Alberta Doctors' Digest

Alzheimer’s dementia is among the most feared of human disorders

“I am a very foolish fond old man,

Fourscore and upward, not an hour more or less;

And, to deal plainly,

I fear I am not in my perfect mind.”

- William Shakespeare, *The Tragedy of King Lear*

An update from the Alzheimer’s Association International Conference (Toronto, July 2025)

While there are many Alzheimer’s organizations around the world, one of the biggest – the Alzheimer’s Association (AA), founded in 1979 – is based in Chicago, Illinois. It funds supportive care and research into Alzheimer’s disease. The association also organizes an annual international conference (AAIC), this year in Toronto.

As a retired oncologist and with a family member with the disease, I’ve always felt it incumbent on me to follow dementia research. At the conference, three broad areas had small yet significant advances reported:

1. Diagnostic blood tests with publication of a clinical guideline.
2. Prevention with the reporting and publication of the US POINTER trial.
3. Drug therapy with increased understanding of the beta-amyloid antagonists lecanemab, donanemab and trontinemab.

Epidemiology

Dementias of various pathogeneses now are among the most feared of human disorders with 400-500,000 people in Canada living with dementia. Alzheimer’s disease is more common in women (two-thirds of seniors with dementia are women). There’s been an increase in incidence of Alzheimer’s and other dementias in the last 50 years, at least partly due to a global increase in longevity with better nutrition and medical successes against cancer, heart disease, infections and other disorders. From 55 million cases globally in 2019, the incidence may reach 139 million for Alzheimer’s dementia in 2050 with around 150 million of Alzheimer’s and other dementias by that time.

History

In 1907, Aloysius Alzheimer described symptoms in a 51-year-old woman:

“Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When reading a test, she skips from line to line or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing she repeats separate syllables many times, omits others and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions (“milk-pourer” instead of cup); sometimes it’s obvious she cannot go on. She doesn’t understand certain questions and doesn’t remember the use of some objects.”

Our family member, May, has suffered cognitive decline typical of Alzheimer’s dementia. After raising our family, she studied for her MSc in psychology, and in 1985, at 37, became a practicing psychologist on the adolescent wards of the University Hospital, Edmonton. She had a bout of facial shingles in her sixties. She started to exhibit occasional symptoms in her mid-sixties such as false memories – being convinced of their accuracy. She was able to continue as a clinical psychologist until retiring at age 65, having become self-aware of difficulty keeping up with changes in the appearance and management of the website she used for her cases – a symptom many of us oldies can sympathize with. She has now progressed to full-time nursing care, unable to participate in conversations, not knowing where she is, not even knowing who is talking to her. Reading my diaries of the progress of this evil condition is harrowing, but I do my best to keep up with the research.

Genetics

A connection has been found between the gene apolipoprotein E (APOE) and the development of Alzheimer’s disease. This gene is responsible for the protein that carries cholesterol in blood vessels. One form of the gene, APOE-e4, has been shown to increase the chances of developing the disease. However, the APOE-e2 form protects against the disease. Rare single gene variants APP, PSEN1 and PSEN2 are associated with the disease.

Diagnosis

There are variable diagnostic criteria for Alzheimer’s disease and other dementias such as alcoholic dementia (Wernicke-Korsakoff syndrome, which is thiamine deficiency) or vascular-related dementia.

Alzheimer’s tends to fall (in the absence of biopsy evidence) into the categories of “probable” or “possible” Alzheimer’s and requires a history of an observable and progressive decline in cognitive function, particularly short-term memory and language. Almost all patients with dementia will develop behavioural and psychological symptoms of dementia (BPSD) such as apathy, depression, sleep problems, agitation, psychosis and socially inappropriate behaviours. However, BPSD is not part of the core diagnostic criteria for dementia. A diagnosis of dementia requires cognitive decline that impairs the ability to live independently.

Blood biomarker studies

Full diagnosis requires at least early clinical symptomatology to be present for likelihood of Alzheimer’s disease, especially (at present) as an indication for prescription of any of the current anti-beta-amyloid drugs. The search for reliable blood biomarkers in the early diagnosis of Alzheimer’s dementia is advancing with the presentation of a clinical

practice guideline at this year's international conference. This guideline proposed that blood tests require 90% both in sensitivity and specificity to be diagnostically useful or, in the case of a lower 75% specificity combined with a 90% sensitivity, they require combination with a PET scan that assesses beta amyloid. Tests that meet these sensitivity and specificity levels are plasma-phosphorylated tau (p-tau) and its ratio to non-p-tau for p-tau types 217, 181 and 231. Amyloid-beta ratios of AB42 to AB40 are also useful.

Causation

Uncovering the precise cause of Alzheimer's dementia is a huge societal objective but remains elusive. Proposed causes range from genetic predispositions (e.g., the APOE-e4 gene), to exposure to environmental agents (e.g., copper and lead), and infections. A recent horrifying paper reported the implication of growth hormone injections taken from cadaver brains contaminated with Creutzfeldt-Jacob prions then given to children to promote growth. Lithium deficiency has recently been mooted as a causal factor in a paper in *Nature*. A paper was presented showing long-term effects of environmental lead poisoning on memory up to 50 years post-contact. Early menopause has also been considered, with hormone therapy being helpful.

