming pregnant while using an IUD, the risk of ectopic pregnancy is about 15%–20%.<sup>7</sup>

The World Health Organization has drafted eligibility guidelines for IUD users. They include refraining from providing an IUD for a woman with active, recent or recurrent PID, a known or suspected pregnancy, or an anatomically distorted uterus. They advise exercising caution in considering an IUD for women with risk factors for PID or STDs, with undiagnosed abnormal vaginal bleeding or with impaired immune responses. They advise that IUD

use not be restricted because of a previous PID or ectopic pregnancy, provided the woman is not currently at risk of STDs.<sup>7</sup>

**Prevention:** Inserting an IUD is a simple office procedure that can be performed by primary care health providers accustomed to office gynecological procedures. Access to good knowledge, a sterilizer, proper equipment (e.g., a tenaculum) and a mentor to demonstrate and supervise several insertions are prerequisites. There is currently a deficit of health care providers trained to offer this primary care service. Interested health care providers will find a more comprehensive review of the literature in the updated consensus statements to be released this fall by the Society of Obstetricians and Gynaecologists of Canada (<http://sogc.medical.org/index.html>).

## Erica Weir

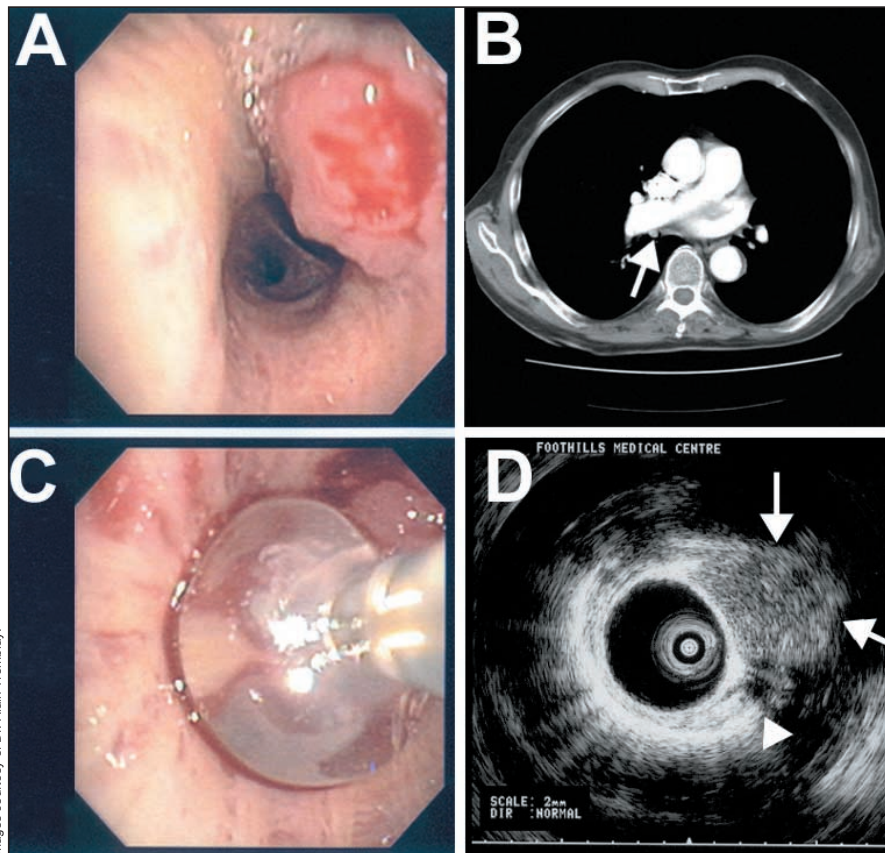
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## Endobronchial ultrasonography: extending the reach of the bronchoscope beyond the airway wall



Images courtesy of Dr. Alain Tremblay.

A 76-year-old man with a past history of hypertension, diabetes and cerebrovascular disease presented with nonresolving pneumonia. He was a long-time smoker. He underwent bronchoscopy and was found to have an endobronchial carcinoid tumour in the bronchus intermedius (Fig. 1, Panel A). Because of his comorbidities and the relatively indolent nature of carcinoid tumours, bilobectomy was not undertaken and the patient was referred for possible endobronchial resection with electrocoagulation.<sup>1</sup> Patients for whom this treatment modality is considered are routinely investigated with CT scans of the chest to determine whether the tumour has

spread through the bronchial wall. If the bronchial wall is compromised, curative endobronchial resection is not possible, because the tumour cannot be completely removed without perforating the airway.

For our patient, it was not possible to determine whether the bronchial wall was compromised (Panel B, white arrow) using a thoracic CT scan with thin-section cuts. It was decided with the patient's consent that a relatively new technique, endobronchial ultrasonography (EBUS),<sup>2</sup> would be used to help resolve the issue. EBUS involves the insertion of a 2.6-mm ultrasound probe into a dedicated balloon sheath (UM-BS20-26R 20-MHz probe, MAJ-

643R sheath; Olympus, Melville, NY) that can be inserted into the working channel of a flexible bronchoscope (diameter of working channel is 2.8 mm). With the patient under conscious sedation, the flexible bronchoscope is advanced in the usual fashion and the balloon is inflated with saline in the area of interest to create an imaging window free of air, which would make clear ultrasound images difficult to obtain. EBUS was performed in our patient at the level of the lesion (Panel C). At the same time, ultrasound radial images of the tissues adjacent to the probe are obtained in real time. Unfortunately in our patient's case, the lesion (Panel D, white arrows) has destroyed the bronchial wall (Panel D, white arrowhead), which is usually seen as a multilayered structure. This made this patient ineligible for curative endobronchial resection. He has had no recurrence of pneumonia to date, but should he develop obstructive symptoms in the future a palliative (partial) endobronchial resection could be considered.

