

## Research and Drugs

Because memory loss is a consistent symptom of AD, it has been the primary target for treatment of the disease. One of the major breakthroughs in understanding the biological basis of AD came in 1976, when three independent groups of researchers found evidence that the neurotransmitter acetylcholine is deficient in the brains of patients with AD. Since acetylcholine had previously been implicated in learning and memory, this made sense and immediately gave researchers a target for therapy. Whilst the replacement of acetylcholine was never considered to have potential as a cure for AD, researchers hoped that it would improve patients' memory and other abilities, at least for a period of time. This logic was based on the great success physicians have had in treating symptoms of Parkinson's disease with L-dopa, a chemical that replenishes dopamine. Dopamine is the primary neurotransmitter depleted in the brains of patients with Parkinson's disease.

While such treatments are definitely important, they will provide at most only temporary relief. This is because they replace a missing neurotransmitter, but do not correct the reason the substance is missing - nerve cell degeneration. And, as with dopamine and Parkinson's disease, large numbers of nerve cells that make and use acetylcholine are completely gone by the time a person reaches the later stages of AD, when even the most basic abilities are lost. Therefore, many scientists believe that the benefits of such drugs will decline as the disease progresses, and that patients with severe AD will not benefit from even the most effective replacement of neurotransmitters.

To date, the most successful strategy to augment acetylcholine in the brains of Alzheimer patients has been to inhibit its natural breakdown. The enzyme that normally breaks down acetylcholine to allow its parts to be reused is called acetylcholinesterase. Drugs such as Aricept are called acetylcholinesterase inhibitors, and work by slowing the natural breakdown of acetylcholine, thereby allowing more of it to be present. So far, however, these drugs have helped only a minority of the Alzheimer patients who have tried them. Why haven't these drugs been as successful? In AD, widespread degeneration of nerve cells takes place throughout the cerebral cortex (the outer layer of the brain). While nerve cells that make acetylcholine seem to be the earliest and most severely affected cells, many other types of nerve cells also deteriorate.

Cholinesterase inhibitors that are licensed for the treatment of mild to moderate Alzheimer's are:-

- Razadyne (galantamine)
- Exelon (rivastigmine)
- Aricept (donepezil)

All of these work in a similar way to prevent the breakdown of acetylcholine in the brain but some people seem to respond better to one drug than another. They may only prevent the symptoms getting worse for a limited time. Another drug Cognex (tacrine) was an early approved inhibitor but was withdrawn because of safety concerns.

For people with moderate to severe Alzheimer's, a medication known as Namenda (memantine), an N-methyl D-aspartate (NMDA) antagonist can be subscribed, but again this is not a cure. Memantine is one of the earliest drugs developed for treating Alzheimer's diseases. By binding to the NMDA receptor, it lowers the level of the neurotransmitter glutamate in the brain. While normal glutamate level is essential for maintaining memory and cognitive skills, too much glutamate kills nerve cells, this is called excitotoxicity, resulting in memory loss. It can help patients in the latter stages of the disease maintain their ability to use the toilet independently for several months, a benefit to both patients and carers. It can be taken together with a cholinesterase inhibitor. Fatigue, vomiting, constipation, headache, dizziness, drowsiness, confusion, coughing and back pain are common side effects of the drug.

Many researchers feel that more effective strategies to treat the cognitive symptoms of AD will have to act on other neurotransmitters in addition to acetylcholine, such as noradrenaline, serotonin, somatostatin, corticotropin etc. While a number of multiple-neurotransmitter drugs are being evaluated in Alzheimer patients, none has yet shown consistent benefit. As this is very complex brain chemistry, we shouldn't expect anything more than a drug with the magnitude of effect of Aricept for example, in the next few years, because of those that are being tested now appear to only show modest benefit, if any at all, but they may help some people that Aricept doesn't help. It is not clear whether the same people will respond to one drug as to another. Researchers assume that the more similar two drugs are in mode of action the more likely it is that they will be similar in effectiveness, though that assumption has yet to be proven.

### Slowing the Progression of Alzheimer's

One aim is to find a drug that would lessen the slope of decline of patients' abilities, thereby allowing people with Alzheimer's disease to retain independence as long as possible. Once the culprits that are attacking nerve cells can be identified, they could be disarmed; or, nerve cells could be fortified so they are better able to withstand assault of any kind.

