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# What's the future of treatment for Alzheimer's disease?

**Accurate diagnosis of the dementia syndrome is essential to provide the best possible therapy. Current treatment options for Alzheimer's disease are limited to symptomatic therapies (including cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists). Potential new treatments are focusing on decreasing amyloid production, increasing amyloid clearance and using immunotherapies.**

With our ageing population the prospect of dementia is of increasing concern to people and their families. Until recently only symptomatic therapy has been available, in the form of cholinesterase inhibitors and memantine. However, with recent advances in the understanding of the pathological mechanisms underlying Alzheimer's disease, a number of newer treatments are being developed, with the aim of further improving symptoms and slowing or even halting the underlying pathological processes.

**IN SUMMARY**

- **Due to our ageing population the prospect of dementia is of increasing concern to people and their families.**
- **Dementia is a syndrome characterised by a decline in memory and at least one other cognitive ability that is severe enough to cause a significant impairment of social or occupational functioning.**
- **Modifiable risk factors include the potentially protective effects of a high antioxidant diet, statin therapy, exercise and higher education.**
- **Current treatment options for Alzheimer's disease are limited to symptomatic therapies. These include cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists.**
- **Nonpharmacological approaches are worth considering because of their low costs and low risks of side effects, as well as their ability to complement pharmacological approaches and their benefits to other health outcomes.**
- **Potential new treatments for Alzheimer's disease are focusing on removing amyloid by decreasing amyloid production, increasing amyloid clearance and using immunotherapies. Other major treatment targets include correcting neuronal damage, neuroprotection and use of anti-inflammatories.**

## Alzheimer's disease in context

Dementia is a syndrome characterised by a decline in memory and at least one other cognitive ability that is severe enough to cause a significant impairment of social or occupational functioning. Most dementias are progressive and irreversible. In people over the age of 50 years, there are many disease processes that are capable of producing and worsening established dementia. Alzheimer's disease is the most common cause of dementia, being the sole process or significantly contributing to over 80% of cases.[1]

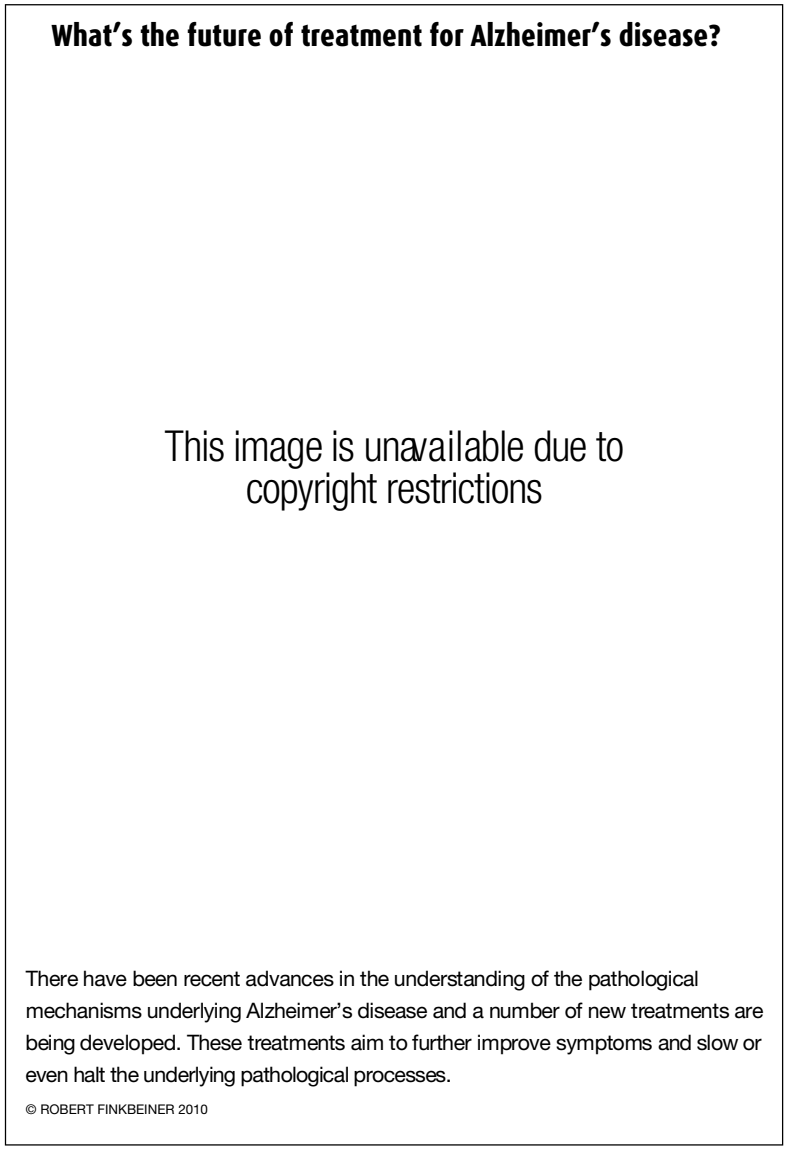
Alzheimer's disease is an age-related disorder and the world's population is rapidly ageing. The number of people affected by dementia is therefore expected to increase dramatically over coming years, with an estimated 40 million cases in 2020 and over 80 million by 2040.[1] In Australia, the number of people affected will rise from just over 200,000 at present (1% of total population) to over a million by 2050 (2.8% of the total population).[2] As dementia produces progressive disability, this increase in the number of people with the condition has profound social, economic and health service implications for our future.

## What is Alzheimer's disease?

Detailed information on the diagnosis and management of Alzheimer's disease is covered in a previous article published in *Medicine Today*.[3] This current article focuses on the aetiology and risk factors of Alzheimer's disease and the treatment options that have become available since 2004, in addition to potential new treatments that may become available in the future.

