Business Trends Editor: Steve Carney
s.carney@elsevier.com

business trends

Alzheimer's disease: a tangled issue

Andrew Benson, andrew.benson@informa.com

Alzheimer's disease (AD) is truly terrifying. The 'Big C' might strike fear into the hearts of people more readily, but with early detection and treatment slowly pushing survival rates upwards, it is diseases of the ageing population, such as AD, that could soon be viewed with greater dread.

Unmet need

AD is the major cause of dementia in older people, with ~10% of those over the age of 65 and 50% of those over 85 affected. Despite these statistics, it should not be seen as part of the normal ageing process – it is a progressive, incurable disease. It can be classified as either familial (multiple family members are affected) or sporadic (one or a few individuals in a family have the disease). As well as late-onset AD, early-onset AD, affecting people between the ages of 35 and 65, is also seen. Pathologically, the presence of two characteristic features defines the disease: (i) plaques of β-amyloid protein; and (ii) neurofibrillary tangles (NFTs) composed of paired helical filaments of abnormally phosphorylated tau proteins. As the disease progresses, neurones – particularly cholinergic – are lost and cognitive impairment develops.

The classical strategy for treating AD has been with acetylcholinesterase inhibitors, and of the seven drugs currently FDA-approved in the USA for the treatment of AD, all but one have this pharmacological activity. Acetylcholinesterase is the enzyme that catalyses the breakdown of acetylcholine, a neurotransmitter important in cognitive function that is depleted in AD patients. The current world status of drugs in development for AD that have the primary pharmacological action of acetylcholinesterase inhibition is presented in Figure 1. Although the efficacy of the five launched drugs (Figure 1) in improving cognitive and global function has been demonstrated, unfortunately they appear to be effective in only approximately a third of patients, and do not actually stop the underlying progression of the disease. Furthermore, the most advanced of the clinical candidates, currently awaiting registration in the USA, is a controlled-release formulation of a launched drug. These observations suggest that there are limitations associated with this approach, and the relatively high number of drugs that fail in this category (discontinued or with no development reported) appears to confirm this proposal.

Amyloid cascade hypothesis

For over a decade, the predominant viewpoint among researchers has been that it is the deposition of β-amyloid protein that is the primary aetiological event in AD, an idea known as the 'amyloid cascade hypothesis'. β-Amyloid is a protein that is formed from the proteolytic cleavage of a larger precursor protein, amyloid precursor protein (APP). It is believed that it is the deposition and subsequent aggregation of insoluble β-amyloid into plaques, which is typically observed in the brains of AD patients, that

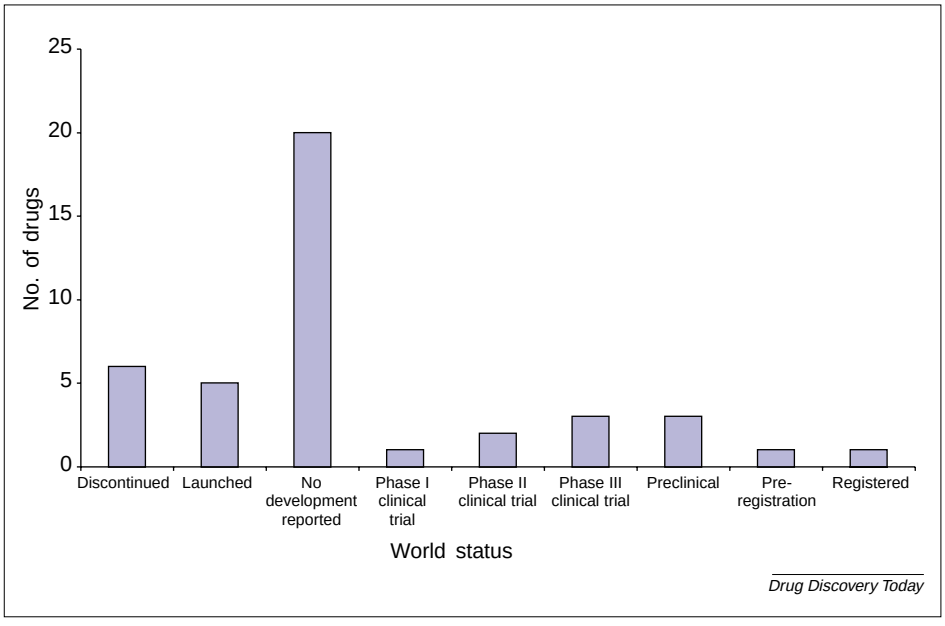

FIGURE 1

Acetylcholinesterase inhibitors for the treatment of Alzheimer's disease.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03482-3

business trends

TABLE 1

Examples of pharmacological strategies under investigation for the treatment of Alzheimer's disease