From the study of basic biological properties of nerve cells, and from research into other diseases and injuries in which nerve cells degenerate, scientists have learned about several processes through which these cells can be damaged. While these mechanisms may not be the primary cause of Alzheimer's, they may be part of a "domino effect," in which some trigger sets off a chain of toxic events. These basic mechanisms of nerve cell death include:

- deterioration of the outer layer (membrane) of the cell, which is especially vital for the activities and maintenance of nerve cells
- decline in the cell's abilities to carry out routine energy production and maintenance (metabolism)
- injury from free radicals, reactive molecules that are by-products of normal cell energy production, but that are usually "cleaned up" by the body
- excitotoxic damage, a chain reaction in which nerve cells become overstimulated which eventually kills them
- a disruption of the normal balance of calcium between the inside and outside of nerve cells.

A number of drugs that may be able to protect nerve cells from assault, or interfere with general detrimental processes, are now being evaluated in Alzheimer patients. Some of these are phosphatidylserine (a cholinergic), acetyl-L-carnitine (a cognitive enhancer), deprenyl (a dopaminergic), and nimodipine (a calcium channel blocker).

### Preventing or Delaying Alzheimer's Disease

To prevent Alzheimer's, factors that place some people at increased risk need to be understood. As risk factors are identified, researchers can learn how they translate into the biological processes that bring about slow but relentless degeneration of nerve cells in the regions of the brain associated with thought, language, memory, and emotion. Are there certain genes that, if inherited, automatically result in Alzheimer's if the person lives long enough? Are people who develop Alzheimer's exposed to something detrimental during their lives? Or do Alzheimer patients have a genetic makeup that causes them to be more sensitive to things everyone is exposed to, and thus more likely to develop the disease? All of these general ideas have been proposed, and are being studied actively today. These are the studies that will ultimately unveil clues to the causes and mechanisms of Alzheimer's, clues that can then be employed to prevent it. Since Alzheimer's usually strikes in late life, another strategy would be to delay the onset of symptoms. This approach is based on the idea that harmful biological processes are at work insidiously for 10, 20, 30, or more years before symptoms appear. Once scientists understand these mechanisms, they can take a systematic approach to developing drugs to interfere with the degenerative process. Then, if they could find a biological marker that would identify people in whom Alzheimer's is silently beginning or who are at risk, doctors could intervene - possibly stopping the disease before symptoms arise. Even if the disease were only slowed and not stopped, such treatment might be able to delay the presentation of symptoms by several years.

If these possibilities are to be realized, a redoubling of efforts for long-term investments in Alzheimer's research is called for, which will allow scientists to continue working toward the fundamental goals of preventing Alzheimer's, delaying its onset, and slowing its progression. At the moment, the contribution from the UK Government for research is tiny in the relative scheme of things.

### Drug Development

Innovative new medicines are required to treat, slow, and prevent Alzheimer's disease. Biopharmaceutical research companies are studying many potential new treatments. However, the path from basic research to new drug treatments is extremely complex with many setbacks along the way, particularly in the case of Alzheimer's. At the molecular level scientists are unravelling the processes that occur as Alzheimer's disease progresses. We know that abnormal fragments of a protein called beta-amyloid accumulate to form "plaques" in the brain of Alzheimer's patients, particularly in regions that handle memory. Another hallmark of Alzheimer's is the formation of "neurofibrillary tangles" inside neurons (brain cells). The tangles are twisted fibres consisting primarily of a protein called tau which is a component of the microtubules, a subcellular transport system for nutrients and other important elements. Ultimately, neurons lose the ability to communicate and they die, which results in atrophy of the brain regions affected. Researchers have improved their understanding of the role of plaques and tangles in this process but still have more to learn.

It remains unclear whether these molecular changes are causes or symptoms of the disease.

Despite the increase in investigative activity, developing a medicine to prevent, delay, slow, or cure it is exceptionally difficult. There are many reasons Alzheimer's research is so challenging for drug developers. For example:

- Progress has been made, but scientists still do not fully understand the underlying causes and mechanisms of the disease, particularly when it comes to separating potential causes from effects of the disease. This makes selection of viable targets for new medicines very difficult.
- The limited utility of current models of the human disease is a huge barrier in preclinical testing of drug candidates.
- The absence of validated non-invasive biomarkers of disease activity and progression, which delays the diagnosis until patients become symptomatic, makes it particularly challenging to evaluate, enrol, follow up, and retain patients in clinical studies. Ultimately this leads to long and very expensive clinical trials.

Researchers believe that no single medicine will be able to defeat Alzheimer's; rather, several medicines will probably be needed to combat the disease. As a result researchers need, not one, but an array of successes to prevent or treat Alzheimer's disease. Listed below are some current possibilities.

