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Current Strategies for Improvements in the Treatment of Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a progressive, age-related dementia characterised by deteriorating short term memory, learning and cognitive functions; anxiety; depression, withdrawal; de-motivation and irritability or aggression (Salloway & Correia, 2009). Over 5 million Americans, including up to half of over 85-year-olds, have AD; costing an estimated $172 billion for treatment and healthcare (Salloway & Correia, 2009; Grammas, 2011). A doubling of dementia cases is expected over the next 30 years (Chertkow,

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2008). AD accounts for 47 % of all dementia cases (Figure 1) but another 25 % are mixed, involving AD and another type, such as vascular dementia (Chertkow, 2008).

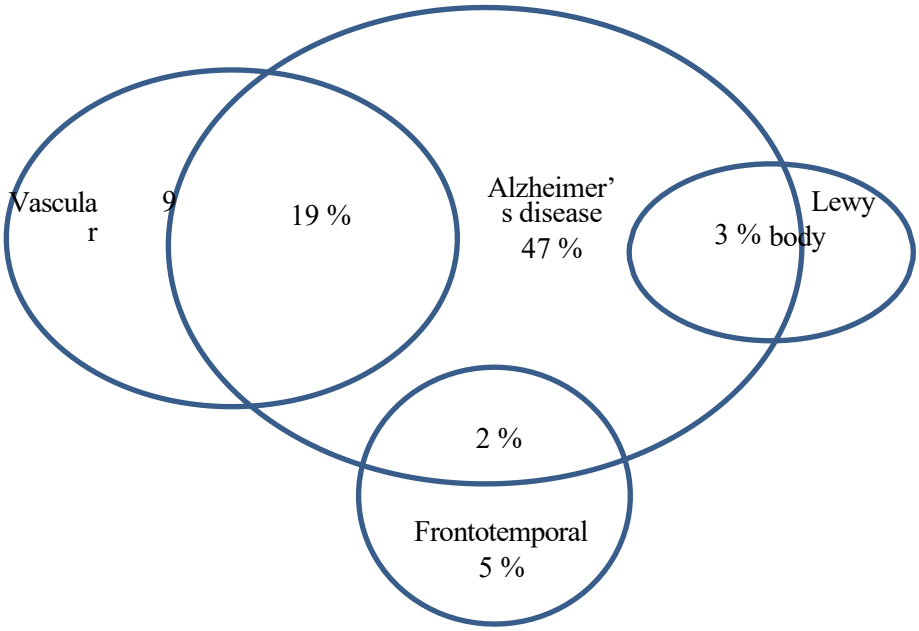

Figure 2: Types of dementia commonly seen in Canadian memory clinics. Note: Other mixed types of dementia make up 10% of the total number of cases (Chertkow, 2008 p317).

Risk factors include age, being female, diet, obesity, diabetes, hypertension, high cholesterol, having relatives with dementia and having the ApoE cholesterol transporter allele ε4 (Solloway & Correia, 2009). AD pathophysiology involves the deposition of β-amyloid as plaques and hyper- phosphorylated tau protein as neurofibrillary tangles (NFTs), increased insulin resistance and inflammation in areas, such as the hippocampal formation and cerebellar cortex (Akter *et al.*, 2010; Bosco *et al.*, 2011; Talbot *et al.*, 2012). There is a loss of cholinergic neurons, reduced acetylcholine levels and a toxic level of glutamate in the brain (Salloway & Correia, 2009). The episodic memory (recalling events, times and places) is affected early (Yamasaki *et al.*, 2012) and functional MRI scans demonstrate changes in networks used to encode and recall memories.

