NEW TREATMENT MODALITIES IN ALZHEIMER’S DEMENTIA

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The World Alzheimer’s Report 2011, reveals that as many as three-quarters of the estimated 36 million people worldwide living with dementia have not been diagnosed and hence cannot benefit from treatment, information and care. In high-income countries, only 20-50% of dementia cases are recognized and documented in primary care. In low- and middle-income countries, this proportion could be as low as 10%.

Failure to diagnose often results from the false belief that dementia is a normal part of aging, and that nothing can be done to help. On the contrary, the new report finds that interventions can make a difference, even in the early stages of the illness. Drugs and psychological interventions for people with early-stage dementia can improve cognition, independence, and quality of life. Support and counseling for caregivers can improve mood, reduce strain and delay institutionalization of people with dementia.

Alzheimer’s disease, the most common cause of dementia is reaching epidemic proportions, with a large human, social, and economic burden. Effective treatments are greatly needed. Current drugs for Alzheimer’s disease target cholinergic and glutamatergic neurotransmission, thus improving symptoms, although their neuroprotective activity is still debated. Much effort is directed towards identifying disease-modifying therapies, with several compounds in different phases of development.

In an effort to understand the development of the newer drugs it is important to understand the pathophysiology of the disease first.

PATHOPHYSIOLOGY OF ALZHEIMER’S DISEASE
New Treatment Modalities in Alzheimer’s Dementia

The pathophysiology of the Alzheimer’s disease is explained by mainly two hypothesis:

1. Amyloid hypothesis
2. Tau protein hypothesis

**AMYLOID HYPOTHESIS**

The most important pathological findings are neuritic “senile” plaques and NFTs. The neuritic plaques contain a central core that includes Ab amyloid, proteoglycans, Apo e4, α1 antichymotrypsin, and other proteins.

Aβ amyloid aggregates are derived from APP by proteolytic cleavage (by β-secretases and γ-secretases) via the amyloidogenic pathway. Aβ1–40 is the most frequent form of Aβ, but the Aβ1–42 form has a higher propensity to aggregate and is greatly enriched in amyloid deposits. The amyloid hypothesis has undergone several modifications, mainly concerning the type of Aβ thought to cause Alzheimer’s disease: initially this was the amyloid plaque, followed by increased concentrations of Aβ1–42, then increased Aβ1–42:Aβ1–40 ratio, and finally oligomeric Aβ.

**TAU PROTEIN HYPOTHESIS**

Tau is a cytoplasmatic protein that binds to tubulin during its polymerisation, stabilising microtubules. In Alzheimer’s disease, tau is abnormally phosphorylated, resulting in the generation of aggregates (neurofibrillary tangles) toxic to neurons.

The neuropathology of Alzheimer’s disease is also characterized by early loss of basal forebrain cholinergic neurons, leading to decreased cholinergic transmission. There is also reduction in norepinephrine levels in brainstem nuclei such as the locus coeruleus.

The newer treatment modalities in Alzheimer’s disease can be broadly divided according to their main mechanism of action

A. Affecting neurotransmission (Cholinergic drugs/NMDA antagonist)

A1. ACh Esterase inhibitors
A2. Muscarinic receptor agonists
A3. Nicotinic receptor agonists

B. Preventing the accumulation of misfolded protein (amyloid b and tau)

B1. Antiamyloid therapy
   B1a. Drugs to reduce Aβ production
   B1a (I) β-secretase inhibitors
   B1a (II) γ-secretase inhibitors and modulators
   B1a (III)a-secretase activators
   B1b. Drugs to prevent Aβ aggregation
   B1c. Drugs to promote Aβ clearance
   B1c (I) Active immunization
   B1c (II) Passive immunization

B2. Drugs to target tau protein

C. Rescuing the mitochondrial function

D. Restoring the growth factors

E. Other approaches

A. **AFFECTING NEUROTRANSMISSION (CHOLINERGIC DRUGS/NMDA ANTAGONIST)**

The decreased cholinergic transmission can be improved with acetylcholinesterase inhibitors or by modulation of muscarinic and nicotinic acetylcholine receptors. In 1993 tacrine became the first agent approved specifically for the treatment of cognitive symptoms in Alzheimer’s disease. The FDA approved other cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—in 1997, 2000, and 2001, respectively, for treatment of cognitive decline in mild to moderate Alzheimer’s disease. These agents are now preferred over tacrine because of tacrine’s reversible hepatic toxicity and the requirement that it be given 4 times per day. Results of a smaller number of clinical trials suggested that cholinesterase inhibitors might have some limited benefits in severe Alzheimer’s disease. In 2006, donepezil was approved by the FDA for this indication.