The presence in an elderly person of the symptoms listed in Table 1, and their progression over months to years, should strongly suggest a diagnosis of Alzheimer's disease. Characteristically, the ability to make new memories is lost early, with the patient unable to convert temporary memories to permanent ones. The patient will rapidly forget newly learned information without benefiting from prompts, often repeating questions or statements. Other causes of impaired cognition, such as psychiatric disorders, delirium, other types of dementia and other focal or systemic causes of cognitive impairment, should be excluded. It is important to note that evidence for the treatments of Alzheimer's disease comes from trials performed on patients with defined Alzheimer's disease. Increasingly, we are aware that many cases of dementia are mixed, rather than pure Alzheimer's dementia, and the efficacy of treatments in this broader dementia population needs to be validated.

**What's the future of treatment for Alzheimer's disease?**




There have been recent advances in the understanding of the pathological mechanisms underlying Alzheimer's disease and a number of new treatments are being developed. These treatments aim to further improve symptoms and slow or even halt the underlying pathological processes.



### Pathology

The presence of extracellular amyloid plaques, intraneuronal neurofibrillary tangles and neuronal death are the main pathological changes seen in patients with Alzheimer's disease. It is currently thought that neuronal damage and death

**Table 1. Symptoms of Alzheimer's disease**

- Forgetting newly learned information more often, with no delayed recall or help from prompts
- Difficulty performing familiar tasks
- Problems with naming or language
- Disorientation to time and place
- Poor judgement and decision making
- Impaired abstract thinking
- Misplacing objects, often in unusual places
- Changes in mood or behaviour, including irritability
- Changes in personality
- Loss of initiative

are the end products of a cascade of pathological events precipitated by the amyloid-β (Aβ) 42 molecule. This molecule is only briefly soluble, following its production as a breakdown product of amyloid precursor protein (APP), before it precipitates out of solution, forming amyloid plaques. Within the brain there is a typical pattern of disease progression, with initial involvement of the hippocampal memory centres progressing to affect the temporal, parietal and frontal lobes.

Although most authorities believe that Aβ 42 is central to the pathological process of Alzheimer's disease, there is wide variation between individuals in the amount of amyloid protein deposited within their brain before they show clinical symptoms of Alzheimer's disease. Individuals with better education and higher intelligence appear to have a higher tolerance for amyloid than those with lesser attainment or ability. This may reflect increased synaptic density formed during the process of education. Individuals with more premorbid synaptic connections can probably sustain more damage before they manifest symptoms of dementia than those with fewer such links.

Current explanatory theories focus on the processing of the APP from which amyloid is derived. Depending upon the point at which it is enzymatically cleaved, either a harmless or a potentially toxic product can be produced. Plaque formation results from overproduction and accumulation of amyloid within the CNS. Neurofibrillary tangles are produced from the phosphorylation and aggregation of the tau protein, a protein whose normal role is to stabilise neuronal microtubules.

Some new therapies are focusing on amyloid processing pathways, amyloid plaques, damaged mitochondria and hyperphosphorylated tau proteins. Other therapies are focusing on neuroprotection and preventing the inflammatory cascade.

### Risk factors

Epidemiological research has identified possible risk and protective factors associated with Alzheimer's disease. Modifiable risk factors include the potentially protective effects of a high antioxidant diet, statin therapy,[4] exercise and higher education. Head injury and vascular factors, including diabetes, mid-life hypercholesterolaemia and hypertension, are apparent risk factors for Alzheimer's disease as well as for vascular dementia.[5,6] These modifiable factors are important as potential targets for population-based interventions, although their individual effects are modest. There is a need for larger prospective studies to demonstrate that such interventions prevent dementia.

The optimal timing of lifestyle interventions is also unclear. There is a lack of data on mid-life risk factors and late-life dementia. Due to the long duration of the asymptomatic phase of Alzheimer's disease, it probably will be necessary to begin interventions during middle age or even earlier.

### Genetics

Dominantly inherited familial Alzheimer's disease represents only a small proportion (3 to 5%) of cases. It usually presents with an early onset (when patients are in their 40s to early 60s) and rapidly progresses to dementia. Mutations have been found in the *APP* gene and in the genes coding for elements of the enzyme complex responsible for this cleavage (presenilin 1 and presenilin 2 mutations). There are three copies of the *APP* gene in patients with Down syndrome and this is thought to explain the high incidence of Alzheimer's disease in this group. New evidence suggests that the *SORL1* gene polymorphisms on chromosome 11 are also associated with a significant risk.[7] The SORL protein is involved in the regulation of *APP* processing within the cell.

Within the general population, the most important inherited risk factors are the history of a first-degree relative with the condition combined with carrying at least one copy of the apolipoprotein E4 gene (*APOE ε4*). Although not leading directly to disease, these risk factors might in the future be used to choose candidates for community screening. It is not currently recommended that ApoE status be routinely tested because this is an unmodifiable risk factor.

## Establishing a diagnosis

In Alzheimer's disease an accurate and reliable history is challenging and extremely important. As patients cannot generally recall details of the duration, progression and nature of their cognitive deficits and confabulation is common, the initial clinical evaluation should include a careful history taken with the help of an informant well known to the patient.

In cognitive assessment, the Mini-Mental State Examination (MMSE)[8] is typically used but alternative assessments such as the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog)[9] and Montreal Cognitive Assessment (MoCA)[10] are increasingly being used.

Using the MMSE and MoCA together can be beneficial because the MoCA has a greater emphasis on executive function, an area covered poorly by the MMSE, and is available free via the internet in 29 languages (www.mocatest.org).

Many of the symptoms associated with dementia, especially behavioural and psychological symptoms of dementia (BPSD),[11] are distressing to both the patient and carer and are important candidates for therapy. For this reason, enquiries about these symptoms are essential. The use of the Neuro Psychiatric Inventory (NPI)[12] can identify and quantify these symptoms.