Although further study is needed, EBUS appears to be a useful, safe and relatively simple tool to allow bronchoscopists to see beyond the airway wall, thus expanding the reach of the bronchoscope.

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# Does early defibrillation improve long-term survival and quality of life after cardiac arrest?

Bunch TJ, White RD, Gersh BJ, Meverden RA, Hodge DO, Ballman KV, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med* 2003;348:2626-33.

**Background:** Out-of-hospital cardiac arrest secondary to ventricular fibrillation (VF) carries a grim prognosis. Early defibrillation is important for successful resuscitation and survival. Automatic external defibrillators (AEDs) are simplified defibrillators that can be used by non-health care professionals. The operator places 2 electrode pads on the chest of a collapsed person. The AED then determines whether or not the person has a ventricular arrhythmia requiring defibrillation. The machine gives the operator instructions (often with voice commands) to either shock the patient by pressing a button, or to initiate cardiopulmonary resuscitation.

**Question:** What is the impact of early defibrillation on long-term survival and quality of life?

**Design:** This single-centre prospective cohort study, conducted in Olmstead County, Minn., involved all patients who had an out-of-hospital cardiac arrest from November 1990 to December 2000 after implementation of a local early defibrillation program. As part of the program, the use of AEDs had been

broadened to include police officers, firefighters and paramedics. All patients were followed to determine long-term survival and quality of life.

**Results:** Of the 200 patients with an out-of-hospital cardiac arrest with ventricular fibrillation, 145 (72%) survived to hospital admission with spontaneous circulation, 84 (42%) survived to hospital discharge, and 79 (40%) were neurologically intact at discharge. Long-term survival was realized by 60 patients (30%). For analysis, patients with significant neurological impairment at discharge were considered nonsurvivors. The key baseline differences between the survivors and nonsurvivors are shown in Table 1. The mean length of follow-up was 4.8 (standard deviation 3.0) years. The expected 5-year survival rate (79%) was identical to that among age-, sex- and disease-matched control subjects from the general population. The quality of life among the majority of survivors was similar to that of the general population.

**Commentary:** Early defibrillation is the key determinant of survival from cardiac arrest. The study by Bunch and associates, although small in numbers and from a single centre, demonstrates impressive results after implementation of an early defibrillation program. Similarly, a trial of AED use in casinos by security personnel demonstrated a rate of

survival to hospital discharge of 59% among people with a witnessed cardiac arrest due to VF.<sup>1</sup> In that study, the mean time to defibrillation was 4.4 minutes.

In contrast, patients with VF in the Ontario Pre-hospital Advanced Life Support study had a rate of survival to hospital discharge of only 10%.<sup>2</sup> This much larger study included 3447 patients with out-of-hospital ventricular arrhythmia. The authors concluded that shorter times to defibrillation are crucial to reducing the rate of death from VF.

Most studies of cardiac arrest have used return of spontaneous circulation and survival to hospital discharge as primary end points. The study by Bunch and associates shows that long-term survival is also possible and that those who survive report a good quality of life.

**Implications:** Broadening access to and training in AED use beyond health care professionals can help reduce the time to defibrillation and therefore increase survival from cardiac arrest. Deciding who to train in AED use (e.g., police officers, security guards, general public), where to place AEDs (e.g., shopping malls, arenas, airports) and how to fund early defibrillation programs will help to determine the success of these programs.



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**Table 1: Key baseline demographic characteristics of patients who had an out-of-hospital cardiac arrest with ventricular fibrillation and who were admitted to hospital**

Characteristic	Survived to discharge n = 79	Died before discharge* n = 63	p value
Age, mean (SD), yr	61.9 (15.9)	68.1 (14.3)	0.02
Hypertension, % of patients	14	36	0.005
Time from 911 call to administration of first shock from defibrillator, mean (SD), min	5.7 (1.6)	6.6 (1.5)	0.002
Witnessed arrest, % of patients	92	75	0.008

Note: SD = standard deviation.

\*Includes patients who had severe neurological impairment at time of discharge.

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## World's first nonprofit drug company launched

One major feature of the existing drug-development industry is that diseases with little profit-making potential fail to attract badly needed investment. But a new organization may change that.

Médecins Sans Frontières (MSF), with backing from health ministries and institutes in several countries, has created the world's first not-for-profit drug research organization. (Canada has yet to commit funds to the project.) Planners hope the Drugs for Neglected Diseases Initiative (DNDI) will spend around US\$250 million over 10 years to develop drugs to combat sleeping sickness, leishmaniasis and Chagas' disease.

The potential impact is great. About 500 000 cases of visceral leishmaniasis occur annually. However, a recent report (*Lancet Infect Dis* 2002;2:494-501) indicates that current treatments "require long courses and parenteral administration, and most are expensive." It said "new and imaginative" approaches are needed because no novel compound for treating the disease is in the pipeline.

But how can a drug company that is not buoyed by profits and investors be created? Where will the money come from?