Apart from their symptomatic activity through AchE inhibition and BChE inhibition (rivastigmine), these drugs have some potential neuroprotective activity through decreasing Aβ production and Aβ-induced toxicity; modulating expression of AChE isofoms; increasing expression of nicotinic receptors.

**Huperzine-A**, that is approved in China for mild-to-moderate stages and as dietary supplement in some
countries also acts through AChE. It’s potential neuroprotective activity is mediated via modulating APP, it’s antioxidant, anti-apoptotic effects and through mitochondrial protection.

Apart from the AChE, Memantine an uncompetitive, voltage-dependent NMDA receptor antagonist, has been approved for moderate to severe (monotherapy and in combination with AChE). It has possible neuroprotective effect via decreasing Aβ toxicity; preventing hyperphosphorylation of tau; decreasing microglia-associated inflammation; and increasing the release of neurotrophic factors from astroglia.

A1. ACh Esterase inhibitors

Apart from the acetylcholinesterase inhibitors already approved, there has been little development of cholinergic drugs.

(−)-phenserine enantiomer
- derivative of physostigmine,
- acetylcholinesterase inhibitor
- also reduce Aβ precursor protein (APP) and Aβ concentrations by decreasing the translation of APP mRNA

(+)-phenserine enantiomer, posiphen,
- poor acetylcholinesterase inhibitor activity
- substantially decrease APP production by reducing APP mRNA translation

Randomised controlled trials (RCTs), of these drugs shows good tolerability and some beneficial effects on cognitive functions in patients with mild-to-moderate Alzheimer’s disease. However, results were not clinically significant and further RCTs for this drug have not been initiated.

A2. Muscarinic receptor agonists:

Talsaclidine, AF-102B, and AF-267B (NGX-267)
- M1 muscarinic receptor agonists
- affect Aβ production

Muscarinic receptor agonists had limited success owing to difficulties in obtaining drugs with few adverse effects. They increase the salivary flow, and for this reason AF-102B and AF-267B have been tested in patients with xerostomia.

A3. Nicotinic receptor agonists

Ispronicline (AZD-3480)
- selective agonist of the nicotinic receptor α4β2
- positive effects on cognition in healthy individuals and in people with age associated memory impairment.
- has been studied in patients with mild-to-moderate Alzheimer’s disease (versus placebo and donepezil), with equivocal findings.

Other drugs with cholinergic activity like ABT-089, EVP-6124, including multifunctional compounds, are still in preclinical stages.

B. PREVENTING THE ACCUMULATION OF MISFOLDED PROTEIN (AMYLOID B AND TAU)

B1. Anti-amyloid therapies

Alzheimer’s disease drug development is driven mainly by the amyloid hypothesis. Results from RCTs have shown that removing amyloid plaques will not reverse the damage or stop the Alzheimer’s dementia. In addition to which Aβ species is toxic, whether Aβ is toxic at all and its role in the pathogenesis of Alzheimer’s disease are unclear. A major concern is the paucity of knowledge on the functions of APP and Aβ. Although the amyloid hypothesis has undoubtedly led to the focusing and structuring of the research field for Alzheimer’s disease, results from RCTs of anti-amyloid drugs have not yet been translated into clinical practice.

B1a. Drugs to reduce Aβ production

B1a(I) β-secretase inhibitors

Development of β-secretase inhibitors is challenging, because
- has many substrates (including neuregulin-1, which is involved in myelination)
- a wide substrate binding domain,
- drugs to modulate this CNS enzyme must cross the blood–brain barrier.

Thiazolidinediones (rosiglitazone-pioglitazone)
- Activation of nuclear peroxisome proliferator-activated receptor γ (PPARγ) which suppress expression of β-secretase and APP, and promotes APP degradation by increasing its ubiquitination.
- Both rosiglitazone and pioglitazone increase peripheral insulin sensitivity and reduce concentrations of insulin, which competes with Aβ for degradation by the insulin degrading enzyme

The phase 3 RCT of rosiglitazone found no efficacy on cognition or global function. The development program for this drug in Alzheimer’s disease has been discontinued, possibly because of negative preliminary results.
No phase 3 RCTs in new β-secretase inhibitors are ongoing, but several new β-secretase inhibitors are under investigation.

B1a (II) γ-secretase inhibitors and modulators

γ-secretase, the enzyme responsible for the final step in Aβ generation, is one of the main complexes involved in intramembranous cleavage of several proteins, including APP, Notch receptor, and various neuronal substrates.

Collateral effects of γ-secretase inhibitors include haematological and gastrointestinal toxicity, skin reactions, and changes to hair colour, mainly caused by inhibition of the Notch signalling pathway, which is involved in cell differentiation.