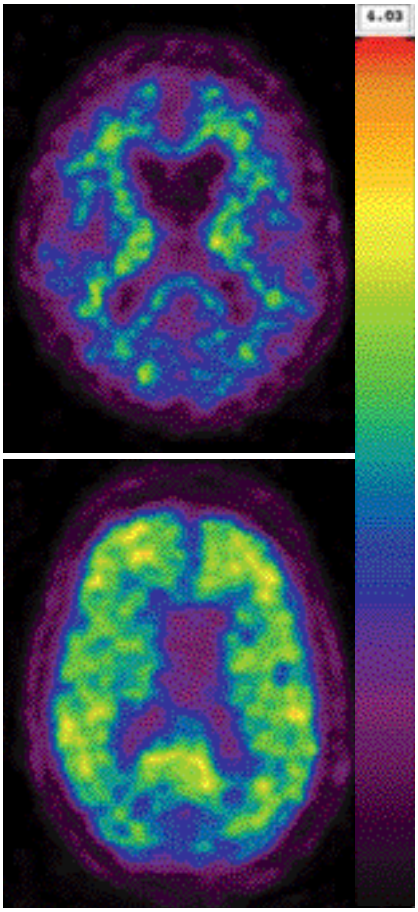
History and physical examination should include a check for the presence of neurological syndromes and disorders (i.e. parkinsonism, macrovascular stroke) as well as cardiovascular risk factors and disease. Typical blood tests recommended for a dementia screen include full blood examination, measurement of serum urea, electrolyte and glucose levels, as well as liver function tests, thyroid function tests and measurement of vitamin $B_{12}$, folate and calcium levels.

Increasing research evidence supports the usefulness of cerebrospinal fluid analysis for an early diagnosis of Alzheimer's disease, even in individuals with very early symptoms. Measuring the decrease in the levels of Aβ 42 and the increased levels of tau protein in the cerebrospinal fluid has been found to be useful in confirming the diagnosis and also in identifying those individuals who are likely to develop Alzheimer's disease in the future. Issues remain around standardisation of analytical techniques and clinical procedure. Therefore, these cerebrospinal fluid biomarkers are not currently available outside the research setting.[13] Measurement of both Aβ 42 and tau protein levels increases the predictiveness of this test, although other neurological conditions can also produce changes in the levels of these proteins. The area of cerebrospinal fluid biomarker work has been extensively reviewed with an overall sensitivity and specificity of between 80% and 90%.[14] Currently, researchers are looking for blood biomarkers that are capable of providing the same information, without the need for a lumbar puncture.

Neuroimaging is used to exclude tumours, strokes, haemorrhage and hydrocephalus as well as to measure the amount of vascular damage and atrophy. MRI is useful to look at regions of focal atrophy, especially in the hippocampi and temporal lobes. Although the above is used routinely, there are new analysis techniques for MRI, positron emission tomography (PET) and single photon emission CT (SPECT) imaging, which have demonstrated utility in research studies. The use of imaging to diagnose Alzheimer's disease is predicted to take a more prominent role in the next decade.

New computer-assisted MRI scans are now able to measure cortical thickness in different brain regions and map changes over time. PET scans can be used to look at patterns of decreased brain metabolism,[15] and there are new radioactive agents, such as 11C-labelled Pittsburgh Compound-B (11C-PiB), that bind to amyloid. Brain amyloid burden can now be measured,[16] as well as the amount and location of amyloid[17] (see Figures 1a and b). Although less accurate, brain SPECT can provide similar information on brain function. These advances promise the ability to detect the presence of Alzheimer's disease pathology early, when clinical symptoms are absent.

A thorough neuropsychological assessment is particularly valuable to differentiate various types of dementia and/or to confirm the presence of mild cognitive impairment. Performance is assessed in a number of cognitive domains (e.g. memory, learning, language, visuospatial, constructional, executive functioning, psychomotor speed and IQ) and compared with age- and education-matched norms.




Figures 1a and b. PiB PET scan. (a, top). A patient with mild cognitive impairment who had no decline in cognition during the next three years. (b, bottom). A patient with Alzheimer's disease who had a rapid decline in cognition during the next three years. 11C-labelled Pittsburgh Compound-B (11C-PiB) permits visualisation of amyloid plaques in the brain. The red and yellow colours indicate that PiB uptake is higher in the brain of the person with Alzheimer's disease than in the cognitively healthy person. The blue-black colour indicates a low uptake of PiB.

## Mild cognitive impairment

Mild cognitive impairment is defined as cognitive deficits (1.5 standard deviations below normal) in the absence of apparent loss of function.[18] Various arbitrary definitions have been proposed and

applied and the chosen definition influences research outcomes.

Current evidence suggests that mild cognitive impairment is an important condition. Approximately 80% of people with amnestic mild cognitive impairment go on to develop Alzheimer's disease over a duration of six years, a conversion rate of approximately 12% per annum compared with 1 to 2% for age-matched community controls.[19]

The literature has identified some factors (e.g. age, multiple deficits, ApoE ε4 status) that make patients more likely to have progressive disease, but there is insufficient evidence to recommend clear management to avoid development of Alzheimer's disease. Clear definitions of mild cognitive impairment will aid the research in this area. Mild cognitive impairment is an important state to investigate when considering the lifestyle alterations and treatments for risk factors that are most likely to affect a patient's outcome.[20]

## Current treatment options

### Education and carer support – essential therapy

Accurate diagnosis of the dementia syndrome is essential to provide the best possible therapy. Information for patients and carers not only educates but can improve their ability to cope with the progression of the disease.[21] During this process it is important to ensure they have reasonable expectations – for example, that the temporary halt of decline of the disease is considered a treatment success.

Carer support is an essential part of patient management. Carers need not only information, education and advice regarding coping strategies from their clinicians but also support for themselves. Research with carers shows that they have an increased rate of medical illness, psychological stress and substance use (e.g. alcohol and tranquillisers).[22] A trial of carer support using educational sessions, group support and practical training shows benefit for both patients with dementia (fewer behavioural and psychiatric symptoms) and their carers (higher satisfaction ratings and fewer with lowered mood).[23] Organisations such as Alzheimer's Australia provide guidance and education as well as carer support.

### Symptomatic therapy

Current treatment options for Alzheimer's disease are limited to symptomatic therapies. These include cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists.