### Some Research Studies

#### a) Insulin

Insulin is critical for normal brain function, and abnormal insulin metabolism has been shown to contribute to the development of Alzheimer's disease. Because patients with Alzheimer's disease also exhibit decreased levels of insulin in the central nervous system, it has been hypothesized that raising these levels to normal might help maintain cognitive ability. Studies involving animals have suggested that insulin deficiency in the brain may possibly be a key factor in the progression of Alzheimer's. Preliminary research suggests that when taken as a nose spray, insulin reaches the brain within a few minutes and improves memory. The novel delivery system enabled the insulin to easily bypass the blood-brain barrier and enter the brain but did not have unwanted side effects elsewhere in the body. Researchers found that the lower of two tested doses improved memory, and that both the lower and higher doses staved off decline in general cognition and functional abilities after 4 months. However, this research involved small groups of participants who had either early Alzheimer's disease or mild cognitive impairment. Although this research is promising, more research on the safety and effectiveness of intranasal insulin therapy for Alzheimer's disease is necessary.

#### Nimodipine

Calcium has an important role in regulating brain functions. Calcium ions link membrane excitation to subsequent intracellular molecular responses. Age-associated changes in calcium homeostasis have possible repercussions on higher cortical functions. Nimodipine is an isopropyl calcium channel blocker which readily crosses the blood-brain barrier. Its primary action is to reduce the number of open calcium channels in cell membranes, thus restricting influx of calcium ions into cells. The usefulness of nimodipine in patients with Alzheimer's disease and vascular dementia and unspecified dementia is still controversial. In spite of the uncertainties about its efficacy in dementia, nimodipine is currently frequently prescribed for cognitive impairment and dementia in several continental European countries. Nimodipine can be of some benefit in the treatment of patients with features of dementia due to unclassified disease or to Alzheimer's disease, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease. It appears to be well tolerated with few side effects.

#### Citalopram

Results from a new study suggest that the antidepressant citalopram (Celexa) may benefit people with Alzheimer's disease. Scientists observed a drop in levels of beta-amyloid, one of the proteins suspected to cause the disease, in the spinal fluid of healthy volunteers after they took citalopram. In mice genetically engineered to develop Alzheimer's disease, the scientists reported that citalopram stopped the growth of beta-amyloid plaques, a promising finding that suggests the drug might slow disease progression. Prior research in mice and isolated human neurons found that citalopram stimulates the formation of new neurons in the hippocampus, the part of the brain responsible for memories that is greatly affected in Alzheimer's disease. Citalopram belongs to a class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs) that function by increasing serotonin

levels in the brain. A previous study reported that citalopram improved symptoms of agitation in patients with Alzheimer's disease, but it remains unknown if citalopram has any impact on cognitive function or disease progression in people with Alzheimer's. Past clinical trials with another SSRI, sertraline (Zoloft™) did not significantly improve cognition in patients with Alzheimer's disease.

#### b) Deep Brain Stimulation

This is not a medication but it is a different strategy that should be mentioned. There is some evidence to support the study of deep brain stimulation of the hippocampal fornix as a novel treatment to improve neuronal circuitry within these integrated networks and thereby sustain memory function in early Alzheimer's disease.

Evidence of functional alterations in memory networks is commonly seen in Alzheimer's patients as well as normal elderly persons who have no cognitive impairment. Thus, Alzheimer's may be both a degenerative disease and a system-level disorder affecting several integrated pathways linking select cortical and subcortical areas that typically work in concert to serve aspects of memory and cognition. If this dual hypothesis is correct, the modulation of neuronal activity within these interconnected dysfunctional networks may sustain or even improve cognitive function in patients with early Alzheimer's. Recent studies suggest that loss of the integrity of the fornix, a major in and outflow track to the hippocampus, may be associated with early memory dysfunction. These recent findings link the fornix to the process of cognitive deterioration in Alzheimer's and to later hippocampal degeneration as well.

DBS involves the neurosurgical implanting of indwelling electrodes within specific brain circuits to modulate the activity of those circuits and has been used in numerous central nervous system (CNS) disorders, including Parkinson's disease, epilepsy, etc. DBS can suppress pathological neuronal activity or drive underactive output. In this way, DBS can modulate brain circuitry activity up or down based upon the specific needs. DBS may be a useful circuitry based treatment for AD if the electrodes are placed in areas of the brain that are implicated in memory, such as the hippocampal fornix.

Trial so far have been small but have shown improved cognitive measures in some patients with mild Alzheimers. Larger studies are underway in the USA and Canada. German studies have targeted the nucleus basalis of Meynert (NBM), a small bundle of neurons in the basal forebrain.

#### Solanezumab

Is a humanised monoclonal antibody being investigated by as a neuroprotector for patients with Alzheimer's disease. It preferentially binds soluble forms of amyloid that make up the protein plaques seen in the brains of people with the disease and in preclinical studies promoted its clearance from the brain. Initial clinical trials in 2012 were only mildly encouraging but were said to be the first evidence that targeting the amyloid cascade can slow the progression of disease. In further trials with randomly assigned 1012 and 1040 patients, respectively, with mild-to-moderate Alzheimer's disease to receive a placebo or solanezumab (administered intravenously at a dose of 400 mg) every 4 weeks for 18 months, failed to improve cognition or functional ability.

