The future of Alzheimer's disease treatment

Serge Gauthier

*McGill Centre for Studies
in Aging, Alzheimer's disease
Study Unit,
6825 LaSalle Blvd,
Verdun, Quebec
H4H 1R3, Canada
E-mail: serge.gauthier@
mcgill.ca*

Serge Gauthier talks to Charlotte Barker

Serge Gauthier is director of the Alzheimer's Disease and Related Disorders Research Unit, at the McGill Center for Studies in Aging, Douglas Hospital, and a Professor of Neurology & Neurosurgery, Psychiatry and Medicine at McGill University (Quebec, Canada). He has authored numerous peer-reviewed papers, as well as editing several major textbooks. He has been instrumental in the development of consensus guidelines on the approval and use of antidementia drugs.

Your early work, with Professor Theodore Sourkes, focused on Parkinson's disease. How did you first become interested in Alzheimer's disease?

My interest in Alzheimer's disease (AD) came from meeting a 33-year-old nurse with the early stages of familial (autosomal dominant) AD, with nine brothers and sisters, most of whom later became my patients. Around the same time, a young psychiatrist (Dr Pierre Etienne) was looking for a neurologist to help him in the diagnosis and treatment of early AD using choline and lecithin.

You were lead author of a 1990 study assessing the safety and efficacy of tacrine for the treatment of AD, published in the *New England Journal of Medicine*. In your opinion, what impact did that study have on the profile of AD research in Canada and on the design of AD studies in general?

The Canadian tacrine study was the first investigator-driven, multicenter study on AD in Canada. We selected the best-available measurement tools for cognition, activities of daily living (ADL) and behavior. Family reports suggested a return of initiative in patients treated with tacrine, lost on stopping the drug. There was measurable benefit, but the side effects and liver-enzyme elevations made the drug unacceptable to us as investigators and to the Canadian Health Protection Branch. The experience gained in this first study led to the development of a Canadian scale to measure ADL and new methods of analysis for behavior.

Your research now focuses on the prevention or delay of AD. What are the main factors influencing susceptibility to AD and which of these do you think will prove most susceptible to intervention?

Prevention (in asymptomatic persons at risk) or delaying progression (from amnesic mild cognitive impairment [MCI] to AD, or mild to moderate/severe AD) is being attempted using different approaches, ranging from a natural antioxidant (Ginkgo biloba), to a statin (atorvastatin calcium), to a gag-mimetic (NC-758). The efficacy of these treatments may depend on the stage of pathology and the expected age of onset. In other words, a person with very early AD (<50 years) in his family would benefit from anti-amyloid therapy, whereas someone with late AD (>75 years) in his family may do better with a statin.

Several acetylcholinesterase inhibitors and the *N*-methyl-D-aspartate-receptor antagonist memantine are now licensed for use in the treatment of AD.

However, the benefits reported are modest and some experts (including the UK National Institute for Clinical Excellence) have suggested that their long-term use is not justified given their cost. How would you respond to this?

The efficacy of cholinesterase inhibitors and memantine for some of the patients with AD over 1–2 years is not in dispute. The difficulty is predicting who will respond (not possible yet), how to measure this improvement (not done using a number such as cholesterol level or blood-pressure recording), and whether the

benefits are worth the costs. I think that they are, if we can agree on stopping rules for patients who do not benefit.

What would you consider to be your greatest professional achievement to date?

My greatest professional achievement to date has been to develop, in Canada, an infrastructure to test new treatments in AD. The Consortium of Canadian Centers for Clinical Cognitive Research (CR) links 33 specialized clinics, giving Canadians access to the best-available treatments early in their development.

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You have been an advocate for AD patients’ right to participate in clinical trials. What are the main practical and ethical barriers to participation for AD patients and how do you propose to overcome these?

The progressive loss of competence associated with AD can be overcome by writing a mandate in case of incapacity – allowing someone you trust to give consent when you cannot any longer. Laws and ethical guidelines protect persons with AD in weighing benefits versus risks

for therapeutic studies. Ethical issues in the care of people with AD also involve end-of-life decisions, respecting their advance directives.

What do you hope to achieve in the next 5 years?

In the next 5 years I will have re-edited my main textbook (*Clinical Diagnosis and Management of Alzheimer’s Disease*), completed a study with NC-758 in mild-to-moderate AD, a study with memantine in moderate-to-severe AD, and hopefully helped initiate disease-prevention studies in at-risk individuals, using a non-steroidal anti-inflammatory drug. I will have helped to update the Canadian Guidelines for Management of Dementia and to disseminate them to interested health professionals and the public at large.

What are the likely targets for future drug therapies?

Likely targets for future drug therapies in AD will be the mechanisms for brain repairs, building on the finding that apolipoprotein (apo)E4 carriers have impaired ability to maintain synaptic integrity.

Do you expect to see a cure for AD in your lifetime?

The cure for AD in my lifetime (I am now 55 years old) will be to decrease the incidence by half using our knowledge of risk (especially systolic hypertension in midlife) and protective factors (a balanced diet, a little red wine and a happy marriage!).