#### Cholinesterase inhibitors

Choline is an important CNS neurotransmitter required for normal functioning of the hippocampal memory centres as well as for attention and concentration. There is a significant deficiency in acetylcholine activity in the brains of patients with Alzheimer's disease. ChEIs reduce the breakdown of acetylcholine and partially correct this deficiency. There are three ChEIs available in Australia, which are donepezil (available in a once daily tablet form), galantamine (available in a capsule form) and rivastigmine (available in a patch, twice daily liquid or capsule forms). A Cochrane review concluded that ChEIs demonstrated modest beneficial effects on symptoms in some, but not all treated patients with Alzheimer's disease.[24]

A slow-release implantable ChEI has been investigated; however, it has not come to the market yet. This may be influenced by the lack of market share for 'yet another cholinesterase inhibitor'.

Side effects are relatively common with all ChEIs and are usually of a gastrointestinal nature (e.g. nausea, diarrhoea, vomiting) due to the increase in peripheral acetylcholine activity. Other possible reactions include urinary urgency, sleep disturbance, weight loss, muscle cramps and syncope. Syncope usually only occurs in the presence of a cardiac conduction abnormality, and an ECG should be performed for all people starting on these medications. Some of these side effects can settle with time and all reverse with ceasing the drug. Side effects of these medications are dose-dependent. There is discussion about the cost versus benefit of these medications given their modest impact on disease, and there have been recent reports of ChEI side effects leading to hospitalisation.[25]

As not all people with Alzheimer's disease benefit from therapy, it is important to review patients for a beneficial response in memory, behaviour and functional domains. In Australia, for PBS funding the baseline MMSE should be 10 or greater; if greater than 25, the ADAS-Cog score must also be quoted. For continued PBS funding an improvement in cognition from baseline must be shown within six months. This is defined as a 2-point increase or greater on the MMSE, or a 4-point decrease on the ADAS-Cog (reverse scale). In those patients who score less than 10 on MMSE because of, for example, language, intellectual disability or lack of education, a documented improvement in the clinician interview-based impression of change severity (CIBIC) score can be utilised.

At times, even in the absence of a documented objective benefit, a rapid deterioration is seen on ceasing the medication. This suggests that trying an alternative ChEI should be considered if the first agent did not produce the required improvement. Alternatively, some patients choose to fund their medication privately.

#### Memantine

Over stimulation of the excitatory gamma-aminobutyric acid (GABA) receptor occurs in patients with Alzheimer's disease, likely due to a combination of leakage of neurotransmitter (glutamate) from damaged neurones and direct stimulation by Aβ 42. This can be blocked using the NMDA receptor antagonist memantine.

A number of trials have demonstrated modest benefits and a good side effect profile of memantine in patients with moderate to severe Alzheimer's disease.[26] To qualify for PBS funding, it is required that the baseline MMSE be 10 to 14 and that a 2-point improvement be documented within six months.

Research examining the combination of two symptomatic therapeutic approaches has shown some evidence of synergistic benefit,[27] but current PBS regulations permit only one therapy be funded at a time. The issue of combined treatment in Australia is an area of debate and the use of private prescriptions for add-on therapy is acknowledged.

## Supplemental therapy

Vitamin E showed initial promise as a treatment for Alzheimer's disease in a small trial; however, a larger trial demonstrated no effect on progression of mild cognitive impairment.[28] Also, there is some evidence of increased haemorrhagic risk at high dose.[29] From a meta-analysis of numerous trials of vitamin E used for various indications, this treatment is no longer recommended for use in patients with cognitive impairment. Ginkgo biloba has similarly weak and inconsistent evidence for efficacy.

Folic acid might improve the response to cholinesterase therapy in patients with Alzheimer's disease and may improve cognition in elderly patients with high homocysteine levels,[30] but this has not been established in large prospective studies. Furthermore, research has shown that patients with ischaemic heart disease may be at greater risk of colon cancer if they are taking folate and vitamin $B_{12}$ supplementation.[31]

The area of supplements is a large burgeoning area of research and has been widely reviewed. There is a great need for assessment of long-term use to determine the safety of these supplements in the older population and in those with comorbidity.

## Managing behavioural and psychiatric symptoms

Challenging behaviours in the context of dementia are best managed initially by modifying the environment and/or the care approach. Medications should be seen as second-line therapy because of their limited efficacy and significant side effects. It is essential to exclude comorbidity as a cause of new behaviour development.

The development of psychotic symptoms (delirium, hallucination, misidentification) is common in the course of dementia and may be due to coexisting perceptual disturbance and cognitive deficits. This often warrants referral of the patient to an old age psychiatrist. Patients with psychotic symptoms can respond well to antipsychotics. A meta-analysis of the effectiveness of antipsychotics in the treatment of psychosis, aggression and agitation provided the conclusions outlined below.[32]

- Risperidone at a dose of 1 to 2 mg/day significantly improved psychosis and aggression, but not agitation.
- Olanzapine at a dose of 5 to 10 mg/day significantly improved aggression but not psychosis or agitation.
- Both risperidone and olanzapine demonstrated significant side effects and are associated with an almost fourfold increase in the risk of adverse cerebrovascular events, including stroke.

In a 2002 meta-analysis, haloperidol showed benefits in aggression, but not agitation in patients with dementia, although with a significant incidence of side effects.[33] There is no evidence that atypical antipsychotics have a lower associated risk of cardiovascular adverse events.

Agitation is commonly treated using mood stabilisers. However, a recent review of sodium valproate could not demonstrate any clear efficacy and noted the risk of significant side effects. [34]

Despite the lack of good trial evidence, it remains common practice to treat agitation with mood stabilisers and/or antipsychotics. Certainly if agitation originates from psychosis or manifests as aggression, antipsychotics might be a necessary part of the short-term management plan, but the indication for their use should be reviewed regularly and the drugs discontinued as soon as practical.

Depression is common in patients with dementia, although diagnosis can at times be challenging. Patients usually respond to treatment with antidepressants, and treatment of depression can significantly improve some behaviours. Patients with Alzheimer's disease and frontal lobe dysfunction can be confused with having depression, with the potential of the development of agitation and restlessness after treatment.

