DEMENTIA NEWSLETTER *for* PHYSICIANS

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In This Issue...

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Clinical Trials in Alzheimer Disease

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Alzheimer disease (AD) is a fatal disorder for which we have no cure, and few treatments. It is an inexorably progressive neurodegenerative disorder which eventually affects all brain functions. In its earlier stages it primarily affects thinking; including memory, and language, attention and personality. It continues to progress, until the person is no longer able to independently take care of their basic daily needs, such as eating, and voiding. Eventually, the person with AD will die, usually due to complications of the disease, such as infections and clots.

Currently, we have medications available in Canada for the treatment of AD: the acetylcholinesterase inhibitors and memantine. As we have come to understand, through the initial pivotal clinical trials and our own clinical use of these medications, these medications are invaluable in the treatment of AD. Unfortunately, these medications affect only the symptoms of the disease, and do not affect the underlying disease process.

The precise mechanism(s) responsible for AD is/are unknown. The most compelling contemporary hypothesis for the neuronal loss and cognitive decline in AD is the amyloid hypothesis, which states that AD is the result of amyloid overproduction and/or ineffective clearance. It maintains that accumulation of Ab peptide in the brain is the critical step in the pathogenesis of AD and that slowing or halting the accumulation of Ab in the brain, or aiding its removal from the brain will slow, halt, or potentially even reverse the course of the disease.

Most of the current and upcoming clinical trials are aimed at decreasing the brain amyloid 'load'. It is hoped that decreasing the amount of brain amyloid will result in either slowing down or possibly even stopping the underlying disease process in AD.

1. Anti-Amyloid Vaccination Studies

This is the most promising area of research in recent years. Initially, active vaccination with Ab in mouse models of AD showed extraordinary results on both tests of cognition and in terms of amyloid plaque clearance in

(continued on page 2...)

Clinical Trials in Alzheimer Disease *(...continued from page 1)*

sacrificed animals. This vaccination was taken in to trials with humans. Unfortunately, there was an approximately 6% rate of encephalitis, which did result in serious complications in some of the participants. Despite this, there was a marked reduction of plaque seen in the few patients that have now come to autopsy.

Since that time, investigators have been looking for a way to make vaccination safer. The main way that this has been done is through passive immunization with monoclonal antibodies to different parts of the amyloid molecule, or active immunization with fragments of amyloid. Currently, these trials are going very well. They are now generally in phase 2 or phase 3, including some very large phase 3 trials which are ongoing.

2. Medications that decrease production of Amyloid

Various medications have tried this in different ways over the last number of years, using a variety of different approaches. One current medication in phase 3 trials is a gamma synthetase inhibitor. Gamma synthetase is one of the enzymes responsible for synthesis of A-b. A recent trial of an anti inflammatory agent, probably working as a gamma synthetase inhibitor, (r-flurbiprofen) was negative.

3. Medications to increase clearance

Recently Neurochem, (a Montreal company), had a medication that interfered with the fibrillization and oligomerization of A-b, thus decreasing the ability of it to form plaques. Unfortunately, the clinical trial did not come out positive.

There are also a number of other new, possibly disease modifying medications coming to late-phase clinical trials.

1. Dimebon

This medication is a medication that was used primarily as a cold medicine in Eastern Europe and Russia. It was found serendipitously to have a possibly disease modifying effect on AD. Its mechanism of action in AD is interesting: it is thought to work through a michondrial mechanism. A large clinical trial in North America, where it will be added on to cholinesterase inhibitors, will start soon.

2. Rember

This medication is now in phase 2 trials. It is an anti-tau medication, and is showing promise as a disease modifying medication in AD. By its mechanism, it should also have some effect on other dementias, such as Fronto-temporal dementia.

In addition to disease modifying medications, companies are also trying to make better/more efficient symptomatic medications, and some of these are now at the phase 2/3 level as well.

The Ottawa Dementia Research Unit is an Academic Clinical Trials Unit, located at Elisabeth Bruyère Hospital. We are associated with the Memory Disorder Clinic, Bruyère Continuing Care, and University of Ottawa. We are endorsed by the Alzheimer Society of Ottawa and Renfrew County, and the Champlain Dementia Network. We are currently recruiting for a number of clinical trials, and are looking for patients with Alzheimer's Disease. If you have a patient that you think would be interested and suitable for one of our trials, or wish more information, please call us at 613-562-6328.

Capacity

Linda Gobessi, MD, FRCP(C) Medical Director, Geriatric Psychiatry Community Services of Ottawa

During your clinical work with patients who have a dementia you will likely encounter a situation where you or someone else is wondering about the capacity of one of your patients. The first thing to establish is what specific capacity is being questioned. Just because someone has a diagnosis of dementia does not necessarily make that person incapable and the specific capacity in question needs to be assessed. There are many different arenas of capacity, but for this newsletter I will focus on the capacity to consent to treatment.

