In the early 1980s, my colleagues and I developed tacrine as the first pragmatic treatment for Alzheimer's disease (AD) [1]. Tacrine was synthesized by Adrian Albert as part of the Australian World War II effort to find an intravenous antiseptic [2]. Use of tacrine to treat AD was unexpected by the scientific community and there was considerable controversy [3–5]. Yet 7 years later, in 1993, tacrine (Cognex®) was the first US FDA-approved treatment for AD.

The theory behind tacrine was the cholinergic hypothesis [6]. According to this theory, drugs that enhanced cholinergic neuronal function would improve memory. This might be by cholinesterase inhibition (CI), stimulation of the nicotinic receptor or enhancement of acetylcholine production.

The intent of tacrine was to assist failing cholinergic neurons. Symptomatic treatment. Prevention or reversal of the disease process was never intended with CI therapy. It was understood that the deficits of the cholinergic system seen in AD were the result of the disease, not the cause.

**Current therapies**

**Pharmacotherapies**

At present there are three other cholinesterase inhibitors – donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®) [6]. The latter has nicotinic receptor agonist effects. Benefits of CI for each patient results from the potency and dose of the pharmaceutical agent, and the severity of the cholinergic deficit, and the ability of the cholinergic system to respond to stimuli. In end-stage AD, when the cholinergic system is largely destroyed, these agents have little value. A defective cholinergic neuron can be stimulated to work more efficiently, but a dead neuron cannot.

Memantine (Namenda) is the first in a novel class of AD medications acting on the glutamatergic system by reversibly blocking NMDA glutamate receptors [10]. The NMDA receptor (NMDAR), a glutamate receptor, is the predominant molecular device for controlling synaptic plasticity and memory function [7]. Calcium flux through NMDARs is thought to play a critical role in synaptic plasticity, a cellular mechanism for learning and memory. At normal levels, glutamate aids in memory and learning, but if levels are too high, glutamate appears to overstimulate nerve cells, triggering the signal for apoptosis, hence killing key brain cells [8]. The common wisdom is that memantine helps Alzheimer’s patients by downmodulation of calcium influx, thus enabling more efficient memory plasticity.

If AD is a progressive disease characterized by the diffuse death of neurons, it seems probable that memantine’s benefit may also be due to blocking both caspase-dependent and/or caspase-independent apoptosis [9,10]. By preserving AD neurons and permitting repair and recovery, memantine may actually be a disease-modifying
Numerous brain insults (e.g., head trauma, metabolic) create free radicals, chronic cytokine responses, oxidative injury, foci of inflammation with development of plaques and tangles. After 15–25 years, Alzheimer’s disease results. Death is associated with immune system failure. Reproduced with permission from [16].

In what may prove to be flawed work, the first meta-analysis of memantine’s value in mild Alzheimer’s did not show promise [11]. The study examined a battery of memory tests over a short period of time, not progression of the illness over years.

Available current alternatives
Memory calisthenics became quite popular in the early 2000s in both academia and alternative medicine [12]. This was not an isolated strategy; rather, the proponents of this approach quickly added the concept of healthy lifestyle. Healthy lifestyle habits include mental stimulation, physical exercise, good nutrition, weight control, stress management and adequate sleep, and healthy lifestyles are said to improve brain fitness [13].

Although the healthy lifestyle hypothesis is intuitive, it remains to be proven. Nevertheless, it is hard not to recommend a healthy lifestyle to patients. One caution is that recent data have shown that mild obesity (BMI of 30–39) in the elderly is protective [14].
The use of health supplements to improve memory has been investigated. Kamat and colleagues recently reviewed 20 years of antioxidant use in human and animal studies [15]. They concluded that the theory that antioxidants could cause neurological conditions was sound, but that the implementation of antioxidant therapies in humans “must be flawed” [15].

**Etiology of AD**

To design an effective treatment, understanding of the etiology and pathophysiology is essential. For example, the cholinergic system deficits seen in AD allowed CI therapies to be developed.

There are currently five dominant hypotheses on the etiology of AD and these are: the amyloid hypothesis (AH), the tau hypothesis (tH), the inflammation hypothesis (IH), oxidative stress hypothesis (OSH) and the vascular hypothesis (VH). These theories are not mutually exclusive. For example, the OSH can accommodate both the inflammation hypothesis, the VH, elements of the Aβ-AH and tH. There are other theories such as mitochondrial deficits, parasitic infections, bacterial infections, viral infections and post-traumatic brain injury. These will not be discussed in detail here. Many of these are also subsets of the OSH (Figure 1) [16]. Finally, there is the theory of neuronal hibernation that has been proposed by Swaab and colleagues [17].

- **Amyloid hypothesis**
  
  **Figure 2** displays the AH. This hypothesis was formulated in the 1980s and is the most widely accepted [102]. As Selkoe explains, the hypothesis is based on ten key observations. Some of these are circular logic, such as the tenth observation that alternative hypotheses do not have rigorous evidence to support them. The hypothesis simply stated that genetic events lead to amyloid-β (Aβ) accumulation in the form of Aβ$_{42}$ in the memory areas of the brain. This Aβ accumulation effects synaptic efficiency, is toxic to neurons, creates diffuse plaques, activates inflammatory response and leads to neurofibrillary tangles (NFTs). This becomes a self-perpetrating downward spiral to clinical AD and death.