Dr. James Orbinski, a Toronto physician and former international president of MSF, emphasizes that this is a "virtual" drug-development initiative and that development costs should be much lower than at typical "bricks-and-mortar" pharmaceutical firms.

In calculating drug-development costs, says Orbinski, the drug industry typically includes the cost of capital — essentially the opportunity cost — and some marketing costs. However, marketing will not be an issue for DNDI, and most of the research will be done in the developing world by public-sector scientists. This means that expenses should be modest. DNDI is also capital-

## Free-access era coming to an end at eBMJ

The small number of medical journals that provide their entire content free online will soon be even smaller, and the loss will be significant. In August, the *British Medical Journal* announced that it will begin charging an annual user fee of £10 (\$22) to £20 (\$44) for annual access (2003;327:241-2). The change will take place in January 2005; access will remain free for 120 low-income countries and BMA members. *BMJ* will also be much cheaper than most restricted-access journals — the *New England Journal of Medicine* charges Can\$14 for a single article and Can\$40 for a day's unlimited access.

In an editorial, Web Editor Tony Delamothe and *BMJ* Editor Richard Smith said the decision was made by the board of the *BMJ* Publishing Group because of "anxiety over falling library subscriptions to the paper journal."



They said the online fee is an attempt to introduce a new source of revenue as other sources begin to weaken. The editorial said that subscriptions account for only 12% of the *BMJ*'s total revenue, compared with 61% for job advertisements. However, the latter revenue stream is threatened by a new National Health Service Web site. Advertising by drug companies is also threatened, with promotional spending by drug companies declining by 8% in the past year.

The editorial attracted dozens of rapid responses at *eBMJ*, and although most writers accepted the argument that new revenue streams are needed, there was also a hint of sadness that an era was drawing to a close. "You will be leaving the *Medical*

*Journal of Australia* and the *Canadian Medical Association Journal* to carry the flag for the national medical society journals," said Stephen Due, chief librarian at the Geelong Hospital in Australia. "Canada, of course, still leads the way with an impressive array of free electronic journals in the specialties, including the *Canadian Journal of Surgery* and the *Canadian Journal of Psychiatry*."

Under the *BMJ* plan, all content will probably be free for "a week or two" following publication, and will then be placed behind access controls for a year or more.

*CMAJ* Editor John Hoey praised the *BMJ* for "its tremendous energy, foresight and leadership in providing free online access, which has made it a lot easier for the rest of us." But at the moment, he said, "we have no plans to follow the *BMJ*'s decision to limit access." — *Patrick Sullivan, CMAJ*

izing on drugs that have already undergone some development or been abandoned at some point along the development pipeline.

Brand-name drug companies have agreed to help. Companies such as Merck Frosst have provided significant support in helping DNDI design the drug-development process, and

GlaxoSmithKline says it will give the organization access to its compound libraries on a project-by-project basis.

Orbinski says the next step is to approach donors, although he acknowledges that this won't be easy. "It's always a challenge to raise money for needs outside the constituency of particular governments." — *Alan Cassels, Victoria*

## Researchers complain as CIHR axes investigator awards

§ See related articles pages 533, 567, 568

The Canadian Institutes of Health Research (CIHR) is eliminating its investigator and senior investigator awards, and many researchers are shocked by the sudden change.

Mark Bisby, CIHR's vice-president of research, says the decision was prompted by budgetary concerns. "This was a tough decision. To cut programs with 20- or 30-year histories is never easy, especially when those programs have such proud and distinguished reputations."

Researchers consider the change significant. They say the awards represented an important revenue stream for them, and many wonder how they will secure time for research.

Although the awards have been around for decades, the body that distributes them is relatively new. CIHR was launched in 2000, and has seen annual budget increases since then. In fiscal year 2002/03 its grants and awards budget was \$527 million, and this jumped by 10%, to \$580 million, in 2003/04.

Despite the growth, CIHR has faced a perennial problem: the inherent conflict between a system based on annual budgets and research funding that is spread over several years. This means that most of the CIHR's budget is already locked into long-term commitments.

Consistent budget increases have allowed the agency to fund programs beyond established obligations, but this appears likely to change. "If there is a budget increase [next year], it may not come early enough in the fiscal year for us to apply it to our major grants and awards competitions," Bisby explained.

This year CIHR has about \$170 million in uncommitted funds, and without a budget increase it predicts it will have \$70 million next year. As a result, the investigator and senior investigator awards were eliminated, and about half of the money earmarked for those programs will be funnelled into new investigator salary awards. "We are continuing to fund new investigators," Bisby said. "We are just getting out of the senior levels, which are very well covered by the Canada Research Chairs."

The federal government has allocated \$900 million to support the establishment

of 2000 new research chairs by 2005. The program is governed by a steering committee of presidents from the CIHR, the Natural Sciences and Engineering Research Council, the Social Sciences and Humanities Research Council and the Canada Foundation for Innovation, as well as the deputy minister of Industry Canada.

In the program, universities are granted a specific number of chairs, which correspond to their federal funding structure.

Bisby argues that the cancelled awards have been duplicated by the chairs program and were an obvious choice for "the chopping block." He also says the chairs program is more lucrative, offering an average of \$200 000 a year per researcher, compared with \$70 000 from CIHR. "Why are we still providing career awards when there is this separate federal program which can do it much better?" asks Bisby.