There is no known cure for AD but some treatments can produce minor improvements in cognitive function and delay disease progression. The most common AD drugs are three cholinesterase inhibitors (ChIs) and an N-methyl-D-aspartate receptor (NMDAR) antagonist: donepezil, galantamine, rivastigmine and memantine respectively. ChIs inhibit acetylcholine breakdown, compensating for the loss of cholinergic neurons while memantine antagonises NMDARs, preventing toxic over- stimulation (Hogan et al., 2008; Salloway & Correia, 2009). ChIs are recommended for "mild to moderate" and memantine (often with ChIs) for "moderate to severe" AD (Salloway & Correia, 2009 p53). These drugs have side-effects ranging from anorexia, nausea and vomiting to urinary incontinence and diarrhoea (Hogan et al., 2008). Donepezil also causes sleep disturbances and nightmares (Hogan et al., 2008). Cholinesterase inhibitors and memantine produce moderate improvements or delay disease progression in some patients but cannot correct the underlying causes of degeneration. However, a number of new drugs are being developed to treat not only the symptoms but also the lesions which lead to Alzheimer's disease.

New Treatments for Alzheimer's Disease

There have been several promising developments in the treatment of AD. Targets range from the β-amyloid and phosphorylated tau aggregates which form in the brain to inflammation, oxidative stress and non-cholinergic neurons. Figure 2 shows some of the existing and emerging drug types.

Anti-TNF: Tumour necrosis factor (TNF) is a gliotransmitter which is released by neuron-associated astrocytes, regulating synaptic function but an excess of TNF leads to inflammation and loss of function in neurons (Griffin, 2008). Etanercept, a drug used to treat rheumatoid arthritis, consists of sections of TNF receptor fused to the C-terminal portion of the immunoglobulin heavy chain (Griffin, 2008). Etanercept binds TNF-α, stimulates immune clearance, reduces inflammation and reduces amyloid-β deposition leading to early and lasting improvements in speech and cognitive function (Griffin, 2008; Potter, 2010).

Anti-inflammatory: Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and celecoxib reduced amyloid-β deposition in animal studies and appear to have a protective effect in younger AD patients (Potter, 2010). Natural products may also reduce AD-related inflammation and curcumin (found in turmeric) has been shown to reduce β-amyloid deposition and protect against its harmful effects in a mouse model (Potter, 2010).

Secretase inhibitors: Cleavage of the membrane-bound amyloid precursor protein (APP) by β-secreatase then either γ-secretase or α-secretase yields the secreted form of APP and one of several β-amyloid isoforms, which form plaques in the brains of AD patients (Portelius *et al.*, 2010). γ- Secretase inhibitors, such as begacestat/GSI-953 and semagacestat/LY450139 reduce the plasma β- amyloid concentration and reduce deposition of β-amyloid in the brain (Martone *et al.*, 2009; Portelius *et al.*, 2010). Drugs have also been developed to target β-secretase (memapsin 2/BACE-1), which is present in higher concentrations in the brains of AD patients, becomes more prevalent as the brain ages and correlates with β-amyloid deposition (Cole & Vassar, 2008; Potter, 2010).

Inhibition of GSK3B: Tau protein stabilises neuronal filaments by binding to microtubules. Hyper-phosphorylation of tau in AD patients triggers the formation of neurofibrillary tangles (NFTs). A major kinase of tau is glycogen synthase kinase 3 beta (GSK3B) and the inhibition of GSK3B by