  In recent years the AH has been questioned [18]. Knockout mice lacking Aβ demonstrate poorer memory than those with excessive Aβ [19]. Summers postulated that Aβ is a downstream product of oxidative injury and cellular death [16]. Accumulations of Aβ are like tombstones. Tombstones rarely kill people, rather they mark where a body is located. Thus, it may be that an amyloid plaque also marks where functional neurons were previously located. The purpose of amyloid appears to be protective – the body’s attempt to protect neurons [20]. Furthermore, many cognitively healthy seniors have significant senile plaques but no sign of Alzheimer’s [18]. Finally, CNS amyloid deposition does not correlate with neuronal, metabolic or synaptic loss [18]. There is also correlation between amyloid deposit density and cognitive deficits [21]. Nevertheless, there are numerous drugs in development based on the Aβ-AH at this time.

- **Tau protein hypothesis**
  
  **Figure 3** displays the tH, which states that hyperphosphorylation of tau protein is the primary causative factor of AD. The tH emerged from studies of the pathology of NFTs as well as from research into the normal biology and functions of tau [22].
<table>
<thead>
<tr>
<th>Candidate</th>
<th>Subclass</th>
<th>Sponsor</th>
<th>Trial phase</th>
<th>Subjects (n)</th>
<th>Comment</th>
<th>Date of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC-001 (parenteral)</td>
<td>Anti-Aβ antibodies (parenteral)</td>
<td>Pfizer/JANSSEN</td>
<td>II</td>
<td>76</td>
<td>Sequel to infamous AN-1792; skin lesions seen. Nine studies completed or in process</td>
<td>March 2010</td>
</tr>
<tr>
<td>CAD106</td>
<td>Anti-Aβ antibodies (parenteral)</td>
<td>Novartis</td>
<td>II</td>
<td>121</td>
<td>Developed by Cytos Biotechnology; five other studies</td>
<td>March 2010</td>
</tr>
<tr>
<td>Bapineuzumab (AA001)</td>
<td>Anti-Aβ antibodies (parenteral)</td>
<td>Pfizer/JANSSEN</td>
<td>II</td>
<td>800</td>
<td>Continuation of other studies; 13 other studies completed or in processes. This is identical to the natural antibody triggered by AN-1792</td>
<td>May 2008</td>
</tr>
<tr>
<td>PF04360365</td>
<td>Anti-Aβ antibodies (parenteral)</td>
<td>Pfizer</td>
<td>II</td>
<td>175</td>
<td>Passive anti-Aβ antibodies</td>
<td>July 2008</td>
</tr>
<tr>
<td>LY450139 (semagacestat)</td>
<td>γ- and β-secretase inhibitor</td>
<td>Eli Lilly and Co</td>
<td>III</td>
<td>1100</td>
<td>This is mixed (and β-secretase inhibitor; five other studies completed or in process</td>
<td>September 2008</td>
</tr>
<tr>
<td>BMS-708163</td>
<td>γ-secretase inhibitor</td>
<td>Bristol–Myers Squibb</td>
<td>II</td>
<td>270</td>
<td>12 other studies completed or in process (γ-secretase inhibitors cause cancer)</td>
<td>May 2009</td>
</tr>
<tr>
<td>CHF 5074</td>
<td>γ-secretase modulator</td>
<td>Chiesi Pharmaceuticals Inc.</td>
<td>II</td>
<td>96</td>
<td>Three other studies completed or in process</td>
<td>March 2011</td>
</tr>
<tr>
<td>Posiphen</td>
<td>β-secretase modulator</td>
<td>QR Pharma Inc.</td>
<td>I</td>
<td>30</td>
<td>Dual action γ-secretase inhibition and ACHEi</td>
<td>February 2010</td>
</tr>
<tr>
<td>E2609</td>
<td>β-secretase inhibitor</td>
<td>Eisai Inc.</td>
<td>I</td>
<td>48</td>
<td>Oral β-secretase inhibitor</td>
<td>December 2010</td>
</tr>
<tr>
<td>MemoryXLM™</td>
<td>Mixed secretase, Aβ inhibitor</td>
<td>U Massachusetts, Worcester</td>
<td>II</td>
<td>300</td>
<td>Six-component nutriceutical said to have both γ- and β-secretase inhibition and reduce Aβ production</td>
<td>March 2011</td>
</tr>
<tr>
<td>AZD103  ELND005</td>
<td>Prevents fibrilization of Aβ</td>
<td>Elan Pharmaceuticals</td>
<td>II</td>
<td>150</td>
<td>Higher dose 1000 and 2000 mg p.o. b.i.d associated with excessive deaths</td>
<td>June 2009</td>
</tr>
<tr>
<td>MABT5102A</td>
<td>Anti-Aβ antibodies, passive (parenteral)</td>
<td>Genentech</td>
<td>II</td>
<td>372</td>
<td>Passive monoclonal Aβ antibody</td>
<td>April 2011</td>
</tr>
<tr>
<td>Solanezumab (LY2062430)</td>
<td>Anti-Aβ antibody (parenteral)</td>
<td>Eli Lilly and Co</td>
<td>III</td>
<td>1275</td>
<td>Binds specifically to soluble amyloid-β. Five studies listed, earlier studies positive</td>
<td>December 2010</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Anti-Aβ antibody (parenteral)</td>
<td>Hoffmann–La Roche</td>
<td>II</td>
<td>360</td>
<td>Positive Phase I study</td>
<td>November 2010</td>
</tr>
<tr>
<td>AFFITOPE AD03 (MimoVax)</td>
<td>Anti-Aβ antibody (parenteral)</td>
<td>Affiris AG</td>
<td>II</td>
<td>420</td>
<td>Nine studies in total. Is thought to be a more selective vaccine</td>
<td>September 2010</td>
</tr>
</tbody>
</table>