As well, the success rate for applicants to the cancelled programs was expected to fall below the 10% level, given the number of applications and the likelihood of no budget increase. "There comes a point where you waste an awful lot of people's time by running competitions that you can't really support very well."

Dr. David Naylor, dean of medicine at the University of Toronto and a CIHR governor, opposed the decision. "I know these awards are competitive, but as a dean of medicine I remain concerned that the CIHR has retreated too far from personnel support, leaving the field to the [chairs] program."

And Dr. Brian Hennen, dean of medicine at the University of Manitoba, says there is no guarantee the chairs program will be preserved after 2005. Even if it is maintained, Hennen says the CIHR awards are an important contribution. "These programs really nourish the scientific community and it is a mistake to discontinue them."

"This decision will make it increasingly

difficult to develop career salary support in this country and will be an incentive for people to look south of the border."

Bisby argues that the investigator awards were never meant to be a career support system. He notes that of the 44 senior investigator awards offered last year, only 4 recipients had previously held a CIHR award.

"Picking up a CIHR salary award if you already have one is a remote possibility, and the probability of getting a Canada Research Chair is probably somewhat better," he says.

Hennen disagrees. "The CIHR awards need to be there to offer scientists more options to continue to grow and develop."

And so does Dr. Peter St George-Hyslop, a past recipient whose pioneering work in the identification of genes causing inherited forms of Alzheimer's disease has revolutionized the field. He is skeptical the Canada Research Chairs program will be able to fill the void and echoed concerns the program may not be renewed after 2005. "CIHR salary awards, whether they are new, senior or distinguished, attract the crème de la crème of Canadian biomedical science. These are the people you can't afford to lose."

Denis Croux, director of operations for the Canada Research Chairs, says concerns about the program being discontinued are unfounded. Croux has "confirmation the intent is the [chairs] will be funded on a continuing basis."

CIHR career awards are granted to individual researchers, but the chairs are awarded to universities. The role of the institution is therefore much greater in the chairs program, and researchers are unable to transfer the award should they relocate.

Bisby says there's always a possibility that program changes will be reversed. "My interpretation of the governing council's decision was that this is permanent, but it can always go back and revisit things. I think the reaction to some of these changes will probably prompt a re-examination. And that's perfectly appropriate." — *Allison Gandy, CMAJ*



**St George-Hyslop: "These are people you can't afford to lose"**

U of T Bulletin

## SARS affects hospital plans?

The provincial government is building 2 new superhospitals in Montreal, but it won't be shutting down all of the city's other hospitals as previously planned. Instead, each of the 2 superhospitals will have to be complemented by another smaller one, says Health and Social Services Minister Philippe Couillard, with the smaller hospitals chosen from existing institutions. Couillard appears to be applying lessons learned during Toronto's recent battle with SARS, when several hospitals closed their doors to patients for varying periods because of the threat of infection. The 1832-bed superhospitals are to be ready by 2010, about 4 years later than originally planned. — *CMAJ*

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## \$1.5 billion at stake as tobacco smuggling lawsuit relaunched

The federal government is relaunching a legal battle to reclaim \$1.5 billion in taxes it lost to cigarette smuggling. In a lawsuit filed Aug. 12, the government alleged that more than 10 tobacco companies had conspired to make illegal profits via smuggling.

In the early 1990s cigarette smuggling was rampant in Canada because of the introduction of high taxes designed to cut consumption. The federal government responded with significant cuts in excise taxes that made the crime less lucrative. The RCMP have called the smuggling operation the largest case of corporate fraud in Canadian history.

The government's decision to pursue the case came after the Coalition Against Tobacco Tax Evasion, a group of nonsmokers' rights activists and medical officers of health from across the country, challenged it to launch a lawsuit before time ran out.

Ottawa had launched a suit in the US in late 1999 against RJR-Macdonald Inc. (now JTI-Macdonald Corp.) and its sister companies, but it was thrown out in November 2002 on a technicality. A new suit had to be filed by the end of August if the government was to pursue the case.

"These tobacco taxes were an important public health measure that was undermined by the tobacco companies," complains Dr. Brent Friesen, a member of the coalition and president of the Alberta Medical Association's Section of Community Health Physicians. "It's appropriate for governments to pursue those revenues. It sends a powerful message to ... boards of directors that they will be held accountable for their actions."

Before the lawsuit was filed, the coalition launched a letter campaign and was preparing a newspaper advertisement complaining about government inaction.

David Sweanor, legal counsel for the Non-Smokers' Rights Association, said it was important that the lawsuit be pursued.

"At a time when governments are cutting back on disease prevention, it's very difficult to see them walk away from what could be billions of dollars in compensation for what the [tobacco] industry did."

In an Aug. 13 statement, JTI-Macdonald Corp. said "these worn-out allegations are being pumped up by an overzealous antitobacco lobby" whose existence depends on "attacking the Canadian tobacco industry." — *Louise Gagnon, Ottawa*



## CMA annual meeting sees rare contested election for presidency

A rare contested election to lead the association and a seemingly innocuous non-smoking resolution prompted intense lobbying during the CMA's August annual meeting in Winnipeg.

By the time the meeting concluded Aug. 20, the CMA had a president-elect, Windsor GP Albert Schumacher, who had not been the official nominee from Ontario. And a resolution that would have forced the CMA to hold its annual meetings only in cities with public smoking bans was amended because of the logistical problems.