Strategy	Example	Clinical trial Phase
AMPA receptor agonist	S18986	Phase I
G-protein stimulant	R1485	Phase I
5 Hydroxytryptamine 4 receptor agonist	PRX03140	Phase I
5 Hydroxytryptamine 6 receptor antagonist	GSK742457	Phase I
Glycosaminoglycans agonist	HF0420	Phase I
Guanylate cyclase stimulant	GT1061	Phase I
Nerve growth factor agonist	CERE110	Phase I
Phosphodiesterase IV inhibitor	MEM1414	Phase I
Calcium channel agonist	MEM10003	Phase II
Cannabinoid 1 receptor antagonist	AVE1625	Phase II
Choline uptake stimulant	Coluracetam	Phase II
Dopamine receptor agonist	SRN001	Phase II
5 Hydroxytryptamine 1A receptor antagonist	SRA333	Phase II
Immunostimulant	Colostrinin	Phase II
LHRH agonist	Leuprolide acetate Voyager	Phase II
Protein synthesis stimulant	PYM50028	Phase II
Dopamine uptake inhibitor	NS2330	Phase III
5 Hydroxytryptamine 1A receptor agonist	Xaliproden hydrochloride	Phase III
HMGCoA reductase inhibitor	Statins Nymox	Phase III
NMDA antagonist	Neramexane	Phase III

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; HMGCoA, hydroxymethylglutaryl coenzyme A; LHRH, luteinizing hormone-releasing hormone; NMDA, *N*-methyl-D-aspartate.

causes the neurotoxic damage and consequent neurodegeneration. Unsurprisingly, pharmaceutical companies have been trying to develop drugs that inhibit the formation or promote the disaggregation of β-amyloid plaques. *Pharmaprojects* data shows several of these drugs in early development, but before large-scale clinical trial data are available, their efficacy remains to be proven. A newer strategy involves trying to prevent the initial formation of β-amyloid itself through inhibition of the secretase enzymes responsible for the incorrect cleavage of APP. β-Secretase has been identified as the aspartyl protease memapsin-2 (BACE1 or Asp2), whereas γ-secretase consists of a complex of membrane proteins, including presenilin-1 and presenilin-2. A multitude of drugs that target these enzymes are in preclinical development, although the only direct inhibitor to enter the clinic to date is LY450139 (Eli-Lilly). The nonsteroidal anti-inflammatory drug *R*-flurbiprofen is also in late-stage trials for AD, based on its ability to inhibit γ-secretase independently of its inhibition of cyclooxygenase enzymes.

Alternative approaches

Despite the interest in the role of β-amyloid in the pathology of AD, there are those who doubt the validity of the amyloid cascade hypothesis. One of the major problems rests with experiments performed in transgenic mice, where amyloid generation failed to induce the predicted cascade. Furthermore, whereas the NFTs observed in AD are also present in other dementias, which suggests that tau pathology is a downstream (but essential) part of the dementing process, in humans, the tangles are separated temporally and spatially from amyloid plaques. Observations such as these have led some researchers to argue that the loss of some common factor (perhaps Wnt signalling) might induce both plaque and tangle formation.

It has been argued that β-amyloid itself might not be the neurotoxic agent at work in AD, but rather a physiological response to injury. One theory is that β-amyloid is produced to bind neurotoxic solutes, such as metal ions, and its precipitation into plaques is an efficient means of presenting these toxins to phagocytes. As the brain ages, there is a natural rise in copper and zinc ions, and the greater incidence of AD in females could be partly explained by the greater constitutive activity of the synaptic zinc transporter, ZnT3. One drug under development that addresses this 'bioflocculant hypothesis' is iodochlorhydroxyquin (Clioquinol). This old antibiotic, which was developed decades ago and was previously used to treat traveller's diarrhoea, chelates high levels of copper and zinc ions, and thus can trap and remove these ions from the brain. Prana Biotechnology is preparing Phase II–III trials of the drug, and also recently initiated Phase I trials with a follow-on compound.

There is also reasonable evidence to suggest that non-genetic AD is not, at least initially, a neurodegenerative disorder, but rather a vascular disorder with neurodegenerative consequences. Many of the risk factors associated with AD are also linked to vascular dementia (VaD), for example, stroke, coronary artery disease, apolipoprotein E4 genotype and diabetes mellitus. These factors can be present decades before any neurodegenerative symptoms develop, and have a common association with vascular nitric oxide. Dysregulation of the nitric oxide system could lead to AD through chronic brain hypoperfusion resulting from vascular-related risk factors coincident with advancing age. It is interesting to note that ~30% of AD brains show cerebrovascular lesions, and 40% of VaD-diagnosed brains have amyloid plaques and NFTs.