Aβ: Amyloid-β; ACHEi: Acetylcholinesterase inhibitor; b.i.d.: Twice daily; p.o. Per orum.
Tau protein has more than 40 known phosphorylation sites and misfolding of tau protein is seen in several neurodegenerative diseases [23,24].

There is criticism of the tH. Su et al. have shown that oxidative stress precedes and causes tau phosphorylation via intracellular signaling of JNK and p38 activation [25]. Thus, NFT is part of the cascade seen in AD and not the cause. Furthermore, NFTs may not be involved in neuronal death, and neurons with NFTs can survive for decades in AD patients [26,27]. Nevertheless, there are potential drugs based on tH in development at this time.

**Inflammation hypothesis**

The IH is actually as old as the dominant AH [28]. In 1989 Griffith et al. demonstrated microglia associated with amyloid plaques in Alzheimer brains, which expressed one of the most potent inflammatory cytokines — IL-1 [29]. In 1994, Breitner et al. observed that patients taking non-steroidal anti-inflammatory drugs (NSAIDs) were less likely to develop AD [30]. Over the next decade other inflammatory cytokines were found in high concentrations such as IL-6, IL-2, IL-3, IFN-α and TGF-β1. At the time it was thought that these cytokines migrated into the CNS. Microglia and astrocytes in the early 1990s were thought by most scientists to simply be “packing styrofoam peanuts” cushioning the important organs separated by the blood–brain barrier. The word ‘glia’ is derived from the Greek for ‘glue’. Microglia, which initially are created in bone marrow, migrate to the CNS to recognize foreign bodies, sample them, and act as antigen-presenting cells activating T-cells. When activated, microglia become cytokine factories. The astrocyte is the most numerous of the macroglia. Recently, it is understood that they regulate neurons, precipitate apoptosis, secure the blood–brain barrier and also actively secrete cytokines and neurotransmitters [16,31].

The IH is well explained by Mrak [31] and can be seen in the middle portion of Figure 1. Aβ plaques are an evolutionary process of four stages with increasing amounts of insoluble Aβ. But in all stages, activated microglia are present and inflammatory cytokines are elevated. Likewise NFTs go through stages to mature NFTs which are said to be toxic. But again the activated microglia are present and inflammatory cytokines are elevated in the earliest stages of NFT formation.

The IH states that glia, especially microglia, form a chronic persistent pathologic inflammation similar to rheumatoid arthritis and ulcerative colitis. What activates the glia? Aging and head trauma are the only two items offered by Mrak. Numerous other potential activating agents are listed at the top of Figure 1.

Proponents of the IH discuss matters upstream from the AH and the tH. However, they do not point to events that precipitate the pathologic initiation of glia. In the OSH of Figure 1, the inflammatory process is incorporated in the middle stages of the chart, while associated causes that precipitate chronic inflammation are listed at the top. This includes infectious agents such as herpes viruses [32] or bacteria such as *Chlamydia pneumonia* [33].

Trials with NSAIDs have been inconclusive to date [34–36]. Use of corticosteroids appears more promising, but both steroids and NSAIDs have serious side effects when chronically used [37].

**Oxidative stress hypothesis**

The OSH was proposed following the observation in 1997 that AD is associated with aging, not genetics [38]. It became apparent that AD was associated with and the result of aging plus an initial brain insult. The initial brain injury could be metabolic, anoxic, vascular, infectious or traumatic (Figure 1). The insult precipitates necrosis and localized inflammation may become chronic [16].