**Dr. Albert Schumacher: nominated from the floor**

Coming into the meeting, Dr. John Tracey, a GP from Brampton, Ont., and a newcomer to national medical politics, had been the official candidate to lead the CMA after the 2004 annual meeting (*CMAJ* 2003;168[11]:1455). Although only about 30% of members cast ballots, he had defeated 5 former Ontario Medical Association (OMA) past presidents in a runoff (*CMAJ* 2003;168[9]:1170). Tracey is a founding member of the Coalition of Family Physicians of Ontario, which has challenged the OMA's moves to negotiate alternative funding mechanisms for family doctors.

During the meeting, however, 2 unsuccessful candidates from the Ontario election, Schumacher and Dr. Ron Wexler, were nominated as president-elect from the floor, a rare although not unprecedented situation. Similar elections were held in 1979 and 1998.

In his nomination speech, Tracey urged delegates to respect the "democratic voice of the physicians of Ontario" and ratify his nomination, while Schumacher stressed his longstanding involvement in medical politics and advocacy on behalf of physicians and Wexler discussed fundamental issues facing the medical profession. Wexler was eliminated after the first round of voting, and Schumacher emerged as the successful candidate after the second round.

The other issue to prompt intense lobbying involved an attempt by Mani-

toba physicians to force the CMA by 2005 to limit its annual meeting sites to cities that have 100% indoor smoking bans in place.

If adopted, the motion would have forced the association to cancel contracts that have already been arranged for annual meetings up to 2008. More significantly, because of the limited number of cities across Canada with strong non-smoking bylaws, it would have prompted a fundamental reassessment of the CMA's traditional policy of electing a president from the province in which the annual meeting is held.

"This speaks to the vision of this association," said Dr. Jay Duncan, who proposed the motion. "There will be some cost, but we can do it."

Others noted that the CMA had already passed a motion urging governments to adopt strong antismoking regulations, and they felt the CMA should also set an example.

However, some delegates questioned the proposed timeframe. "We're all against smoking" said Dr. Harry Callaghan of PEI, "but the motion is going too far too quickly."

An attempt to refer the motion to the CMA board was unsuccessful, but an amendment proposed by outgoing President Dana Hanson to remove the strict timeframe and substitute the words "once current contractual commitments are honoured" was adopted. — *CMAJ*

## Restore flexibility in postgraduate education, MDs beg

Correcting fundamental problems with medical education in Canada and addressing the shortage of family physicians appeared to be major priorities for delegates to the CMA's 2003 annual meeting.

They strongly endorsed motions supporting creation of a common PGY-1 year for medical graduates in order to provide more flexibility and encourage more students to enter family medicine.

Support for some form of rotating internship or common PGY-1 year has long been endorsed by the CMA. However, the decline in the popularity of family medicine and growing complaints from students forced to choose a specialty early

in training have caused alarm bells to ring.

The resolutions were debated after a session on issues surrounding the physician shortage and problems with medical education. Dr. Alecs Chochinov, chair of the CMA's Council on Medical Education, said the proportion of medical students choosing to enter family medicine has declined from 34.7% in 1997 to 24.8% this year. He said the growing debt load is one factor forcing students to select higher-paying specialties.

Chochinov also bolstered the case for a common PGY-1 year by noting that the number of physicians starting their careers in family medicine has declined from 80%

in the early 1990s to 45% today.

The only opposition came from an Ontario physician, a former nurse who said that the common entry year was "a year of service rather than education. I worked with you then. You were exhausted. You weren't learning."

Other resolutions called for:

- development of a national locum licence;
- establishment of an independent health institute for human resources to conduct research;
- more financial aid to offset escalating tuition fees for medical students. — *Pat Rich, CMAJ*

## New editorial fellow has journalistic roots

Perhaps Stephen Choi's path to *CMAJ*'s editorial fellowship was preordained.

His grandfather, Jong-In Hong, was a nationally renowned journalist in Korea who received birthday presents from the country's president, while his father's passion for literature led him to give his only son the middle name Bernard — in homage to George Bernard Shaw.

Choi, who completed his residency in emergency medicine at Queen's University earlier this year, has opted to spend his first year at *CMAJ* instead of in an emergency department, in part because he felt it would help fulfil his latent literary leanings.

"I've always had an interest in writing because I'm a big reader, and the two go hand in hand. Science writing can also include a nice turn of phrase, and I like the idea of translating medical knowledge into something that's more understandable.

"I'm also interested in the goings-on at a medical journal. How do you manage to publish every couple of weeks? What do you publish? What should you publish?"

The position of editorial fellow has existed for 6 years. The fellow, who acts as an associate scientific editor, spends a year reviewing submissions, corresponding with authors and working closely with the senior editorial team to develop clinical and editorial content.

Previous fellows have had a significant impact on the journal. Two are now part-time associate editors: Dr. Erica Weir contributes regularly to the Public Health column, while Dr. Eric Wooltorton launched and oversees *CMAJ*'s well-received Practice section. The 2002 fellow, Dr. James Maskalyk, will launch a section on international health this fall. Choi has already set his sights on the journal's section for Review articles — he'd like to see them refined — and he is also working to make the journal's layout more reader-friendly.