An important consideration is that both agitation and psychosis can potentially be worsened by antidepressants, benzodiazepines and anticholinergic drugs. A full medication review is recommended if a patient develops new behavioural symptoms.

## Nonpharmacological therapy

The use of nonpharmacological therapies in the management of Alzheimer's disease and the prevention of cognitive decline could be the subject of an entire review paper. Nonpharmacological approaches are worth considering because of their low costs and low risks of side effects, as well as their ability to complement pharmacological approaches and their benefits to other health outcomes.

Modest results have been reported in the prevention of cognitive decline using both cognitive retraining and physical activity. Cognitive retraining is likely to also have supportive effects that have been demonstrated to improve wellbeing.[35] Cognitive intervention is yet to be shown to prevent Alzheimer's disease; however, studies to date have been limited.[36] This area is one of active research that will eventually yield results to guide therapy.[37]

Physical activity has slight benefits in improving cognition in older people

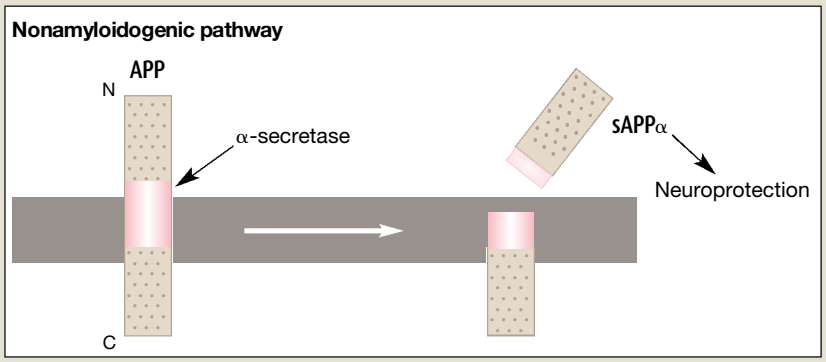
with mild memory impairment,[38,39] but has not yet been demonstrated to be effective in those with Alzheimer's disease, although research is under way. Again, this approach is likely to have additional supportive and socialising effects.

Lifestyle interventions include physical activity, cognitive retraining, social engagement, nutritional supplements and dietary factors, all of which show promise for affected patients. The mechanism of action by which these lifestyle factors have effect is not yet clear. Also, the specific duration, intensity and type of activities is not yet elucidated. Several large scale multimodal intervention studies are now under way.

## Amyloid production

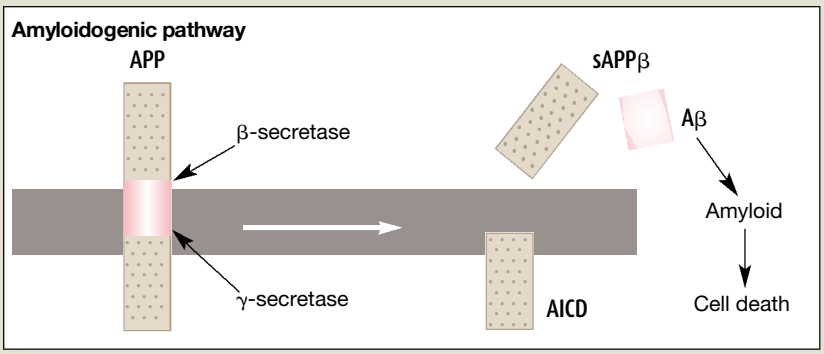
**Nonamyloidogenic pathway**

Cleavage of the amyloid precursor protein (APP) by α-secretase interior to the amyloid-β (Aβ) peptide sequence initiates nonamyloidogenic processing. A large amyloid precursor protein (sAPPα) ectodomain is released, leaving behind an 83-residue carboxy-terminal fragment. This fragment is then digested by γ-secretase, liberating an extracellular portion and the amyloid intracellular domain (AICD).




**Amyloidogenic pathway**

The amyloidogenic processing is initiated by β-secretase (β-site amyloid precursor protein cleaving enzyme 1 [BACE-1]), releasing a shortened sAPPβ. The retained product is also a γ-secretase substrate, generating Aβ and AICD. Gamma-secretase cleavage occurs within the cell membrane in a unique process termed 'regulated intramembranous proteolysis'. sAPPα and sAPPβ are the secreted APP fragments after α-secretase and β-secretase cleavages, respectively. AICD is a short tail (approximately 50 amino acids) that is released into the cytoplasm after progressive ε-to-γ cleavages by γ-secretase. AICD is targeted to the nucleus, signalling transcription activation. Soluble Aβ is prone to aggregation.




## Latest advances in treatment

Potential new treatments for Alzheimer's disease are focusing on removing amyloid by decreasing amyloid production, increasing amyloid clearance or using immunotherapies. Other major treatment targets include correcting neuronal damage, neuroprotection and use of anti-inflammatories. There are a number of new potentials for therapy, the most exciting of which is disease-modifying therapy. However, it is likely that these disease-modifying therapies will be utilised in addition to symptomatic therapies.

### Decreasing amyloid production

There are a number of strategies designed to reduce amyloid production due to its association with Alzheimer's disease. In addition, although this area has the most interest due to the strong associations between amyloid and Alzheimer's disease, there still is some disagreement about whether this association implies causation (see the box on this page).

Gamma-secretase inhibitors act on the enzyme complex that is specifically responsible for the production of toxic amyloid. Unfortunately their activity is not specific and broader inhibition of signalling pathways can result in significant side effects on the gastrointestinal tract, skin, thymus and spleen. One γ-secretase inhibitor, tarenflurbil, showed promise in initial trials,[40] but recently failed to show benefit in a large scale clinical trial. Another γ-secretase inhibitor has shown some biochemical response but at the risk of side effects,[41] and a phase III trial is currently under way.

