Background
There has been immense growth in the aging population. Alongside this, there has been an increased prevalence in Alzheimer’s disease (AD). Alarming trends have been discovered in AD, such as: a) One person will be diagnosed with Alzheimer’s Disease (AD) every five minutes in Canada as of 2008; b) the prevalence of AD will more than double, from nearly half a million to over 900,000 Canadians, from 2008 to 2030; c) hours of informal care provided for those with dementia will more than triple during the same time period; d) this is echoed in a stifling current economic burden of fifteen billion dollars that is predicted to double every decade; and e) the average life expectancy postdiagnosis is seven years.[1] The economic, therapeutic, and social burdens associated with AD will heavily impact individuals, communities, and governments, such that the necessity for health-care sustainability will drive the need for therapeutic intervention that targets disease management as well as prevention.

Before 1960, Alzheimer’s was associated with the normal process of aging, until correlations were found between senile plaques and cognitive decline.[2] The Alzheimer Society was founded in 1978, a genetic component to Alzheimer’s was identified in 1990, and the first drug treatment and vaccine for Alzheimer’s surfaced from 1997 to 1999.[1] Despite recent advances, however, the prognosis remains terminal.

Causes and Disease of the Pathology
Alzheimer’s disease has several causes and can be understood from physiological, molecular, biochemical, environmental, and genetic standpoints. Alzheimer’s may develop as a secondary complication of tumours, cerebrovascular accidents (CVA), and head trauma. Chemical causes include hypoxemia and electrolyte imbalances.
Environmental causes include drug and metal toxicities, as well as nutritional deficiencies.\(^3\)

Although there are many streams of thought postulating about what is involved in disease pathogenesis, there are four major hypotheses that evolved from branches of biochemical, genetic, and molecular research: The cholinergic hypothesis proposes that AD is caused by decreased activity in cortical, pyramidal neurons due to decreased excitatory amino acid activity and decreased nicotinic/muscarinic levels of acetylcholine, such that altered presynaptic neuron function is associated with cognitive decline.\(^4\)\(^5\) The genetic hypothesis of Alzheimer’sattributes it to autosomal dominant mutations in genes on chromosomes 1, 14, 19, and 21 that occur in 0.1% of the population; these mutations encode amyloid precursor protein (APP), as well as presenilins 1 and 2 (crucial to the APP protease complex) that result in dysfunctional A\(\beta\) protein fragments, which contribute to plaque formation.\(^6\) The biochemical hypothesis is built on a protein misfolding theory. APP is crucial to neuronal development and repair; however, in Alzheimer’s, abnormal proteolysis of APP by \(\beta/\gamma\) secretases in the endosomal/lysosomal pathway results in plaque deposition. The last major hypothesis is the molecular one. Plaques are associated structurally with paired helical filaments (PHF) or straight filaments (SF), of which the main protein present is a microtubule-linked protein called tau (crucial in signal transduction and cytoskeletal organization).\(^7\) Hyperphosphorylated tau relocates to somatodendritic rather than axonal cellular compartments and dissociates from microtubules to form neurofibrillary tangles.\(^8\) It is imperative to understand these theories, as they unveil the origin of disease and associated molecular pathology.

**Diagnosis and Symptoms**

Early symptoms include, but are not limited to, short-term memory loss, inability to concentrate, and apraxia at the initiation of fine motor tasks. Moderate symptoms of progressive disease include long-term memory loss as well as difficulties with speech, reading, and visuospatial tasks. Terminal symptoms most often include delusion, aggression, depression, apathy, and incontinence.\(^9\)

Diagnosis of Alzheimer’s is done through an in-depth history taken from the patient and their family members, cognitive/neurological testing (mini mental-state exam and electroencephalogram) (MMSE and EEG), brain imaging (PET, SPECT, MRI and CT), and histopathological examination (confirmatory). The National Institute of Neurological and Communicative Disorders and Stroke, the Alzheimer’s Disease and Related Disorders Association, and the DSM IV outline the methods by which to exact an accurate diagnosis of Alzheimer’s.\(^10\) The following clinical criteria are evaluated: memory, attention, perception, language, orientation, problem solving, and functional/constructive capabilities.\(^11\)
Therapy

The hallmarks of Alzheimer’s neuropathology are the presence of neurofibrillary tangles from tau accumulation and β-amyloid–induced senile plaques. Currently, the Food and Drug Administration (FDA)–approved treatment of Alzheimer’s consists of two drug classes. The N-methyl-D-aspartate (NMDA) receptor antagonists (memantine) regulate glutamate function (active in memory and learning processes), while the more commonly utilized acetylcholinesterase inhibitors (ACI) (donepezil, galantamine, rivastigmine) increase Ach to offset the deterioration of Ach presynaptic terminals. There are several limitations to pharmacological management of Alzheimer’s; these demonstrate efficacy in moderate AD at best, lose effectiveness after six months, and have numerous side effects. Therefore, there is an urgent need to better manage the disease, while considering safety, efficacy, and prophylactic potential. Recently, there have been studies examining novel therapeutic agents, such as acetyl-L-carnitine, vitamin E, L-phenylalanine, and citicoline.