Halliwell and Gutteridge brilliantly noted that the brain is uniquely vulnerable to oxidative injury [39]. First, oxygen is highly utilized

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Subclass</th>
<th>Sponsor</th>
<th>Trial phase</th>
<th>Subjects (n)</th>
<th>Comment</th>
<th>Date of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Tau aggregation inhibitor</td>
<td>University of Sao Paulo</td>
<td>II</td>
<td>80</td>
<td>Poor commercial viability</td>
<td>March 2007</td>
</tr>
<tr>
<td>Davetide (AL108)</td>
<td>Tau aggregation inhibitor</td>
<td>Allon Therapeutics</td>
<td>II and III</td>
<td>300</td>
<td>Previous positive Alzheimer’s disease study</td>
<td>October 2010</td>
</tr>
<tr>
<td>Tidegusib (NP-12 or NP031112)</td>
<td>Tau aggregation inhibitor</td>
<td>Noscira SA</td>
<td>II</td>
<td>280</td>
<td>Three studies. Application in supranuclear palsy. Blocks glycogen synthase kinase-3</td>
<td>April 2011</td>
</tr>
</tbody>
</table>
by neurons. As such the brain receives 20% of cardiac output, but is only 1% of a person’s body by weight. Second, neurons have a large cell surface because of the long axons. This means energy production via ATP metabolism in mitochondria occurs at a high level. This metabolic pathway is a principle generator of free radicals that create oxidative injury to cells. A normal brain (10¹¹–10¹² neurons) requires 4 × 10²¹ molecules of ATP per moment. This is a massive energy requirement and produces large quantities of free radical byproducts. Third, the principle substrate of brain is glucose (glycolysis and Krebs cycle). Because glycogen is not stored in neurons, any interruption in glucose metabolism creates huge quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Fourth, high calcium ion traffic across neuronal membranes causes potentially high intracellular free calcium. This leads to the production of ROS and RNS. Fifth, common catecholamine neurotransmitters (dopa, dopamine, serotonin and noradrenaline) create ROS and RNS when metabolized [39]. Interactions between catecholamines generate the superoxide radical. Metabolism of the amine moiety (R-CH₂-NH₂) by monoamine oxidases results in reactive hydrogen peroxide (H₂O₂) and reactive ammonia (NH₃). Sixth, some neurotransmitters are by nature excitotoxic. Glutamate, aspartate and nitric oxide are such neurotransmitters. Excess concentrations of excitotoxins result in intracellular signaling, which leads to apoptosis [39]. Seventh, metalloproteins are essential components in cytochromes, ferritin tyrosine hydroxylase, tryptophane hydroxylase and others. In traumatic, anoxic and other brain injuries, these metalloproteins are released into the intracellular space [39–41]. The release of the iron, copper and zinc, often from the mitochondria, reacts with lipids, free hydroxyl radicals and hydrogen peroxide. Although Aβ is an efficient antioxidant of iron, copper and zinc, it is membrane-bound and when overwhelmed can promote neuron death [42–44]. The result is lipid peroxidation, further free radical production, mitochondrial dysfunction, and neuronal apoptosis, inactivation or necrosis [16,45].

Figure 4 accentuates the importance of where oxidative injury occurs. Physically oxidative injury occurs in compartmentalized locations: blood–brain barrier, intercellular spaces, cell lipid membranes, cell receptors, cytosol, nucleus, mitochondria lipid membranes, endoplasmic reticulum, Golgi apparatus and other organelles.

In general, oxidative injury occurs at four chemical levels:
- Lipid membranes – lipid peroxidation: cell membrane, mitochondrial membrane, nuclear membrane, endoplasmic reticulum and Golgi apparatus;
- Nucleic acids – nucleic oxidation: DNA, mRNA, mcRNA, tmRNA, rRNA, RNAi, siRNA and mitochondrial DNA;
- Protein oxidation – protein peroxides: peptides, enzymes, structural, cell signaling, membrane or receptor proteins;
- Alkaline earth and transition metals – metal dysregulation: calcium, iron and copper.

Research agents previously used in OSH therapies are vitamin E (only the d-α tocopherol form), vitamin C and CoQ10. However, vitamin E comes in eight natural forms. Vitamin E is lipophilic and a potent scavenger of peroxyl radicals in the intracellular space and intracellularly at the mitochondria [39]. It cooperates with vitamin C, which regenerates α-tocopherol from α-tocopheryl radicals within membranes and lipoproteins. However, vitamin C is water soluble and largely isolated to vascular, intracellular and cytosol compartments. Its principle activity in the body as a whole is regeneration of reduced uric acid (urate radical). Uric acid accounts for over half of the free radical scavenging in the blood and intracellular space [46]. Use of vitamin E plus vitamin C would likely still not fully address free radical damage in the nucleus, endoplasmic reticulum, Golgi apparatus, misfolded proteins, peroxidation of cellular membranes or transition metal ions released by cellular death. The transition metal ions frequently released by mitochondrial dysfunction or cellular death are iron, copper, zinc and in certain cases mercury [44]. Aβ is the principal host defense that complexes transition metals, as well as some post-transition metals (aluminum and lead). Within the mitochondria itself, vitamin CoQ10 is effective at attenuating dysfunction [47]. CoQ10 is a lipophilic electron carrier in the electron transport chain of oxidative phosphorylation that is embedded in the inner mitochondrial membrane.

It is apparent that single, simple antioxidants should not work. An effective agent would be complex, working in multiple locations in both aqueous and lipid environments. Kamat et al. extensively reviewed the use of antioxidants in CNS diseases [15]. In animal models of AD Kamat et al. concluded that antioxidants were promising. He also noted that the massive doses required were not practical in humans. In human studies results are mixed at best.