The similarities between AD and VaD suggest that they are the same overlapping disorder that initially affects the vascular architecture. If this is the case, then many of the current treatments for AD are not aimed at the pathological events that lead to AD but rather at events that appear during cognitive decline (e.g. plaques) – at a time when it might be too late for drug therapy to be effective. Recent studies have shown a link between AD and cholesterol metabolism in a transgenic mouse model of AD, as well as between AD and dietary

business trends

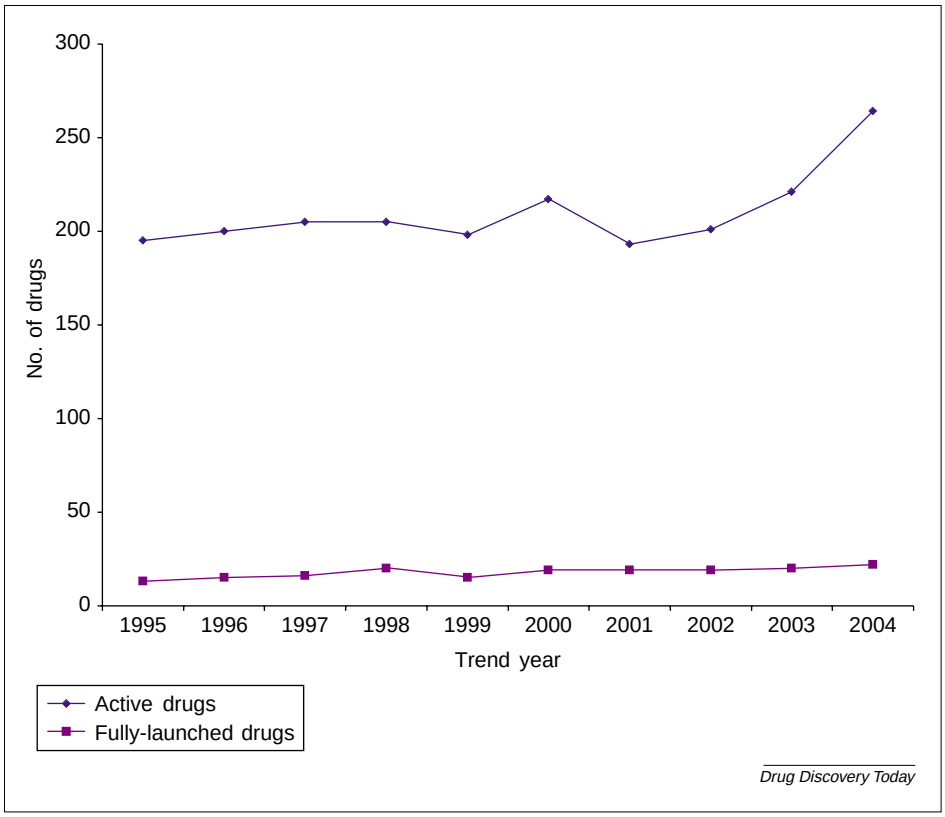

FIGURE 2

Drugs for the treatment of Alzheimer's disease in active development and fully launched, 1995–2004.

fat. Presuming this theory is correct, antioxidant therapy and cholesterol-lowering drugs, such as statins, could prove effective therapies for AD.

There are many other strategies being tested in the clinic for the treatment of AD (Table 1), including nerve growth factor (NGF) agonists and glycosaminoglycans (GAGs). NGF promotes the growth and maintains the health of neurones producing acetylcholine, and it has been proposed that NGF levels are reduced in AD, rendering neurones vulnerable to degeneration. Low-molecular weight GAGs have also been shown to have neuroprotective and neurotrophic activities. In addition, compounds affecting the serotonin and dopamine neurotransmitter systems are being evaluated.

Development bottleneck

The number of drugs in development for AD remained fairly constant (at around 200) until 2002, after which a steady increase in drug candidates has been recorded (Figure 2). This trend confirms that there has never been a lack of interest or incentive for pharmaceutical companies to develop AD drugs. Unfortunately, further analysis of these drugs shows a wealth of compounds in preclinical development over the past ten years, but with few making it into the clinic, let alone late-stage trials. Indeed, it would seem that AD drug development has a generally high failure rate. With the basis of the disease still in dispute and the real possibility that many of the current pharmacological strategies are flawed or addressing only part of the puzzle, scientists, sufferers and their families must be hoping that a breakthrough is just over the horizon.

Andrew Benson
Pharmaprojects,
PJB Publications,
69–77 Paul Street,
London,
UK, EC2A 4LQ
e-mail: andrew.benson@informa.com
www.pharmaprojects.com