Choi, whose parents emigrated to Canada in 1969, was born in Sudbury, Ont., and raised in Toronto, and decided to pursue a medical career after completing his

first year at Queen's University. "I wanted something practical, not theoretical. I later chose emergency medicine because it's such a hands-on field."

Medical school provided a chance to spend 2 months in Guyana with Queen's Medical Outreach, and he also proved a diligent student. His awards included the Professor's Prize in Emergency Medicine.

He was also able to maintain his outside interests. He was drummer for a Kingston band, Cellar, which was inspired by bands like U2 and Radiohead. "It's fun to hit things," he says of the drums.

He also hosted a campus radio show called *Sing It on Stage*, in which he commented on and played songs from musicals ranging from *West Side Story* to *Rent*. During his second year he was director/drummer for the Medical Variety Night of skits, song and dance, which raised about \$13 000 for charity.

Choi, an avid golfer, has also nurtured an interest in photography, and especially appreciates how photography allows him to attend to small details that in the end constitute the big picture. He views his work at *CMAJ* in the same light: "Out of the little bits of scientific editing," he says, "you construct a big picture."

He chose emergency medicine for the excitement of working under pressure on all types of cases, and will keep his clinical skills sharp while at *CMAJ* by working at emergency departments in Ottawa. Working at *CMAJ* won't be Choi's only change in 2003/04. This January he will marry psychology student Lisa Couldridge at a family ceremony in Antigua.

Applications for the 2004 editorial fellowship must be received by Dec. 17, 2003 ([www.cmaj.ca/misc/fellowship.shtml](http://www.cmaj.ca/misc/fellowship.shtml)). — Barbara Sibbald, CMAJ



Barbara Sibbald

**Dr. Steve Choi: setting his own beat at CMAJ**

## FDA seeks distance from "parasitic-Canada" comment

The US Food and Drug Administration (FDA) says its commissioner, Dr. Mark McClellan, meant "no offence" when he appeared to support a journalist's observations that Canada's drug policies are "parasitic" and that the country has not produced a new drug since 1940.

In a late July airing of the Public Broadcasting Service current affairs show *One on One*, McClellan responded "that's right" after interviewer John McLaughlin said: "Do you think — without causing an international crisis here — that Canada's behaviour is parasitic? They're parasitic because they're living off of the research that we do, and that research is paid for by the taxpayer who has to pay the prices for it through the price of prescription drugs."

The FDA later said the word "parasitic" was pressed upon McClellan and does not reflect his true feelings. "It was a word introduced by McLaughlin," says Peter Pitts, associate commissioner for external relations. "[McClellan] did not use that word. It is not his word and it is not what he thinks."

Members of the Canadian pharmaceutical industry were dismayed after the original interview aired. "I think there must have been a lack of information," says Jacques Lefebvre, spokesperson at Canada's Research Based Pharmaceutical Companies.

He points to a list of more than 40 drugs that have been discovered or largely developed in Canada since 1987. The list includes a high-profile asthma drug, the leukotriene blocker montelukast sodium (Singulair), as well as one of the prime components of the drug cocktail that has been successfully battling HIV and AIDS, lamivudine (Epivir).

Pitts also downplayed the claim that Canada has not developed a drug since 1940. "I think that we would be more than willing to defer to the people that have done the research," he said. "No offence was intended against Canada's medical establishment." — Brian Whitwham, Ottawa

## News @ a glance

**Dalhousie goes smoke-free:** This month, Dalhousie University in Halifax became the first in Canada to ban smoking on its property, but 6 other universities are already showing interest in the program. "We don't want to persecute people who smoke," says William Louch, director of environmental health and safety at Dalhousie, who notes that smokers can still move to public property, such as sidewalks, to light up. "We are controlling what we can." Dalhousie's decision follows a survey last winter in which 82% of respondents said they supported a ban. Dalhousie introduced a scent-free policy in 1998 that has been "hugely successful," Louch told *CMAJ*. The smoking ban was launched with an educational campaign, and smoking-cessation programs are being offered.

**\$1 billion for disease fight:** The president of the European Commission says he will fight for a \$1-billion contribution to the Global Fund to Fight AIDS, Tuberculosis and Malaria for 2004. "History will judge us harshly if we do not use our power to reduce poverty ... and avert the threat of death hanging over mankind," said President Romano Prodi. "I am guarantor for the one billion." Thus far, the 15 member states of the EC have committed 460 million Euros to the fund, accounting for 55% of its total. French President Jacques Chirac wants Europe and the US to contribute \$1 billion each annually. Since the fund was founded in January 2002, \$1.5 billion has been approved for 150 programs in 92 countries.

**Federal rule targets BSE:** As a result of last spring's case of bovine spongiform encephalopathy (BSE) in an Alberta cow, the federal government has prohibited human consumption of "specified risk materials," including the brain and spinal cord. In BSE-infected cattle, the abnormal prion proteins concentrate in tissues such as the brain, and there may be a link between the consumption of these tissues



from infected cattle and the incidence of variant Creutzfeldt-Jakob disease (vCJD), the human equivalent of BSE. The ban on using these body parts for human consumption took effect Aug. 23.