Although results to date are disappointing, the OSH is growing in favor. It is inclusive of most of the AH, the tH and the IH. To some extent the VH may fall under the umbrella of the OSH. It should be noted that the previous agents explored were of poor design [48].

### Vascular hypothesis

The VH, proposed in 1993, is not necessarily about stroke and acute hypoxia [49]. Rather it is about chronic hypoxia by means of endothelial cell dysfunction due to aging [18,50]. Endothelial cells are part of a neurovascular unit, which consists of neurons, glial cells and endothelial cells. Endothelial dysfunction precipitates Aβ, and Aβ causes endothelial toxicity. Further signaling between glia, neurons and endothelial cells promotes neuroinflammation and incompetence of the blood–brain barrier. AD then follows.

Experimental VH follows the sequence seen in Figure 5 [51]. Note that chronic brain hypoperfusion is a central feature of the VH and the beginning of the final common pathway to AD.

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**Figure 5. Vascular hypothesis.** Chronic brain hypoperfusion results in brain atrophy and death.
Table 3. Potential therapies: inflammation hypothesis.

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Subclass</th>
<th>Sponsor</th>
<th>Trial phase</th>
<th>Subjects (n)</th>
<th>Comment</th>
<th>Date of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERE-110</td>
<td>Cytokine modulation</td>
<td>Ceregene</td>
<td>I</td>
<td>50</td>
<td>NGF gene delivered by adeno virus with induction of NGF</td>
<td>September 2009</td>
</tr>
<tr>
<td>Bryostatin 1</td>
<td>Intracellular signaling modulation</td>
<td>Blanchette Rockefeller Neuroscience Institute</td>
<td>II</td>
<td>9</td>
<td>Protein kinase C modulation. Myalgia side effect. Parenteral</td>
<td>April 2008</td>
</tr>
<tr>
<td>Etanercept (Enbrel®)</td>
<td>Cytokine modulation</td>
<td>University of Southampton</td>
<td>II</td>
<td>40</td>
<td>TNF-α inhibitor used in autoimmune diseases</td>
<td>January 2011</td>
</tr>
<tr>
<td>Lornoxicam (Xefo®)</td>
<td>COX-1 and -2 inhibition</td>
<td>JSW Lifesciences</td>
<td>II</td>
<td>220</td>
<td>One study. Cox-1 and -2 inhibitor</td>
<td>September 2009</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>TNF-α inhibitor</td>
<td>Bannor Health</td>
<td>II and III</td>
<td>20</td>
<td>Vague outcome measurements</td>
<td>March 2010</td>
</tr>
</tbody>
</table>

Diagnosis of AD is by carotid artery ultrasound and echocardiogram. Treatment is vigorous treatment of discovered cardiovascular problems, presumably to increase cerebral vascular flow. Experimental treatments would focus on neoangiogenesis and vasculogenesis [18].

The VH is intriguing, but open to criticism. Doubtless there is evidence of endothelial dysfunction in AD [50,51]. As yet treatment modalities have not been tested in animal or human studies. Further, it excludes direct parenchymal pathology as causal. It follows that viral- or bacterial-induced dementias must initially affect cerebral blood flow. Head trauma, per this theory, must initially induce chronic cerebral hypoperfusion before the dementia progresses. Oxidative stress occurs late in the sequence of the VH. Memory loss occurs before Aβ1-41 upregulation and deposition [51]. This sequence does not seem to match the human pathological sequence.

Hibernation hypothesis

Swaab et al. proposed the hypothesis that neurons do not die due to AD, but rather the neurons undergo atrophy and possibly hibernate [17]. Swaab demonstrated that the number of neurons in key locations is the same for AD and age-matched controls, and suggested that the ‘missing neurons’ are merely atrophied. Swaab also reviewed the evidence that the atrophic neurons are dramatically hypometabolic using Golgi apparatus markers, nucleolus size and NGF receptors (p75). The well-recognized 50–70% reduction in CNS glucose metabolism may be due to atrophic hibernating neurons. The question is how to wake hibernating atrophic neurons.

Future therapies

There are currently 914 clinical trials related to AD listed on the US government clinical trials website and 157 of these have an FDA Phase III status [103]. Alzheimer’s drug development appears to be stalled. Since the introduction of tacrine in 1993 and Namenda in 2003, there have been no approved new medications for AD. In part this is due to the insensitive testing instruments used to test outcomes [48,52]. Most cognitive testing instruments in popular use were developed before it was suspected that memory problems could be reversed. The original intent of the test was to diagnose a condition, not to measure improvement, for example, the Longitudinal Aging Study Amsterdam used the Mini-Mental State Exam (MMSE) to measure cognitive decline [55]. Yet, the MMSE suffers from both floor and ceiling effects, making it a crude unreliable tool [52]. Some studies use a battery of ‘cognitive tests’ to measure change [54]. These tests often take hours, and the data may be affected by the subject’s response to fatigue. For example, the Boston Naming Test was developed for assessment of aphasia, has a 135 page instruction book and requires 90 min to complete [104].