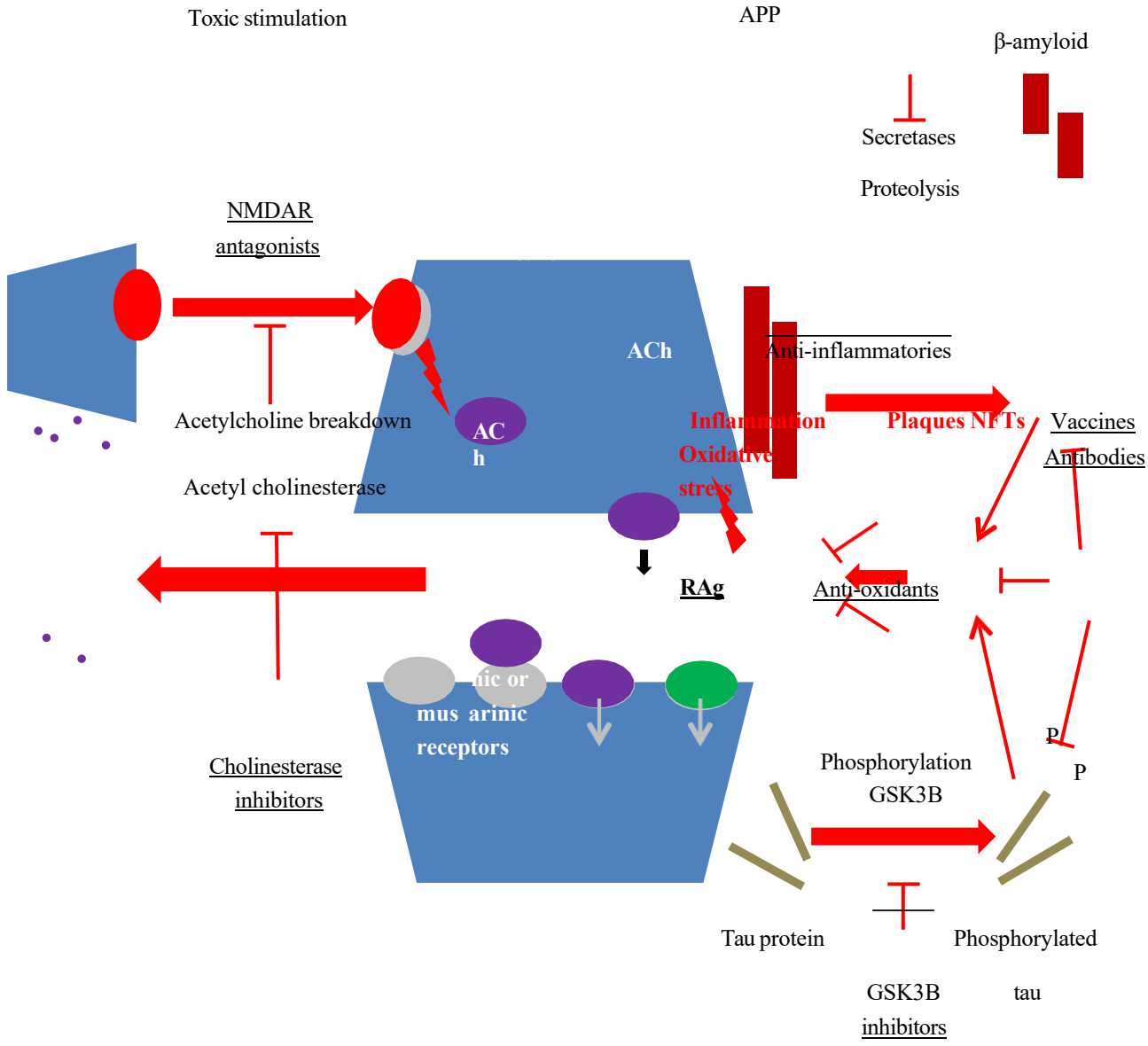

Figure 2. Some existing and emerging drug types for the treatment of Alzheimer's disease. Alzheimer's disease is characterised by toxic levels of glutamate (Glu), the formation of β-amyloid plaques and neurofibrillary tangles (NFTs), inflammation, oxidative stress, a loss of cholinergic neurons and low levels of acetylcholine (ACh). Existing drugs include cholinesterase inhibitors, which increase acetylcholine levels by inhibiting its breakdown and memantine, which antagonises N-methyl-D-aspartate receptors (NMDARs) to prevent glutamate-induced neuronal damage. Emerging drugs include nicotinic and muscarinic receptor agonists (RAg), which compensate for low acetylcholine levels by stimulating one of the two sub-classes of acetylcholine receptors directly. Anti-inflammatories and anti-oxidants reduce the inflammation and oxidative stress, which damage cholinergic neurons. Inhibitors of β- and γ-secretases prevent the amyloidogenic degradation of amyloid precursor protein (APP) which yields β-amyloid and leads to the formation of plaques. Inhibition of glycogen synthase kinase 3 beta (GSK3B) prevents the phosphorylation of tau protein which leads to the formation of neurofibrillary tangles (NFTs). Vaccines and antibodies target β-amyloid, phosphorylated tau, plaques and NFTs. Types of drug not shown include anti-tumour necrosis factor which targets TNF-α and reduces TNF-induced inflammation and drugs which stabilise microtubules.

lithium salts (believed to reduce the risk of dementia in those with bipolar disorder) has been shown in trials to reduce tau phosphorylation and improve cognitive functions (Forlenza *et al.*, 2011).