Beta-secretase (also called β-site of APP cleaving enzyme [BACE]) inhibitors stop amyloid generation upstream at the rate limiting step in the early processing

of APP. Dual knockout mice without β-secretase activity do not manifest significant side effects and have reduced levels of Aβ peptide in the CNS.[42] Stage II trials of BACE inhibitors are currently under way. Small molecule inhibitors of BACE are in development; these can cross the blood–brain barrier, have generated decreased Aβ levels and have improved cognitive performance in mice.[43]

Alpha-secretase has the ability to cleave APP into two harmless fragments that lack the ability to form amyloid (see the box on page 26). In mouse models, overexpression of the α-secretase *ADAM10* gene (which produces the proteins A disintegrin and metallopeptidase-ADAM) was able to prevent the deposition of amyloid.[44] Further basic research is required into the regulation of this system and the means of increasing its activity.

## Increasing amyloid clearance

As amyloid is a naturally occurring protein in neurones, mechanisms exist within the CNS to clear it and thus prevent accumulation. These systems appear to be largely dependant upon the action of metalloproteinases (metal-containing extracellular proteinases).

Neprilysin is one such proteinase that is present in a range of tissues throughout the body, including neuronal membranes. There it breaks down peptide neurotransmitters, although its levels also increase dramatically in response to neuronal damage. Neprilysin has been shown to cleave Aβ both *in vitro* and in mouse models. Both increasing and decreasing neprilysin activity significantly decreases and increases brain amyloid, respectively.[45] It is interesting to note that 'lifestyle interventions' combined with exercise in a transgenic mouse population increased brain neprilysin activity with an associated decrease in brain amyloid.[46] This suggests that the lifestyle programs may be providing benefit at a physiological level in addition to their social and risk-factor reduction improvement.

Other proteases that may contribute to catabolism of Aβ within the brain are insulin-degrading enzyme, angiotensin converting enzyme and matrix metalloproteinases. It has been suggested that the ability of peroxisome proliferator-activated receptor (PPAR-γ) agonists to increase the availability of CNS insulin-degrading enzyme underlies their apparent antiamyloid action in some studies.[47] A recent large phase III trial of rosiglitazone, however, failed to show any significant benefit.[48] The overlap between diabetes and dementia and the role of glucose and insulin in the regulation of brain activity is an area of increasing interest and more studies will be carried out in the next decade to decipher these interactions and relationships.

PBT2, a compound derived from clioquinol that attenuates metal proteins, has also been shown to increase amyloid clearance *in vitro* and in animal models, although its exact mode of action is unclear. This agent binds metal ions and appears to modify their availability at various sites in the amyloid processing and plaque formation process. A small phase IIa study has shown a dose-dependant reduction in cerebrospinal fluid Aβ 42, as well as some improvement in tests of executive function,[49] and the drug was well tolerated.

## Immunotherapy

Several attempts have been made to remove amyloid using vaccination to mobilise the patient's own immune system to make antibodies. Although early trials involving vaccination with whole amyloid showed good amyloid clearance in mice, human trials were stopped early following cases of encephalitis.[50] Subsequent attempts have focused on controlling the immune response by selecting fragments of Aβ. Although there has yet to be any clear success from this approach, attempts continue.[51]

There are also anti-Aβ DNA antibodies being developed, with the aim of preventing APP transcription. An $A\beta_{1-6}$ epitope encased by a biosphere is in a phase I trial, with the strategy being to allow B-cell stimulation without activating Aβ-reactive T-cells. This may allow antibody production without stimulating a T-cell reaction against the brain, and thus reduce the risk of encephalitis.[52]

Several monoclonal antibodies are currently undergoing phase I to III trials. These are directed against different regions of Aβ, with not all agents crossing the blood–brain barrier. Bapineuzumab crosses into the CNS and is directed against the N-terminus of Aβ. Unfortunately, it also removes amyloid from CNS blood vessel walls and both microhaemorrhages and vasogenic oedema have been seen in some subjects. The C-terminus antibodies currently under trial do not cross the blood–brain barrier and are therefore not associated with these side effects.[53] These remove Aβ from the peripheral circulation, acting as a 'sink' to theoretically cause secondary removal of brain amyloid. Solanezumab crosses into the CNS and has been developed to be directed towards mid-Aβ; early trials indicate efficacy.

## Neurofibrillary tangles

The kinase inhibitors reduce the formation of neurofibrillary tangles by reducing tau hyperphosphorylation. An early human trial has been completed with methylene blue, with significant benefits seen compared with placebo.[54] This agent decreases tangles by both breaking up the accumulation and decreasing the production of hyperphosphorylated tau.

## Cell survival – neuroprotection

A number of 'neuroprotective agents' are being investigated with the aim of interfering with the cell death cascades. These include NMDA receptor antagonists that block glutamate-related excitotoxicity, the ampakines that prevent the entry of calcium into cells, and caspases. Caspases are normally involved in cell death and are thought to mediate the toxic effects

of Aβ monomers, as well as potentially inducing further Aβ production.[55] Nicotine has been shown to promote cell survival and is under consideration for human use in early stage trials.[56,57] A CNS nicotinic acetylcholine receptor agonist, varenicline, is undergoing phase II trials.[58]

The benefits from this therapeutic approach have been questioned in that once a cell is so damaged as to precipitate its self-destruction (apoptosis), maintenance of this damaged cell may not improve function. The 25-year-old Russian antihistamine, latrepirdine, has received publicity following the release of recent trial data. This agent was reported to halt cognitive decline over an 18-month period in a small group of patients with mild to moderate Alzheimer's disease.[59] Its method of action is thought to be via prevention of mitochondrial dysfunction, although it also demonstrates weak memantine and cholinesterase-like properties. A large international trial is due for completion in 2011, with the potential for its availability for clinical use soon after should results be positive.

In patients with an ageing brain or Alzheimer's disease, dysfunctional mitochondria have been identified as a possible source of added oxidative stress.[60] Randomised trials of antioxidants have not shown good results;[61] however, it is worthwhile to consider PBT2 and latrepirdine's antioxidative effects in evaluating the efficacy of targeting the mitochondrial dysfunction.