There are also more novel therapies coming out that involve stem cell-use. Stem-cell treatments attempt to replace lost neurons by ones given subcutaneously or intravenously. There are multiple types of stem cells and proteins that could be targeted with this approach. There are neural stem cells (NSC), mesenchymal stem cells (MSC), embryonic stem cells (ECS), and pluripotent stem cells (PSC) that could be used in treatment. Overall, this treatment is very much still in research. Therefore, natural therapies are another good option to consider.

The Exact Role of Citicoline in Alzheimer’s Disease

Citicoline, also known as cytidine 5′-diphosphocholine (CDP choline), is a unique molecule that is involved in the formation of phospholipids and neurotransmitter precursors. It has shown considerable treatment potential after cerebrovascular accident (CVA), by improving neurological and cognitive function. It has also been known for its use in spinal-cord injury, neurotransmitter dysfunction, neurological eye disease, and Alzheimer’s disease. The mechanisms of action (MOA) of citicoline in the context of AD can be better-illustrated through a diathesis of functions: neuroprotective (membrane-preserving) versus neurochemical (acetylcholine-sustaining) function. Citicoline is hypothesized to combat abnormal protein accumulation of tau within cells and β-amyloid around cells by sustaining cell-membrane fluidity and integrity. Citicoline is thought to have a phospholipid-sparing effect and prevents choline depletion from peripheral stores that can be utilized for the purpose of synthesizing acetylcholine in the CNS.
Citicoline demonstrates excellent therapeutic promise in Alzheimer’s because of: a) its high bioavailability (> 90%); b) its long half-life (56 hours through respiratory and 71 hours through renal elimination); c) neurotransmitter formation—the ability to sustain adequate levels of Ach precursors and phospholipids for cell membranes; d) phospholipid regulation—convertibility in the gut to choline and cytidine, travel to peripheral tissues as needed, and reconversion to citicoline in the brain; and e) biochemical plasticity—phosphorylcholine synthesis or betaine oxidation to meet cellular demands.[13] Citicoline was shown to be efficacious in a dosage range of 500 to 2000 mg, with few side effects, administered through oral, intravenous (IV), or intramuscular (IM) routes.[18][19] Toxicity studies performed in humans have demonstrated that oral administration (500–2000 mg) was not associated with any noted side effects. IV administration of 500–2000 mg for an average 5-day duration resulted in stomach pain, diarrhea, and headaches in less than 20% of patients, and vascular symptoms of hypertension with altered heart rates in approximately 0.5% of patients.[20]

Conclusion
A current analysis of research has identified citicoline as an indirect yet potent therapeutic agent that is supportive of the acetylcholine hypothesis and the β-amyloid/tau hypothesis of AD. Research has demonstrated that citicoline has halted disease progression, and in some cases participated in regression; however, it is equivocal whether disease prevention is equally plausible. There are a plethora of advantages demonstrated from citicoline use, such as: a) it has a diverse repertoire of MOA, such as increasing choline metabolites as neurotransmitter precursors, Na+/K+ ATPase activity, and phospholipid synthesis for lipid bilayer stability; b) it benefits other neurological diseases, such as CVA and Parkinson’s Disease; c) it has minimal side effects (headache and gastrointestinal upset) as well as a low toxicity profile; and d) it works well in EOAD and LOAD at oral doses of 1000 mg, administered for six weeks.[18]

Citicoline is an excellent candidate for the treatment of Alzheimer’s disease because it targets the cell membrane, thereby modulating receptor binding, enzyme function, and ion-channel activity.[19] Future direction of research involves a thorough examination of the mechanisms of action and correlations with clinical cognitive-scoring components. Additionally, baseline biochemical measurements and imaging will enable a better
examination of molecular alterations in neurons within the CNS. An examination of citicoline in prevention will require an in-depth assessment of phospholipid metabolism, turnover, and distribution in the body versus the brain. It would also be interesting to investigate the effects of citicoline alongside conventional drugs (ACIs) in order to examine whether an additive therapeutic effect is present. As these questions are answered, the focus can go from management of disease progression and regression to prevention.

References