**NHL concussion rate plateaus:** The reported concussion rate among National Hockey League athletes over the last 5 years is triple that of the previous decade but has now plateaued, a new study indicates (*Can J Neurol Sci* 2003; 30:206-9). In 1986/87, 4 concussions were reported per 1000 games; by 2000, there were 30. Initially the researchers thought bigger, faster players, new equipment and harder boards were responsible for the increase. But the rapid rise and subsequent settling at the higher rate suggest that "increased medical recognition of concussion and increased reporting are responsible for much of the apparent increase," states neurologist Richard Wennberg of the Toronto Western Hospital. The increase in reported concussions began in 1997, about the same time the NHL started a program to lessen the danger. "Neurologists, trainers and players are more aware now of the concussion problem than they were even 10 years ago," says coauthor Dr. Charles Tator. The authors gleaned their data from weekly injury reports in the *Hockey News*.



**Meningitis risk for cochlear implant recipients:** A new study shows that children with cochlear implants are at a much greater risk of bacterial meningitis than other children (*N Engl J Med* 2003;349:435-45). Researchers followed 4264 children in the US between Jan. 1, 1997, and Aug. 6, 2002, and found that 26 had developed bacterial meningitis caused by *Streptococcus pneumoniae*. The incidence was 138.2 cases per 100 000 person years, more than 30 times higher than among children in the general population. The risk was greatest in children whose implants included a Silastic wedge positioner, which the manufac-

turers recalled in July 2002. There was also an increased risk among children with inner-ear malformations or cerebrospinal fluid leaks. A commentary in *NEJM* and in *CMAJ* (2002;167:670) called for appropriate vaccination for anyone using these implants.

**US bill up in smoke:** A surprisingly strong bid to allow medicinal marijuana use in California and 9 other US states was defeated by the US House of Representatives, 273 to 152. A similar bid in 1998 was defeated by 311 to 94. The 10 states allow medicinal use of marijuana, but federal prosecutors are still charging people for such use. Representatives from these states wanted to shield these smokers from federal prosecution.

**SARS claims first North American doctor:** Toronto FP Nestor Yanga died Aug. 13 after battling SARS since April. Yanga, 54, contracted SARS in the first few weeks of the outbreak after treating a patient who had the illness. He was placed in intensive care Apr. 8 and remained on a respirator during most of his stay. Yanga, past-president of the Filipino Canadian Medical Association, is survived by his wife and 2 sons. His death was the 44th related to SARS in the Toronto area, and he was the first physician in North America to succumb. Two Toronto nurses, Tecla Lin and Nelia Laroza also died.

**Triple HIV-treatment warning:** Glaxo-SmithKline is warning health care providers about a high rate of early virologic non-response in a clinical trial of therapy-naïve adults receiving once-daily combination therapy with lamivudine (Epivir), abacavir (Ziagen) and tenofovir (Viread). The company reported poor efficacy in patients receiving the triple-treatment and terminated that arm of its clinical trial. It also says that abacavir and lamivudine should not be used in combination with tenofovir as a triple antiretroviral therapy in naïve patients or those already receiving treatment. — *Barbara Sibbald, CMAJ*

## PULSE

## Health care bill reaches \$3245 per Canadian

Total spending on health in Canada is projected to have reached \$112 billion and to have accounted for 9.8% of the gross domestic product in 2002, the Canadian Institute for Health Information says. This compares with projected totals of \$106 billion and 9.7% in 2001.

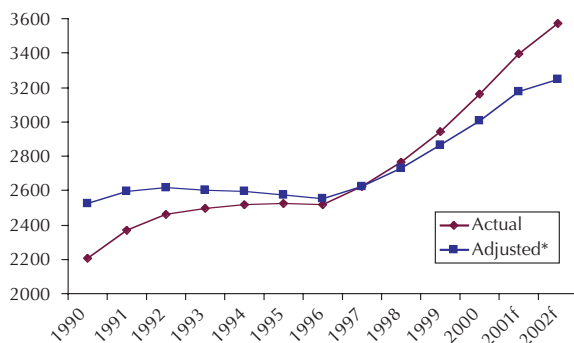
The shares of the expenditure pie held by the public and private sectors are holding steady at about 71% and 29%, respectively. However, in the case of drugs, about 65% of spending is done through private sources, such as employer-provided insurance or the consumer's wallet.

Over time, data on health expenditures can be adjusted to eliminate the effects of inflation. In terms of these constant dollars, there were decreases in per capita spending for 4 years in the early 1990s. In recent years there have been spending increases of between 3% and 5% each year. In 2000, spending averaged \$3006 per person in Canada, compared with adjusted per capita forecasts of \$3172 in 2001 and \$3245 for 2002.

Drugs continue to represent a growing share of expenditures. They accounted for 15.4% of total spending in 2000, up 35% from the 11.4% level set a decade earlier. Drug spending is forecast to exceed 16% by 2002. In contrast, physicians' share of total expenditures has decreased from 15.2% of the total in 1990 to 13.3% in 2000.

After some years of decreased expenditures between 1991 and 1997, capital spending is again on the rise, and has averaged double-digit percentage increases in recent years. Between 1990 and 2000, spending in this area increased by 65%. — *Lynda Buske*, Associate Director of Research, CMA

Trends in health expenditures (per capita spending)



\* in constant 1997 dollars  
f – forecast data

Source: National Health Expenditure Trends, 1975-2002, CIHI



**Notice** — *CMAJ* welcomes obituaries submitted within 60 days of a death. These should be no longer than 200 words, and colourful writing is encouraged. Send to Patrick Sullivan, [patrick.sullivan@cma.ca](mailto:patrick.sullivan@cma.ca); fax 613 565-2382.