### Anti-inflammatory drugs

The role of inflammation in the pathophysiology of Alzheimer's disease has not been fully defined but inflammation appears to be part of the pathological amyloid cascade that leads to dendritic disconnection and cell death. The cell loss associated with dementia is certainly occurring via many of the apoptotic pathways, which are fed by the inflammatory cascade. Antioxidants to reduce oxidative injury to cell membranes and monoamine oxidase inhibitors to reduce free radical generation are both strategies that are under investigation for potential treatment. These plus NSAIDs are the main candidates in anti-inflammatory therapy. To date, clinical trials have been negative as to a therapy for Alzheimer's disease; however, the roles of anti-inflammatories in delaying onset and in prevention are currently being examined.

Receptor for advanced glycation end products (RAGE) proteins are part of the inflammatory response of a variety of tissues. In the CNS, soluble Aβ monomers are thought to activate this system and produce inflammation and neuronal death, a process that in cell cultures can be blocked by RAGE inhibitors.[62] At least one inhibitor of this process is undergoing phase II trials.

## Summary

With our ageing population and the increasing prevalence of Alzheimer's disease, the need for disease-modifying therapy is crucial. Progress in this area has been limited in part by a lack of understanding of the pathophysiology of Alzheimer's disease. The next generation of therapies for Alzheimer's disease have the potential to slow significantly or even halt disease progression by directing their actions against the underlying disease processes of Alzheimer's disease (Table 2).

Future therapies will be directed against the production of Aβ 42, blocking its apparent modes of action for neurotoxicity and clearing deposits of amyloid. At the same time derangements in the levels of neurotransmitters can be treated with ChEIs, NMDA receptor inhibitors and potentially nicotinic cholinesterase agonists. The costs of these new therapies will not be trivial. Those that have the potential to be closest to market are secretase modulators, monoclonal antibodies and latrepirdine; however, further trial evidence is needed. For these reasons, there is likely to be a delay in these drugs getting to the market.

### Table 2. Potential new treatments of Alzheimer's disease by mechanism

**Amyloid**
- Immunisation†
- Antibodies*
- Gamma-secretase inhibition/modulation*
- Beta-secretase inhibition/modulation†
- Alpha-secretase inhibition/modulation†
- Amyloid aggregation inhibitors†

**Tau protein**
- Immunotherapy†
- Aggregation inhibitor†
- Phosphorylation inhibitors†

**Neurones and synapses**
- Nerve growth factors§
- Neuroprotective agents‡
- Neurotransmitters† – histamine, 5HT, AMPA, nicotinic, cholinesterase, muscarinic

**Inflammation**
- RAGE antagonists‡
- NSAIDs§
- Etanercept‡

**Antioxidants**
- Vitamin E§
- Folate‡
- B group vitamins‡

**Cardiovascular**
- Lipids§
- PPAR agonists‡
- Rosiglitazone§

**Other**
- Latrepirdine*
- Metal chelators†
- Hormone therapy§
- *APOE* modulation of expression‡

ABBREVIATIONS: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APO E = apolipoprotein E; 5HT = 5-hydroxytryptamine (serotonin); PPAR = peroxisome proliferator-activated receptor; RAGE = receptor for advanced glycation and products.

* Phase III clinical trials; † Early in the pipeline; ‡ Insufficient evidence; § Some negative results.

The moment that disease-modifying therapies become available, it will become crucial to be able to diagnose people at risk prior to the development of significant and irreversible neuronal death. Population screening focusing on all people over 60 years of age and younger individuals with a family history will be required at the general practice level. It will also be necessary to be able to confirm the presence of Alzheimer's disease pathology in patients demonstrating early deterioration through the use of blood and cerebrospinal fluid biomarkers, as well as advanced brain imaging. Thus the process of intervention is linked to the need for early diagnostics. The area of lifestyle therapies and neuroprotective agents for prevention is the ultimate goal and the development of an early diagnostic test will aid this goal.

The management of the behavioural and psychological symptoms of dementia remains challenging with no new safe drug treatment on the horizon. At present, services to diagnose and treat patients with dementia are under pressure and are unlikely to be able to cope with the potential avalanche of referrals possible should the mood of therapeutic nihilism be lifted by the availability of effective new therapies. The future holds both promise and challenge for clinicians and affected families alike. MT

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## References

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# What's the future of treatment for Alzheimer's disease?

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## References

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366: 2112-2117.
2. Access Economics; for Alzheimer's Australia. Making choices. Future dementia care: projection, problems and preferences. Canberra: Alzheimer's Australia; 2009.
3. Peisah C, Brodaty H. Managing Alzheimer's disease, the role of the GP. Med Today 2004; 5(11): 16-24.
4. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry, 2008; 16: 343-354.
5. Cechetto DF, Hachinski V, Whitehead SN. Vascular risk factors and Alzheimer's disease. Expert Rev Neurother 2008; 8: 743-750.
6. Ampuero I, Ros R, Royuela A, et al. Risk factors for dementia of Alzheimer type and aging-associated cognitive decline in a Spanish population based sample, and in brains with pathology confirmed Alzheimer's disease. J Alzheimers Dis 2008; 14: 179-191.
7. Rogaeva E, Meng Y, Lee JH, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 2007; 39: 168-177.
8. Folstein, MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.
9. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141: 1356-1364.
10. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695-699.
11. Finkel SI, Costa E, Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr 1996; 8 Suppl 3: 497-500.
12. Kaufer DI, Cummings JL, Ketchel P, et al., Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000; 12: 233-239.
13. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009; 302: 385-393.
14. Hampel H, Bürger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. Alzheimers Dement 2008; 4: 38-48.
15. Silverman DH, Small GW, Chang CY, et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. JAMA 2001; 286: 2120-2127.
16. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol, 2004; 55: 306-319.
17. Rowe CC, Ackerman U, Browne W, et al. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. Lancet Neurol 2008; 7: 129-135.
18. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56(3): 303-308.
19. Petersen RC, Morris JC. Clinical features. In Petersen RC, ed. Mild cognitive impairment: aging to Alzheimer's disease. New York; Oxford University Press; 2003. p. 15-40.
20. Aisen PS. Treatment for MCI: is the evidence sufficient? Neurology 2008; 70: 2020-2021.
21. Brodaty H, Green A. Who cares for the carer? The often forgotten patient. Aust Fam Physician 2002; 31: 833-836.
22. Davis LL, Weaver M, Zamrini E, Stevens A, Kang DH, Parker CR Jr. Biopsychological markers of distress in informal caregivers. Biol Res Nurs 2004; 6: 90-99.
23. Callahan CM, Boustani MA, Unverzagt FW, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a