Physically targeting tau: An octapeptide, NAPVSIPQ (known as NAP) binds and protects microtubules. Anti-tau antibodies and methylene blue appear to prevent the formation of neurofibrillary tangles by tau

and all three have been tested in clinical trials and/or animals (Potter, 2010). Drugs are also being developed to induce proteolysis of tau. In two studies, immunisation of a mouse model with a section of phosphorylated tau and an adjuvant resulted in the clearance of NFTs and improved behavioural functions (Kayed, 2010).

Anti-oxidants: Coenzyme Q10 reduces the deposition of β-amyloid and up-regulates the anti-oxidant superoxide dismutase (SOD) in a mice model (Yang *et al.*, 2008). Resveratrol in red wine and flavonoids in green tea are other anti-oxidants believed to reduce the incidence of AD (Salloway & Correia, 2009).

Neurotransmitter Agonists

Agonists have been developed for the two major sub-classes of acetylcholine receptor: the nicotinic and muscarinic receptors (Salloway & Correia, 2009). Interestingly, the low affinity binding of β- amyloid to α4β2 nicotinic receptors inhibits the acetylcholine-induced release of GABA, glutamate or aspartate, depending upon neuron type while the very high affinity binding of β-amyloid to α7 nicotinic receptors promotes the release of glutamate or aspartate but not of GABA in the hippocampus (Mura *et al.*, 2012). This suggests a possible mechanism for the toxicity of β-amyloid.

Gene Modification: The brains of AD rats were injected with bone marrow stromal cells which had been transfected with recombinant human nerve growth factor (NGF) DNA (Li *et al.*, 2008). The cells expressed NGF, differentiated into cholinergic neurons and resulted in improved cognitive function. This is a rare example of a treatment which could restore lost function rather than simply compensating for, reducing or delaying the effects of AD.

Challenges to the Treatment of Alzheimer's disease

There are many obstacles to the introduction of new drugs. These include drug efficacy, delivery and side effects. Given the age and health problems of many AD patients, the obstacles may be even greater.

Anti-TNF: Etanercept is too large to cross the blood/brain barrier and so must be administered perispinally (Griffin, 2008). Etanercept is already approved for use in rheumatoid arthritis treatment but has only been shown to be beneficial in treating AD in one trial and a very small number of subjects (Woodward, 2012).

Anti-Inflammatory: Although there is a lower incidence of AD among chronic users of NSAIDs, no trial has demonstrated a beneficial therapeutic effect and naproxen increased the risk of cardiovascular problems (Potter, 2010; Woodward, 2012).

Secretase Inhibitors: One γ-secretase inhibitor (BMS-708163) has been shown to reduce the concentration of β-amyloid in the CSF of humans but two others (begacestat/GSI-953 and PF-3084014) reduced the concentration in the plasma but not the CSF (Potter, 2010). The γ-secretase inhibitor, tarenflurbil showed great promise in animal models, phase 1 and phase 2 trials but produced no beneficial effect in phase 3 trials (Green *et al.*, 2009; Woodward, 2012). One of the problems with γ-secretase inhibitors is that γ-secretase has other functions, such as the processing of cell differentiation-mediating Notch receptors and so there is a risk of toxicity if drugs are not specific (Potter, 2010). No phase 3 trials of β-secretase inhibitors have been completed but tests are on-going (Potter, 2010).