Another possible cause of poor outcomes is the ‘Epic Research Project’. Here, blue panel academicians conduct a multicenter, multimillion dollar, multiyear research study; thousands of people (subjects and research assistants) are employed. The findings are reported and often such epic projects find no benefit from, for example, the use of vitamin/health supplements in humans [55–58].

The problem of the epic study is the methodology. Adherence to rigorous protocols is very difficult in these colossal projects. Thus, placebo and active treatment data merge into a nonstatistical gray zone.

Finally, if the OSH is correct (Figure 1) there are multiple opportunities to interrupt the chain of events, but shutting down the pathway limits the bodies ability to respond to oxidative insults such as infections or trauma.
As noted above, the location of injury is quite variable. Thus, the safest and possibly most effective approach would be complex synergistic modulations of the free radicals and chronic inflammatory response.

The pipeline of therapeutic agents should be reviewed per the order of the hypothesis of AD etiology [103].

**Therapies via the AH**

| Table 1 lists 16 drugs related to manipulation of Aβ [103]. Three approaches are under investigation. Anti-aggregation agents include metal chelation therapies (e.g., EDTA, desferrioxamine, and clinoquinol) that are available in alternative health clinics. There is no funding for studies to bring these treatments through the FDA process. Melatonin, an antioxidant, also has anti-Aβ properties. AZD103 (Scylo-inositol) is a stereoisomer of inositol. In December 2009 a study using 1000 and 2000 mg of AZD103 twice daily was withdrawn due to safety issues [105]. The current study uses AZD103 orally 250 mg twice a day.

There are eight anti-Aβ immune modulators under investigation by large pharmaceutical concerns. The drug companies and FDA label these anti-Aβ antibodies. These parenteral treatments are inspired by AN-1792 (Elan Pharmaceuticals), which was found unacceptable due to a high rate of meningoencephalitis. ACC-001 is actually a derivative of AN-1792. Bapineuzumab (AA001) from Pfizer/Janssen is identical to the natural antibody triggered by AN-1792. The other anti-Aβ antibodies are said to be ‘passive’ or more selective.

Tramiprosate (3APS), another anti-Aβ aggregation therapy, was in Phase III studies, but failed to show significant findings and is no longer under study. Results are this group have been disappointing to date with no improvement in cognitive performance tests, except in the *post-hoc* analyses [59,60].

Production of Aβ is dependent on two enzymes—γ- and β-secretase. The pharmaceutical companies have five candidates inhibiting these secretases (Table 1). Of the five, semagacestat from Eli Lilly has had the most publicity and expectation. Like other attempts to interfere with Aβ physiology, this drug failed its end points. It actually appears to have worsened the condition of the subjects taking the drug [106]. The long-term toxicity of these agents is a serious concern. γ-secretases have been implicated in tumorigenesis via proteolytic release of Notch intracellular domain [64].

Posiphen® inhibits amyloid precursor protein synthesis by inhibition of β-secretase, and reduces Aβ [103,107]. It is a small molecule, the positive isomer of phenserine, is orally available and has a high brain:plasma ratio (7:1). It also has a slow-onset acetylcholinesterase inhibitory action. Posiphen is distinct from the AD drugs currently available or in development, because it has a dual mechanism of action: it is disease modifying by reducing plaques through inhibition of amyloid precursor protein synthesis and it provides some symptomatic relief through acetylcholinesterase inhibition [108].

There is a new mixed secretase inhibitor under study by the University of Massachusetts (MA, USA) that is a complex nutraceutical (MemoryXL). It contains folic acid (400 µg), vitamin B12 (6 µg), vitamin E (as α-tocopherol 30 IU), S-adenosylmethionine (400 mg), α-acetyl cysteine (600 mg) and acetyl-L-carnitine (500 mg). Results of any testing are not available.

To summarize, the clinical trials of Aβ modulators have been disappointing. Furthermore, these trials fail to prove the AH.

**Therapies via tH**

| Table 2 lists the active trials of therapies addressing the tH [103]. Lithium is one therapy that is thought to produce its therapeutic effects via the tH. However, it has been shown to have poor commercial viability. Davunetide (AL-108; Allon Therapeutics) is an eight amino acid peptide that was granted orphan status by the FDA. The current active study by Allon is based on prior positive results in early AD. Tideglusib (NP-12 or NP031112) blocks glycogen synthase kinase-3. Glycogen synthase kinase-3 is one of the main factors that causes the tau protein to become ‘sticky’, forming the neurofibrillary tangles. Tideglusib also has an orphan medicinal status.

To summarize, the clinical trials of drugs that target the τH are uncertain.

**Therapies via the IH**

| There are five candidates that could be classified as therapies based on the IH (Table 3). CERE-110 uses a virus (an adenovirus) to transfer a gene that makes NGF, a protein that may make nerve cells in the brain healthier and protect them from dying. CERE-110 has been studied in laboratory animals and is in the early stages of being tested in humans [62].