randomized controlled trial. JAMA 2006; 295: 2148-2157.
24. Birks J. The evidence for the efficacy of cholinesterase inhibitors in the treatment of Alzheimer's disease is convincing. Int Psychogeriatr 2008; Feb 6: 1-7 (epub ahead of print).
25. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 2009; 169: 867-873.
26. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. Int J Geriatr Psychiatry 2008; 23: 537-545.
27. Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2008; 22: 209-221.
28. Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2008; (3): CD002854.
29. Ames D, Ritchie C. Antioxidants and Alzheimer's disease: time to stop feeding vitamin E to dementia patients? Int Psychogeriatr 2007; 19: 1-8.
30. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people (Review). Cochrane Database Syst Rev. 2009; (4): CD004514.
31. Ebbing M, Bønaa KH, Nygård O, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 2009; 302: 2119-2126.
32. Ballard C, Waite J, Birks J. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. Cochrane Database of Syst Rev. 2006, (1): CD003476.
33. Lonergan E, Luxenberg J, Colford JM, Birks J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev, 2002; (2): CD002852.
34. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev. 2009; (3): CD003945.
35. Avila R, Carvalho IA, Bottino CM, Miotto EC. Neuropsychological rehabilitation in mild and moderate Alzheimer's disease patients. Behav Neurol 2007; 18: 225-233.
36. Papp KV, Walsh SJ, Snyder PJ. Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. Alzheimers Dement 2009; 5: 50-60.
37. Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B; MAPT Study Group. Commentary on 'a roadmap for the prevention of dementia II. Leon Thal Symposium 2008.' The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimers Dement 2009; 5: 114-1121.
38. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008; 300: 1027-1037.
39. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 2009; 39: 3-11.
40. Wilcock DM, Colton CA. Anti-amyloid-beta immunotherapy in Alzheimer's disease: relevance of transgenic mouse studies to clinical trials. J Alzheimers Dis 2008; 15: 555-569.
41. Fleisher AS, Raman R, Siemers ER, et al. Phase 2 safety trial targeting amyloid beta production with a gamma-secretase inhibitor in Alzheimer disease. Arch Neurol 2008; 65: 1031-1038.
42. Roberds SL, Anderson J, Basi G, et al. BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics. Hum Mol Genet 2001; 10: 1317-1324.
43. Lerchner A, Machauer R, Betschart C, et al. Macrocyclic BACE-1 inhibitors acutely reduce Abeta in brain after po application. Bioorg Med Chem Lett 2010; 20: 603-607.
44. Lichtenthaler SF, Haass C. Amyloid at the cutting edge: activation of alpha-secretase prevents amyloidogenesis in an Alzheimer disease mouse model. J Clin Invest, 2004; 113: 1384-1387.
45. Carson JA, Turner AJ. β-Amyloid catabolism: roles for neprilysin (NEP) and other metallopeptidases? J Neurochem 2002; 81: 1-8.
46. Lazarov O, Robinson J, Tang YP, et al. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. Cell 2005; 120: 701-713.
47. Escribano L, Simón AM, Pérez-Mediavilla A, Salazar-Colocho P, Del Río J, Frechilla D. Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model. Biochem Biophys Res Commun 2009; 379: 406-410.
48. Risner ME, Saunders AM, Altman JF, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 2006; 6: 246-254.
49. Lannfelt L, Blennow K, Zetterberg H, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2008; 7: 779-786.
50. Vellas B, Black R, Thal LJ, et al. Long-term follow-up of patients immunized with AN1792: reduced functional decline in antibody responders. Curr Alzheimer Res 2009; 6: 144-151.
51. Okura Y, Matsumoto Y. Recent advance in immunotherapies for Alzheimer disease: with special reference to DNA vaccination. Hum Vaccin 2009; 5: 373-80.
52. Woodhouse A, Dickson TC, Vickers JC. Vaccination strategies for Alzheimer's disease: a new hope? Drugs Aging 2007; 24: 107-119.
53. Chauhan NB, Siegel GJ. Intracerebroventricular passive immunization in transgenic mouse models of Alzheimer's disease. Expert Rev Vaccines 2004; 3: 717-725.
54. Chang E, Honson NS, Bandyopadhyay B, et al. Modulation and detection of tau aggregation with small-molecule ligands. Curr Alzheimer Res 2009; 6: 409-414.
55. Rohn TT, Head E. Caspases as therapeutic targets in Alzheimer's disease: is it time to 'cut' to the chase? Int J Clin Exp Pathol 2009; 2: 108-118.
56. Jonnala RR, Buccafusco JJ. Relationship between the increased cell surface alpha7 nicotinic receptor expression and neuroprotection induced by several nicotinic receptor agonists. J Neurosci Res 2001; 66: 565-572.
57. Seo J, Kim S, Kim H, et al. Effects of nicotine on APP secretion and Abeta- or CT(105)-induced toxicity. Biol Psychiatry 2001; 49: 240-247.
58. Wang HY, Stucky A, Liu J, Shen C, Trocme-Thibierge C, Morain P. Dissociating beta-amyloid from alpha 7 nicotinic acetylcholine receptor by a novel therapeutic agent, S 24795, normalizes alpha 7 nicotinic acetylcholine and NMDA receptor function in Alzheimer's disease brain. J Neurosci 2009; 29: 10961-10973.
59. Doody RS, Gavrilova SI, Sano M, et al. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet 2008; 372: 207-215.
60. Smith MA, Perry G, Richey PL, et al. Oxidative damage in Alzheimer's. Nature 1996; 382(6587): 120-121.
61. Pratico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. Trends Pharmacol Sci 2008; 29: 609-615.
62. Sparvero LJ, Asafu-Adjei D, Kang R, et al. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med 2009; 7: 17.