Inhibition of GSK3B: Several GSK3B inhibitors are in pre-clinical trials while lithium carbonate and the thiadiazoladinone, tideglusib/NP-12 are undergoing phase 2 trials for the treatment of AD (Kramer *et al.*, 2012). It should be noted that although lithium is already used in treating bipolar disorder, it has many targets and so the outcome of trials is uncertain (Kramer *et al.*, 2012).

Physically targeting tau: Phase 2 trials, using methylene blue to treat AD produced promising results but the formulation does not work well with high doses, the drug is not absorbed efficiently and it

causes diarrhoea (Woodward, 2012). Anti-tau antibodies have yet to undergo clinical trials (Woodward, 2012).

Anti-oxidants: Vitamin E appeared promising but when used to treat patients with mild cognitive dysfunction it did not delay the onset of AD, compared with control subjects (Woodward, 2012) and the dose is high enough to significantly increase the risk of cardiovascular complications. Selegiline and *Gingko biloba* extract have also failed to produce significant improvements to cognitive function in meta-analyses or double-blind trials (Woodward, 2012).

Neurotransmitter agonists: An α4β2 nicotinic receptor agonist failed in clinical trials but several α7 nicotinic receptor agonists are currently undergoing testing, including ABT-107 and EVP-6124 (Potter, 2010). TC-1734 is undergoing phase 2 testing (Woodward, 2012). The first muscarinic receptor agonists tested for AD treatment produced severe side-effects due to lack of specificity but M1- specific muscarinic receptor agonists such as AF267B have produced beneficial results in animal models and are undergoing further tests (Woodward, 2012).

Gene modification: Patients' own fibroblasts were gene-modified to express recombinant NGF and injected into the brain, resulting in nerve growth and reduced cognitive decline but no further testing has been carried out (Woodward, 2012). A phase 2 trial is currently recruiting individuals with mild to moderate AD for a phase 2 gene therapy trial, using a virus to deliver the NGF gene (Alzheimer's Disease Cooperative Study, 2012).

Improvements in the use of Existing Drugs: Galantamine is excreted unchanged in the urine and so the dose must be reduced and the patient closely monitored in cases of kidney dysfunction (Farlow *et al.*, 2008). Rivastigmine may be administered *via* trans-dermal patch, rather than orally in order to reduce side-effects (Farlow *et al.*, 2008).

Treatment of Behavioural Problems: Individuals with Alzheimer's disease often suffer from depression, anxiety, irritability, aggression and poor sleeping patterns (Salloway & Correia, 2009). A number of non-drug strategies may be beneficial. Among these strategies are music therapy to calm patients, walks to provide light and exercise, use of a light box during the day to improve sleeping pattern, the provision of a less stressful environment, simplified and repetitive tasks to improve performance, cognitive exercises, reminiscence, pet therapy, carer training, support and day-care (Farlow *et al.*, 2008; Hogan *et al.*, 2008). Many anti-psychotics carry a greater risk of stroke in AD patients and tricyclic anti-depressants have significant side effects as well as anti-cholinergic activities which make them unsuitable for AD patients but even high risk drugs may be prescribed where patients are extremely distressed or are a very significant risk to others (Locca *et al.*, 2008).

Conclusion

There have been many promising developments in recent years. Several new targets have been identified and new drugs developed, or existing drugs adapted, to treat AD. However, there are problems with side-effects and specificity. A number of drugs have reduced β-amyloid/ phosphorylated tau levels and improved cognitive function in animal models and in humans but then produced no significant benefit in AD patients in phase 3 trials. Several strategies of treating AD have not been covered here due to lack of space. These include diabetic drugs which are being used to treat AD, metal chaelators, mitochondrial drugs, histamine receptor antagonists and hormone therapy. As our understanding of the links between inflammation, oxidative stress, neuronal damage and the plaques and NFTs found in AD brains improves, new targets may be identified and, perhaps whole new classes of drugs developed. Gene therapy trials are a particularly fascinating

development and hold out the hope of restoring lost neuronal function and improving memory, learning and cognition. However, in the short term there is little hope of significant improvement in the quality of life of patients and carers.

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