The γ-secretase inhibitors in clinical testing: semagacestat (LY-450139), MK-0752, E-2012, BMS-708163, PF-3084014, begacestat (GSI-953), and NIC5-15.

The γ-secretase modulators can selectively block APP proteolysis without any Notch-based adverse effects.

NSAIDs, including ibuprofen, indomethacin, and sulindac sulfide, bind to APP and act as γ-secretase modulators, decreasing Aβ1–40 and Aβ1–42 production, with increased generation of Aβ1–38 fragments.

Selective β-amyloid-lowering agents (SALAs), tarenflurbil was tested in phase 3 RCTs in patients with mild Alzheimer’s disease, but did not show clinical effects.

For another γ-secretase modulator, CHF-5074, a phase 1 study to evaluate drug safety and tolerability in healthy volunteers is ongoing.

B1a (III) a-secretase activators

Upregulation of α-secretase activity, can decrease Aβ formation and increase production of a soluble domain (sAPPα), which is potentially neuroprotective. Several drugs can stimulate α-secretase activity (agonists of muscarinic, glutamate, and serotonin receptors; statins; oestrogens; testosterone; and protein kinase C activators) and have been tested in clinical trials, but no evidence supports their use in Alzheimer’s disease yet.

Other a-secretase activators such as Etazolate, Bryostatin-1 and Exebryl-1 are under investigation.

B1b. Drugs to prevent Aβ aggregation

Evidence for the neurotoxic and synaptotoxic activity of Aβ oligomers constitutes the scientific basis for the development of compounds that inhibit Aβ aggregation or destabilise Aβ oligomeric species.

Antiaggregants can act by binding to Aβ monomers, thus preventing oligomerisation and allowing elimination; alternatively, antiaggregants can react with Aβ oligomers, neutralizing their toxicity and promoting clearance.


Other drugs tested or are being tested includes Clioquinol (PBT1), PBT2, Scyllo-inositol and Epigallocatechin-3-gallate (EGCg).

B1c. Drugs to promote Aβ clearance

Active and passive immunizations were developed to inhibit generation of toxic Aβ aggregates, and to remove soluble and aggregated Aβ.

At least three different immune-mediated mechanisms can promote Aβ removal:

- solubilisation by antibody binding to Aβ;
- phagocytosis of opsonised Aβ by microglia; and
- Aβ extraction from the brain by plasma antibodies (the “sink” hypothesis).

B1c (I) Active immunotherapy

In a phase 2 RCT of AN-1972 (QS-21), an anti-Aβ vaccine, in patients with mild-to-moderate Alzheimer’s disease, patients responded to immunisation with Aβ1–42, developing significant Aβ-antibody titres, although not all individuals produced high IgG concentrations. However, this study was stopped because of aseptic meningoencephalitis in some patients, which was attributed to cytotoxic T cells and/or autoimmune reactions to AN-1972. To avoid neuroinflammation and toxicity, new vaccines that selectively target B-cell epitopes without stimulating T cells have been developed.

Different adjuvants and mechanisms of vaccine delivery are used, such as adenoviruses, DNA vaccines, and single-chain antibody fragments.

Vaccines such as CAD-106A (β1–6 peptide coupled to the Qβ virus-like particle), ACC-001 (conjugated to the mutated diphtheria toxin protein), V-950 (aluminium-containing adjuvant with or without ISCOMATRIX) and ACI-24 (Aβ1–15 embedded within a liposomal surface) are under study.

Another active immunisation strategy is based on Affitopes, short peptides mimicking parts of native Aβ1–42 without its sequence identity. Affitopes AD-01 and AD-02 target the N-terminal Aβ fragment and both had disease modifying properties in animal models of Alzheimer’s disease.
Alzheimer’s disease.

B1c (II) Passive immunotherapy

Passive immunotherapy is based on monoclonal antibodies or polyclonal immunoglobulins targeting Aβ to promote its clearance. Results from animal studies have shown that anti-Aβ antibodies can prevent oligomer formation and reduce brain amyloid load with improvement in cognitive functions.

Several monoclonal antibodies, generally given intravenously, are being tested in patients with Alzheimer’s disease: bapineuzumab (AAB-001), solanezumab (LY-2062430), PF-04360365, GSK-933776, R-1450 (RO-4909832), and MABT-5102A.

Passive immunisation can also be achieved by intravenous infusion of immunoglobulins (IVIg), from healthy donors, which include naturally occurring polyclonal anti-Aβ antibodies. IVIg is already approved as therapy for immune deficiency, with good safety and tolerability evidence. In two small studies, short-term immunoglobulin administration in patients with Alzheimer’s disease was well tolerated, promoted a decrease of total Aβ CSF concentrations, and increased plasma total Aβ concentrations, with evidence of improvement or stabilisation of cognitive functions. Preliminary data from a phase 2 RCT confirmed the positive effects on cognition; a phase 3 study is ongoing.