**Bell, David N.**, Nepean, Ont.; University of Toronto, 1953; anesthesia; FRCPC; former staff, Ottawa Civic Hospital. Died May 24, 2003, aged 75; survived by his wife, Catherine, and 4 children.

**Cossette, Honoré**, Charette (Qué.); Université Laval, 1950; ancien membre du personnel agrégé du Centre Hospitalier Régional de la Mauricie (Shawinigan-Sud) et Centre Hôpital Ste-Thérèse, Shawinigan; médecin légiste de district. Décédé le 27 décembre 2002, à l'âge de 77 ans.

**Dimmick, James E.**, Vancouver; University of British Columbia, 1968; FRCPC; former head, Pathology and Laboratory Medicine, Children's Hospital, Vancouver, and University of British Columbia; president, International Society of Pediatric Pathology. Died of Alzheimer's disease June 30, 2003, aged 62; survived by his wife, Mildred, and 2 stepsons. "He pioneered the field of pediatric pathology and developed Western Canada's first pediatric organ bank."

**Dionne, Jean-Marie**, Québec; Université Laval, 1940. Décédé le 5 avril 2003, à l'âge de 90 ans.

**Doherty, George B.**, Oshawa, Ont.; McGill University, 1950; general practice; former staff, Oshawa General Hospital. Died Apr. 23, 2003, aged 78; survived by his wife, Ann, and 6 children. "He was one of the last 'old-time' doctors, as no night was complete unless he lost at least some sleep to a house call."

**Fried, Bernice A.**, North York, Ont.; University of Cape Town (South

Africa), 1972. Died May 21, 2003, aged 54; survived by her husband, Jack, and 2 children.

**Gault, Mathew H.**, St. John's; McGill University, 1954; nephrology; FACP, FRCPC; former director, Nephrology, Health Sciences Centre; head, Clinical Chemistry and Nephrology, Queen Mary Hospital, Montreal; professor emeritus, Memorial University; president, Canadian Society of Nephrologists; officer, Order of Canada. Died May 23, 2003, aged 78; survived by his wife, Phyllis, and 1 son.

**Goldberg, Karolina**, Outremont, Qué.; University of Bologna (Italy), 1938; general practice; former staff, Reddy Memorial and Jewish General hospitals. Died Apr. 21, 2003, aged 90.

**Hopson, W.L. Gilbert**, Sault Ste. Marie, Ont.; Queen's University, 1967; plastic surgery; former consulting staff, Sault Area hospitals—General and Plummer sites. Died of cancer Apr. 18, 2003, aged 59; survived by his wife, Ruth, and a daughter. Dr. Tim Best told the *Sault Star*: "He was hailed as the best hand surgeon in Northern Ontario, whose excellent reputation provided the foundation for what is now a 'thriving' specialty in Algoma — we basically wouldn't exist without him."

**Hudson, John E.**, Hamiota, Man.; University of Manitoba, 1941; MCFP; former chief of medical staff, Hamiota District Health Centre; staff, Hamiota District, Shoal Lake and Riverdale hospitals; senior member, CMA. Died May 19, 2003, aged 86; survived by his wife, Dorothy, and 4 children.

**Lloyd, J. Ewart**, Kelowna, BC; University of Wales, 1940; former medical director, Family Life Assurance and Sovereign Assurance companies; assistant professor, University of Calgary. Died June 11, 2003, aged 86; survived by his wife, Elizabeth. His daughter-in-law Judy stated: "His many achievements were driven by his desire to cope with

dyslexia, a condition that kept him out of the army. But the man who was not good enough to be a soldier proved to be an extraordinary doctor."

**MacKay, Kenneth H.**, Campbell River, BC; University of Toronto, 1950; obstetrics/gynecology; flight instructor, RCAF, WW II; former chief, Obstetrics/Gynecology, Scarborough General Hospital. Died May 27, 2003, aged 82; survived by his wife, Miriam, and 4 children. His daughter Ruth stated: "Many thousands of babies were delivered by and welcomed into this world by Dad."

**Murray, Bernard V.**, Corner Brook, Nfld.; National University of Ireland, 1949. Died May 23, 2003, aged 84; survived by his wife, Ursula, and 2 sons.

**Paquin, Jean-Louis**, L'Île-Bizard (Qué.); Université de Montréal, 1945. Décédé le 30 mars 2003, à l'âge de 86 ans.

**Simms, G. Graham**, Bedford, NS; Dalhousie University, 1938; FRCPC, CRCPC; DPH; public health; former vice-chair and executive director, Nova Scotia Hospital Insurance Commission; associate professor, Dalhousie University. Died Apr. 5, 2003, aged 89.

**Stein, Samuel**, Toronto; University of Saskatchewan, 1962; psychiatry; FRCPC; former assistant professor, University of Toronto; president, Toronto and Canadian Psychoanalytic societies and institutes. Died of cancer July 10, 2003, aged 65; survived by his wife, Betty, and 3 daughters. Son-in-law Aleixo Muise stated: "He loved teaching, dancing, classical music and books, good food and wine, his canoe, spending money, flying to Chicago or Africa on his flight simulator, his Portuguese water dog, Pepper, and living life to the fullest."

**Stitt, Howard S.**, Llano, Texas; University of Toronto, 1958; MCFP; former staff, St. Catharines General Hospital. Died Jan. 13, 2003, aged 71.