In Ontario, the Health Care Consent Act (HCCA) governs health practitioners including physicians. This act sets the standard used to determine whether someone is capable of consenting to treatment and who may act as a substitute decision maker (SDM) if the person is incapable. The Act is available at www.e-laws.gov.on.ca. Physicians are encouraged to consult the Act in order to familiarize themselves with the legislative provisions. The goals of the HCCA include promoting individual autonomy and decision-making capacity, and facilitating communication between health care practitioners and their patients.

A person is presumed to be capable with respect to treatment decisions unless reasonable grounds to suspect incapacity exist. What constitutes reasonable grounds is not spelled out, but you may become concerned based on your observations during a clinical assessment or from information obtained from family or other caregivers. If you are proposing treatment, it is your responsibility to obtain consent. Treatment means anything that is done for a therapeutic, preventive, palliative, diagnostic, cosmetic, or health-related purpose and includes a course or plan of treatment.

According to the HCCA one is capable of consenting to a treatment if the person is able to understand the information that is relevant to making a decision about the treatment, and appreciate the reasonably foreseeable consequences of a decision or lack of decision. The key words are understand and appreciate. Therefore the person needs to have the cognitive abilities to process, understand and retain pertinent facts; to communicate his or her understanding; and the ability to weigh risks and benefits of different options in the context of his or her personal circumstances. It is not the presence of risk that is important, but the appreciation of risk that matters. One must take into account the individual's personal beliefs and values, his or her religious beliefs and cultural background and be aware of one's own potential biases. Simple things such as ensuring that the person's sensory deficits are optimally accommodated and providing privacy and time for the individual to consider the information are essential. Above all, we do not want to infringe on someone's right to self-determination inappropriately.

In my experience as a geriatric psychiatrist treating individuals with dementia, these evaluations are often straightforward, but can sometimes be very difficult particularly if the consequences of accepting treatment or not accepting treatment are grave. If you are uncertain about your assessment, a second opinion may be requested. It is important to remember that a person may agree with your treatment plan, but may not in fact be capable of consenting to the plan according to the standard set out in the HCCA. It is of course also possible for capable patients to refuse recommended treatment.

It is important that adequate information about the treatment has in fact been given as consent must be informed, and given voluntarily. You are expected to review the nature of the treatment, expected benefits, material risks and side effects, alternative courses of action and likely consequences of not having the treatment. Questions or requests for additional information also need to be addressed. It is often helpful to ask the person to tell you what they have understood from your discussion. If at the end of your assessment you find the person incapable of consenting to the proposed treatment, the person must be advised of his or her legal rights, unless the situation constitutes an emergency as defined by the HCCA. According to the College of Physicians and Surgeons of Ontario, physicians must tell the incapable person that a substitute decision maker will assist the patient and will

(continued on page 4...)

Capacity *(...continued from page 3)*

be responsible for making the final decision. You should involve the patient as much as possible. If the person disagrees with your finding of incapacity or disagrees with the need for a SDM you must advise the person of his or her options. This includes finding another SDM of the same or more senior rank as listed in the hierarchy in the HCCA and or applying to the Consent and Capacity Board for a review of the finding of incapacity. The information given to the person and his or her response should be documented in the health record.

In Canada, it is a fundamental right of individuals to decide which medical interventions will be accepted and which will not. Physicians have the obligation to secure consent and patients have the legal right to consent to or refuse treatment. It is important that individuals at high risk of becoming incapable, such as someone who has a progressive dementia, are given opportunities to discuss their future care. As a physician, you are in a position to review the potential benefits of obtaining a power of attorney for personal care and who would be the person's SDM according to the HCCA if no power of attorney for personal care exists. I have found that having this discussion early on helps to ease the transition of including the SDM in health care decisions once the person is incapable and sometimes individuals request this prior to any incapacity as a way of ensuring everyone is aware of the treatment plan.

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First Link™ – Your partner in caring for patients affected by Alzheimer's disease and other related dementias. The First Link™ program, initially a piloted by the Alzheimer Society of Ottawa and Renfrew County (2002) is now rolling out in 26 Alzheimer Society Chapters in Ontario. The Canadian Consensus Guidelines on Dementia (Hogan et. al., 2007), developed by 45 medical experts, recommend that primary care providers utilize First Link™ as a support to persons and families affected by dementia. A First Link™ referral will save you valuable time and energy. It's simple – just fax a referral form and First Link™ will take it from there.

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For more information: **www.alzheimer-ottawa-rc.org/calendar/cal2.htm#n1** or phone 613-523-4004

Did You Know That...

You can download all previous editions of the Dementia Newsletter for Physicians at the Champlain Dementia Network website at: **www.champlaindementianetwork.org**

THANK YOU

The Champlain Dementia Network would like to thank Janssen-Ortho, Lundbeck, Novartis and Pfizer for supporting this edition of the Dementia Newsletter for Physicians.