Immunisation strategies have advantages and disadvantages.

Active immunotherapy guarantees constant high antibody concentrations, requiring few follow-up visits, with reduced costs. However, rapid reduction of antibody concentrations, to limit adverse effects, is difficult.

With passive immunotherapy, specific Aβ epitopes can be targeted more easily, and more rapid control of antibody titres is possible. Passive immunisation could be more effective in elderly people than active immunotherapy, because these individuals have reduced responsiveness to vaccines. Nevertheless, administration of antibodies is time consuming and costly, and, the risk of vasogenic oedema and cerebral amyloid angiopathy with microhaemorrhages might be higher for passive immunotherapy than for active immunotherapy.

B2. Drugs to target tau protein

The hypothesis that tau pathology causes Alzheimer’s disease has been the main competitor of the amyloid hypothesis.

There are two main therapeutic approaches to target the tau protein:

- modulation of tau phosphorylation with inhibitors of tau-phosphorylating kinases and
- compounds that inhibit tau aggregation and/or promote aggregate disassembly.

Tau hyperphosphorylation and neurofibrillary tangle formation can be promoted by imbalanced activity of protein kinases (glycogen-synthase-kinase-3 [GSK3] and p70-S6-kinase) and the phosphatase PP2A.

GSK3 deregulation might have a role in Alzheimer’s disease pathogenesis, because GSK3 is involved in tau and amyloid processing, cellular signalling, and gene transcription.

Both lithium and valproate, well known for the treatment of psychiatric disorders, inhibit GSK3, to reduce tau phosphorylation and prevent or reverse aspects of tauopathy in animal models. However, both of them had disappointing results because there were no effects on cognition and functional status.

Several GSK3 inhibitors, such as NP-031112 (a thiadiazolidinone-derived compound, a non-ATP competitive inhibitor of GSK3), Methylthioninium chloride (a tau anti-aggregant), Davunetide and Nicotinamide are under investigation.

C. DRUGS TO TARGET MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction occurs early in Alzheimer’s disease, can promote synaptic damage and apoptosis, and is thought to have a causal role in neurodegeneration.

APP and Aβ can be imported into mitochondria, where they can interact with mitochondrial components, impair ATP production, and increase oxidative damage.

Latrepirdine, a non-selective antihistamine, was suggested to inhibit the mitochondrial permeability transition pore (Aβ-induced activation of this pore can induce apoptosis) and protect neuronal mitochondria from Aβ-mediated toxicity and other insults. Latrepirdine can also increase mitochondrial membrane potential and ATP production.

However the results of phase 3 RCT (CONNECTION study) of the drug has been disappointing. Results from other ongoing RCTs (latrepirdine in combination with donepezil and memantine) are awaited.

D. NEUROTROPHINS

Neurogenesis can occur in the adult brain and in response to damage. Basal forebrain cholinergic neurons depend on NGF for survival and fibre outgrowth, and re-
cent findings have suggested a causal link between NGF imbalance, activation of the amyloidogenic pathway, and neurodegeneration in Alzheimer’s disease.

Targeted delivery of NGF to basal forebrain cholinergic neurons can be accomplished with
- intracerebroventricular administration of NGF,
- intracerebral injection of autologous fibroblasts genetically modified to produce human NGF,
- encapsulated-cell biodelivery, a strategy developed to provide local NGF release
- Intranasal delivery and topical application of an NGF solution on the ocular surface

E. OTHER POTENTIAL THERAPEUTIC STRATEGIES

Omega-3 polyunsaturated fatty acids (eg, docosahexaenoic acid) or antioxidants (eg, vitamin E) have been tested in RCTs without any significant benefit.

RCTs that have studied statins in patients with Alzheimer’s disease have not produced any evidence of beneficial effects so far.

Serotonergic drugs and drugs that target phosphodiesterase are also being studied.

Receptor for advanced glycation endproducts (RAGE) binds to Aβ, promoting its influx into the CNS across the blood–brain barrier. A phase 2 study on the RAGE inhibitor is also ongoing.

CONCLUSIONS

To summarize, many clinical and experimental studies for the treatment of Alzheimer’s disease targeting neurotransmitter release, misfolded proteins (amyloid and tau), mitochondrial function and growth factors are ongoing. Research on Alzheimer’s disease therapy has so far had some success in terms of symptomatic treatments, although it has also had several failures for disease-modifying drugs. How close we are to effective treatment of Alzheimer’s disease is difficult to estimate, but available results from RCTs are not in line with previous optimistic predictions of an imminent breakthrough.