#### Amyloid Vaccine

The idea of an anti-Alzheimer's vaccine is considered by researchers to be a promising emerging strategy. The aim has been for a synthetic vaccine using naturally occurring biological molecules (peptides) designed to mimic beta-amyloid antigens, induces antibody production against this protein without creating a systemic immune response (which would raise safety concerns). The vaccine would work by solubilising the plaque. However, 14 years of research has not yet produced a safe and effective vaccine. Critics would point out that not only do 20% of adults have the same brain abnormalities as Alzheimer's patients but also that amyloid plaque accumulation is not correlated with memory deficits but the accumulation of tau protein is. Antibodies have been shown during the past five to seven years to be effective in removing amyloid-beta from the brain, but they haven't shown that they can significantly prevent the progression of dementia. Older vaccines carried the risk of activating specific T-cells that could lead to meningoencephalitis ( meningitis, an infection or inflammation of the meninges, and encephalitis, an infection or inflammation of the brain

#### Tau Vaccine

A number of drugs are being tested to target misfolded tau protein, a common denominator of neurofibrillary pathology. Based on preclinical results, such an intervention is expected to reduce the number of neurofibrillary tangles, remove hyperphosphorylated tau protein ( fully saturated with phosphate groups) and reduce the amount of oligomerized ( a chemical process that converts monomers to macromolecular complexes) and insoluble pathological tau in the brain, to halt the spread of neurofibrillary pathology through the brain, and thus prevent associated cognitive decline. Antibodies against tau are relatively new, with work still in the preclinical stage. Animals treated with monoclonal antibodies that target tau showed improvement in Alzheimer's symptoms.

Because of the central role of pathological misfolded tau protein in the causation of Alzheimer's, the vaccine is expected to be more effective than active or passive immunotherapies aiming to eliminate the amyloid  $\beta$  plaques that have been clinically investigated so far. Other tau-based technology focuses on preventing the breakdown of tau protein. Tau stabilizes microtubules, which can tangle and cause Alzheimer's and other neurodegenerative diseases when tau breaks down.

c) Nicotine Therapy

A small, preliminary trial showed that nicotine delivered via a skin patch alleviated some symptoms of MCI in non-smoking older volunteers. A pilot study, involved more than 70 participants; 39 received 15 mg of nicotine daily while 33 wore a placebo patch. Cognitive testing showed improvements in attention, memory, and mental processing in volunteers receiving nicotine compared to the placebo group. The nicotine patch was also shown to be safe. A larger study is required to further examine this promising intervention.

d) Gene Therapy to Restore Neuronal Function

Gene therapy is controversial. It can be defined as the introduction of nucleic acids, usually DNA or genes, into cells to prevent or reverse a pathologic process. The therapy is not expected to cure Alzheimer's disease but to protect and possibly even restore some brain cells. It may also alleviate some symptoms, such as short-term memory loss. Nerve Growth Factor (NGF) has been shown to prevent both lesion-induced and spontaneous, age-related degeneration of cholinergic neurons in the brain. NGF is a naturally occurring protein important for neuron survival. The gene treatment is injected into the brain region where the cells are damaged in Alzheimer's patients. It is thought that the resulting sustained expression of NGF in the neurons can restore their lost function, leading to memory and cognition improvement. However, delivery of proteins to the appropriate part of the brain, in a manner that enables them to have a therapeutic effect, has proved challenging due to the blood brain barrier.

e) Resveratrol

One of the problems Alzheimer's patients face is that due to impaired blood flow to the brain with advancing age the brain compensates and begins to generate new blood vessels, a process called angiogenesis. The eradication of beta amyloid plaque neutralizes the biological trigger that produces new blood vessels (angiogenesis). Natural molecules like resveratrol have been shown to exert strong anti-angiogenic action and may serve to inhibit the development of abnormal blood vessels in the brain with advancing age. Resveratrol is an antioxidant compound found in grapes and red wine. Observational studies have shown that moderate consumption of red wine is associated with a lower incidence of Alzheimer's disease, and animal studies have demonstrated resveratrol's neuroprotective properties. Resveratrol works synergistically with vitamin D in this regard. Resveratrol, a polyphenolic compound known for its antioxidant properties, does not inhibit or block the production of amyloid like the failed monoclonal antibody drugs that modern pharmacology has fabricated but rather works to degrade beta amyloid and assist in its removal from the brain.