Studies presented at the 2024 conference and at the 2025 continue to show that the administration of recombinant zoster vaccine (Shingrix) may be associated with a lower risk of dementia compared to non-vaccinated groups and also compared to other vaccines (including influenza and tetanus, diphtheria, and pertussis.) This is a fascinating story, though it lacks an absolutely concurrent control group. The baseline hypothesis is fascinating: varicella virus still lurking in one's body from childhood chickenpox can access the central nervous system and set up inflammatory responses deleterious to neural function, but this can be modified by shingles vaccine. Other studies, e.g., Zoster-122, also show a statistically significant association between Shingrix vaccination and a 17% increase in dementia-diagnosis-free time (164 additional diagnosis-free days) as well as a reduced risk of shingles at six years post-vaccination but no difference in all-cause mortality.

Possible chemotherapy related cognitive effects

As an oncologist, I've been concerned about this entity, sometimes called "chemo-brain," though I've found it unusual in following up large numbers of patients after chemotherapy for breast cancer over many years. Patients complain of fatigue and malaise that may temporarily impact cerebral function, but these usually start improving three to six months after completion of their protocols (highly dependent on drugs used). But a study presented at this year's AAIC suggested women receiving certain drugs may have decline in memory and thinking detectable even three years after treatment completion.

This study from Imperial College, London, involved 270 breast cancer patients who received anthracyclines and taxanes in the previous year. Participants underwent neurocognitive pre-screening with an artificial-intelligence-based online platform. From this group, 18 patients with lower scores and 19 matched controls were selected for further in-person cognitive testing and brain imaging.

Many of the 18 in the chemo group were found to have inflammatory changes and shrinkage in cerebral areas typical of changes seen in Alzheimer's dementia. There may

be many different causes for this. These studies are urgent in oncology since a knowledge of competing causes (age, other non-chemotherapeutic drugs used, types of cytotoxic drugs implicated) and precise long-term cognitive effects in this group where major survival gains have been achieved is critical.

Prevention studies

The US POINTER clinical trial, a study of prevention of age-related cognitive decline in older at-risk populations, was presented this year. The trial tested a structured program of physical activity, nutrition, cognitive support and social activity against an unstructured, self-guided support program (published by the *Journal of the American Medical Association* online, July 28, 2025.) The supervised intensive program showed a statistically significant improvement in age-related decline compared to the self-guided group.

Another US study of supplemental nutrition assistance showed “a slower decline in cognitive impairment” in those participating compared to a non-participating similar group. And, not surprisingly, five studies of the early treatment of hypertension, cholesterol abnormalities and diabetes showed such treatment slowed cognitive decline.

Another study showed walking and lifestyle activities benefitted the incidence and rate of cognitive decline in those with the APOE-e4 genetic variant.

New therapies

Several drugs are being assessed in clinical trials. These include the anti-amyloid agents lecanemab and donanemab. Studies were presented of assessments of patients on these agents regarding comparative safety with patient interviews assessing satisfaction with the results.

Exidavnemab (Bioarctic): a new anti-amyloid agent, mooted to be active also against Parkinson’s disease, is entering phase 2 studies.

Lecanemab: requires subcutaneous injection maintenance and is approved for treatment of Alzheimer’s disease in patients with mild cognitive impairment, though not yet in Canada (see more below). Studies in those with moderate or severe impairment are not yet ongoing. Esai has several studies of lecanemab in those who have intermediate or elevated levels of amyloid in their brains but who are clinically normal.

However, a December 2024 editorial in *The Lancet* aimed at “tempering hype and hope” around lecanemab said that the research results so far “might not be clinically meaningful.” Those editorial writers looked closely at the cognition test the study used, called the CDR-SB. The writers pointed out that the total impact of lecanemab on cognition amounted to “a 0.45-point difference on … an 18-point scale.” The writers also pointed out that a 0.98 to 1.63 difference in CDR-SB points is what some scientists say is needed to make a substantial difference in the everyday life of a person with mild cognitive impairment or early Alzheimer’s disease. In other words, the editorial writers say, “whether lecanemab is the game changer that some have suggested remains to be seen.”

Lecanemab was approved in the UK last year after trials suggested its effectiveness in slowing progression of the disease. Similar drugs, like donanemab, have also suggested some slowing of the rate of memory and thinking decline. Both drugs are approved by

the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK but were rejected for use by the National Health Service because the benefits were deemed too small.

New data presented at the international conference suggested that the drug was most promising in those with low levels of tau (the protein that in some cases increases as Alzheimer's progresses). In the Clarity AD trial, a double-blind, placebo-controlled trial of 1795 patients, lecanemab was found to bind to soluble amyloid-beta protofibrils. Amyloid-beta related imaging abnormalities were more common in APOE-e4 positive patients.

New long-term data show that the benefits of donanemab may continue even after treatment ends. Some patients on lecanemab maintained cognitive gains for up to four years. Among those treated early with lecanemab and with low levels of tau, over half showed no decline after four years.

In Canada, lecanemab and similar drugs are under review but not fully approved. Further up-dated reports are awaited.

Other trials reported include a 1,600 patient study of the new drug trontinemab. This could be the most powerful drug yet against dementia, slowing down disease progression with visible markers of the disease regressing. In a follow-up in 18 months, it's hoped these biological changes will facilitate improvements in memory.

Pathway to relief

So we have three areas where small steps have been made on the pathway to relief from the awful purgatory inflicted by this disease on innocent people through no fault of their own.

Editor's note

The views, perspectives and opinions in this article are solely the author's and do not necessarily represent those of the AMA.

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