Bryostatin 1 is part of a group of 20 macrolide lactones first isolated in the 1960s by George Pettit from extracts of a species of bryozoan, Bugula neritina. The structure of bryostatin 1
was determined in 1982. Bryostatins are potent modulators of protein kinase C. Bryostatin 1, which is also under investigation for cancer therapy, has been shown to improve memory in marine slug (Hermissenda crassicornis) and rats. The current small study is primarily for human safety [63–65].

Etanercept (Enbrel®), is a Pfizer/Amgen product principally marketed for psoriasis and rheumatoid arthritis. Etanercept is a fusion protein produced through expression of recombinant DNA. Etanercept acts by interfering with TNF, an inflammatory cytokine that is secreted by activated astrocytes. A study being conducted by the University of Southampton (UK) is principally looking at safety of etanercept in mild-to-moderate AD.

Lornoxicam (Xefo®) is a NSAID of the oxicam class. Lornoxicam inhibits both isoforms, cyclooxygenase-1 and -2, equally. The object of lornoxicam is to downmodulate CNS prostaglandins. Prostaglandins are paracrine secretions (local hormones) that are released from astrocytes and cause changes in neighboring neurons and glia that carry specific membrane prostaglandin receptors. Prostaglandins essentially function as proinflammatory cytokines [16]. NSAIDs have been used in prior studies with mixed results [34–37].

Thalidomide is the drug that allowed the FDA to press legislation that stated that drugs needed to be "safe and effective" rather than just safe [66]. Currently, thalidomide is an immunomodulatory agent used primarily, combined with dexamethasone, to treat multiple myeloma. Thalidomide may reduce the levels of TNF-α, which is a proinflammatory cytokine produced by astrocytes [16]. The downmodulation of TNF-α in the CNS may slow progression of AD, but the metrics stated by Bannor Health may not be able to measure this.

Therapies via OSH

Table 4 lists potential antioxidant therapies for AD. Currently eight studies are underway investigating these therapies. Most therapies are being developed by universities, which makes commercialization difficult. The targets of the current OSH candidates are quite diffuse, ranging from hormonal (exdendin-4) to a single lipid antioxidant (secoisolariciresinol). The current investigational OSH agents have simple compounds with single foci of intervention (Figure 4) and use insensitive testing instruments. Thus, the current OSH agents are unlikely to be used to treat AD.

Dimebon® (latrepirdine), which was in Phase III trials, was dropped from development in March 2010. This Russian over-the-counter small molecule (3,6-dimethyl-9-[2-methyl-pyridyl-5]-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride) has a broad and pleiotropic spectrum of pharmacological properties. It is an antihistamine that has been available in Russia for 23 years. Latrepirdine blocks the mitochondrial permeability transition pore (MPTP) that stabilizes the mitochondria. It is also an L-type calcium channel antagonist. As such, latrepirdine inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis. The drug is also thought to have activity as a CI and

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Subclass</th>
<th>Sponsor</th>
<th>Trial phase</th>
<th>Subjects (n)</th>
<th>Comment</th>
<th>Date of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exdendin-4</td>
<td>Neuroprotection, hormonal</td>
<td>NIH clinical center</td>
<td>II</td>
<td>230</td>
<td>Neuroprotective via glucagon-like peptide-1</td>
<td>November 2010</td>
</tr>
<tr>
<td>Tamibarotene (OAM80)</td>
<td>Single antioxidant</td>
<td>Osaka City University</td>
<td>II</td>
<td>50</td>
<td>Synthetic retinoid</td>
<td>April 2010</td>
</tr>
<tr>
<td>Sunphenon EGCG</td>
<td>Neuroprotection, herbal</td>
<td>Charite University, Berlin, Germany</td>
<td>II and III</td>
<td>50</td>
<td>Modified single herbal (green tea) which affects intracellular signaling</td>
<td>August 2009</td>
</tr>
<tr>
<td>Acitretin (Soriatane)</td>
<td>Single antioxidant</td>
<td>Johannes Gutenberg University Mainz</td>
<td>II</td>
<td>76</td>
<td>Second generation retinoid</td>
<td>March 2010</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Single antioxidant</td>
<td>UCLA</td>
<td>III</td>
<td>132</td>
<td>Three other studies by other institutions, often with a second antioxidant</td>
<td>July 2011</td>
</tr>
<tr>
<td>DCB-AD1 (Fo Ti)</td>
<td>Single antioxidant</td>
<td>National Taiwan University</td>
<td>II</td>
<td>80</td>
<td>Derivative of Fo-ti</td>
<td>September 2005</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Single antioxidant</td>
<td>Neurim Pharmaceuticals Ltd</td>
<td>II</td>
<td>50</td>
<td>Only study for memory</td>
<td>October 2007</td>
</tr>
</tbody>
</table>
NMDAR. *In vitro*, latrepirdine protected primary neuron cultures against Aβ toxicity, and it was suggested that it worked at multiple levels.

The first clinical trial of latrepirdine (by Medivation, conducted in Russia) on 183 subjects demonstrated efficacy in five independent measures of cognitive improvement [67]. The statistical significance between latrepirdine and placebo was astonishing, with p < 0.0001 in many cases. Another study of latrepirdine in 600 subjects failed to demonstrate any statistical response using the ADAS-cog and CIBIC-plus scales [108].

One recent human study involving OSH therapies should be highlighted [48]. A potent 34-component antioxidant blend (Memory reVITALIZER®) or placebo was given using a double-blind protocol to 113 normal subjects age 50–75 years. Memory reVITALIZER has multiple representatives of each of the five basic antioxidant classes. The memory metrics were sensitive to change. The 16 week duration of the study would allow change in CNS by oxidative repair. The design of the study was simple (three subject visits of 30 min) and only at one center with minimal personnel involvement. The results showed significant improvement in working memory (20 word recall task) and declarative memory (50 part paired association task) [68–70].

Perhaps if some of these principles were incorporated into OSH therapy research, the results of human studies would become more positive.

**Therapies via the VH**

There are five clinical trials that address the VH of AD listed on the Clinical Trials website [103]. The principal proponent of the VH seems to advocate more aggressive screening for presence of cardiovascular disease [71]. Four candidates are currently marketed medications that are being studied by universities (Table 5). One candidate (AC-1204) is novel, and approaches the problem of hypofunction with a lipid metabolic enhancer.

**Therapies via the hibernation hypothesis**

The Clinical Trials website lists 19 studies currently recruiting for therapies based on the hibernation hypothesis [103]. These therapies include ‘light therapy’, deep brain stimulation, magnetic stimulation, melatonin, cognitive training, aerobic exercises and other brain stimulation approaches. Earlier studies of structured exercise and peripheral nerve stimulation with transcutaneous electrical nerve stimulations improved memory of early AD cases [72]. Light therapy and exercise have been found to be effective in early AD [73,74].

**Future perspective**

Despite the fact that there are 914 clinical trials related to AD are listed, and 157 of these are in-phase III trials, there appears to little likelihood of an effective new treatment in the near future [103]. Therapies based on the popular Aβ-AH or the hH are failing the safety and efficacy end points. Such failures reinforce the position that Aβ and NFTs are the host’s attempt to establish homeostasis [20]. The OSH and VH candidates do not receive such large pharmaceutical industry support.

The OSH is inclusive of the other hypothetical causes of AD. The OSH does offer hope as there have been positive animal models and one study in elderly subjects without AD [15,48]. However, researchers in the field are handicapped by the view that a massive single agent intervention is appropriate. Synergistic polypharmacy of complex formulations studied over a long period is alien to this construct.

The field of Alzheimer’s research has further been handicapped by the crudeness of the tools used. Studies in the field use antiquated psychometrics not developed for rapid administration and to measure improvement of dementia subjects. More sensitive instruments might demonstrate the benefit of treatments based on the hibernation hypothesis.

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Subclass</th>
<th>Sponsor</th>
<th>Trial phase</th>
<th>Subjects (n)</th>
<th>Comment</th>
<th>Date of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (Coreg)</td>
<td>Antihypertensive</td>
<td>Johns Hopkins University</td>
<td>IV</td>
<td>50</td>
<td>Nonselective β/α-1 adrenergic blocker</td>
<td>May 2011</td>
</tr>
<tr>
<td>Prazosin (Minipress®)</td>
<td>Antihypertensive</td>
<td>The Seattle Institute for Biomedical and Clinical Research</td>
<td>III</td>
<td>120</td>
<td>α-adrenergic blockers</td>
<td>May 2011</td>
</tr>
<tr>
<td>AC-1204 (Ketasyn®)</td>
<td>Metabolic enhancer</td>
<td>Accera, Inc.</td>
<td>II and III</td>
<td>400</td>
<td>Oral lipid that metabolizes in the CNS to energy enhancing ketone bodies</td>
<td>October 2011</td>
</tr>
<tr>
<td>Ramipril (Altace®)</td>
<td>Antihypertensive</td>
<td>University of Wisconsin</td>
<td>IV</td>
<td>20</td>
<td>ACE inhibitor</td>
<td>April 2009</td>
</tr>
</tbody>
</table>
Executive summary

The current state of therapy for Alzheimer’s disease

- Symptomatic relief can be achieved via cholinesterase inhibitors.
- Symptomatic relief and possible disease modification can be achieved via memantine.
- No new therapies for Alzheimer’s disease (AD) have been approved since 2003.

Current research therapies for AD should modify the course of the illness

- There are six theories on the cause of AD.
- There are 914 clinical trials on the treatment of AD listed and 157 are in Phase III.
- Analysis of these on the basis of the six theories of AD do not demonstrate viable therapeutic candidates likely to be marketed within the near future.

Future therapies for AD

- The amyloid, tau, vascular and inflammation theories appear to be downstream from the etiology of AD.
- More sensitive means measuring change in early-to-moderate AD needs to be addressed.
- Synergistic combinations of antioxidants or anti-inflammatory agents appear to have promise.
- Clinical trial designs should be simplified and more efficient.
- The possibility of awakening hibernating neurons is intriguing.

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