DRUGS IN ALZHEIMER'S DISEASE DEMENTIA: AN OVERVIEW OF CURRENT PHARMACOLOGICAL MANAGEMENT AND FUTURE DIRECTIONS

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SUMMARY

Background: *Alzheimer's dementia is one of the most significant health burdens of the modern age in both industrialised and non-industrialised nations as it is a major cause of morbidity and functional impairment in the elderly. Currently there are no cures for progressive dementias, including Alzheimer's disease, and no treatments that would modify their progress. Intervention involves pharmacological treatment to temporarily relieve the symptoms, including three cholinesterase inhibitors and a noncompetitive NMDA antagonist, and the efficacy of these is widely debated. While our understanding of the underlying pathology of Alzheimer's continues to grow, we have yet to fully elucidate the mechanisms that drive neuronal loss in this condition. Any truly disease-modifying treatment must be developed to target these pathological pathways.*

Methods: *An extensive analysis of the available literature is presented here, including a number of trials, meta-analyses and reviews, with the aim of assessing current management, establishing best practice and summarising the future of dementia care.*

Results: *The efficacy of acetylcholinesterase inhibitors remains controversial due to uncertainty over what change is considered clinically significant. Any derived benefit seems to be independent of dementia severity and donepezil is the most cost-effective for Alzheimer's dementia. Memantine potentially influences the underlying pathological processes in Alzheimer's disease and may be more effective in moderate to severe Alzheimer's dementia. The role of combination therapy remains uncertain. Future therapies are aimed at modulating the disease process by using chemical agents to inhibit amyloid and tau deposition. None have been approved clinically.*

Conclusions: *Current pharmacological therapy for Alzheimer's dementia is very limited and primarily aims at achieving symptom control. A major limitation is our lack of knowledge of the underlying pathology and it is only by better understanding the disease process that we can optimize therapeutic agents that modify disease progression.*

Key words: *Alzheimer's dementia – pharmacological treatment – future directions*

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INTRODUCTION

Dementia refers to a general decline in mental ability that causes functional impairment. The most common cause is Alzheimer's disease accounting for 60-80% of cases. Pathologically, Alzheimer's disease is characterized by amyloid plaques (Aβ) and neurofibrillary tangles (protein tau) which lead to neuronal damage and loss (Ballard et al. 2011). Therefore, possible treatment options for Alzheimer's disease could include compounds that target plaque aggregation and tau deposition. Many such agents are currently in development but require further research. While there is no curative treatment for dementia currently, acetyl-cholinesterase inhibitors and memantine (an NMDA receptor antagonist) are medications licensed for its treatment (NICE Clinical Guideline 2011) A large body of evidence suggests that these drugs effectively relieve symptoms and emerging evidence suggests that they may influence the underlying pathophysiological processes, which is reviewed here. Novel pharmacological avenues exist, yet the safety of any intervention relies on a complete understanding of the disease process and its identification prior to the manifestation of symptoms, as it is believed that this period is the optimal therapeutic window.

AIM

Currently there are no cures for progressive dementias, including Alzheimer's disease (AD), and no treatments that would modify their progress. Intervention involves pharmacological treatment to temporarily relieve the symptoms and the efficacy of this is widely debated. An extensive analysis of the available literature is presented here, including a number of trials, meta-analyses and reviews, with the aim of assessing current management, establishing best practice and summarising the future of dementia care.

METHODS

An extensive literature search was performed within multiple databases. PubMed was searched using the MeSH terms 'dementia' and 'Alzheimer's' and 'memantine' or 'rivastigmine' or 'galantamine' or 'donepezil' as well as 'dementia' and 'Alzheimer's' and 'acetylcholinesterase inhibitors' or 'pharmacological.' I also used the terms 'Alzheimer's' and 'current' or 'future.' The Cochrane library and Ovid Medline were searched using similar terms. Relevant trials and reviews were selected from the results.

RESULTS

Acetylcholinesterase inhibitors

These operate through inhibiting the enzyme acetyl-cholinesterase, resulting in an increased availability of acetylcholine in the synaptic cleft. Rivastigmine, galanatamine and donepezil are currently licensed for the management of AD. A systematic review of these drugs considered 22 placebo-controlled trials meeting the inclusion criteria (Hansen et al. 2008), 14 of which used cognition as a pre-specified outcome. Within these, all three cholinesterase inhibitors demonstrated an approximate benefit of 2.7 points (2.3–3.0 95% CI) using the 70-point Alzheimer's disease assessment scale cognitive section. Improvements with treatment were also seen in studies assessing function, behavior and global change. There is no clear evidence to support one acetychlolinesterase inhibitor over another. There remains controversy over what level of change may be considered clinically significant especially as, in one study, ADAS-Cog decline did not reflect clinical decline and only a 4-point change was considered clinically important (Rockwood et al. 2007). A critical issue remains that mean changes may result from a few patients improving substantially while others don't at all. An additional pooled data analysis (3 RCTs) showed greater clinical decline in those on placebo compared to those taking donepezil using multiple domains such as cognition, function and global outcome (Wilkinson et al. 2009). Therefore even those who are classified as 'non-responders' may still derive benefit from treatment.

Evaluating long-term treatment is difficult as the majority of RCTs took place over 6 months and results of the longest running trial (Courtney et al. 2004) were limited by a 70% dropout rate and a multiple washout design. The DOMINO study has demonstrated that maintaining donepezil therapy provided greater functional and cognitive benefit over 12 months than discontinuing it measured as 1.9 points of benefit (1.3–2.5 95% CI) on the standardised MMSE (Howard et al. 2012). These drugs are also currently prescribed and funded according to precise upper and lower cut off scores of cognitive tests, yet a recent meta-analysis found that, apart from memantine, the efficacy of these drugs seems to be independent of dementia severity (Di Santo et al. 2013). Additionally, a recent systematic review and economic model of these drugs confirmed the effectiveness of these drugs in alleviating AD symptoms and in mild to moderate AD, donepezil is stated to be the most cost-effective based on probabilistic sensitivity analysis (Bond et al. 2012).

Memantine

It is believed that memantine acts primarily as a NMDA receptor antagonist thereby reducing glutamate-mediated excitotoxicity. The evidence suggests that its efficacy varies depending on the severity of Alzheimer's disease (AD). There was no difference found between memantine and a placebo for any cognitive measure in mild to moderate AD in both an independent meta-analysis (Schneider et al. 2011) and a Cochrane review (McShane et al. 2006). On the other hand, there is evidence for a clinically significant benefit of memantine in moderate to severe Alzheimer's disease on cognition, behavior and activities of daily living (McShane et al. 2006). This data originated from three pooled randomized controlled trials showing a positive effect at 6 months on cognition (2.97 (1.68-4.26 95% CI) points on a 100 point severe impairment battery). It has also shown some benefit in behavioural disturbances and psychotic symptoms in moderate to severe AD with improved neuropsychiatric inventory scores and significantly reduced caregiver distress (Schmidt et al. 2010).

It remains unclear whether memantine affects the underlying pathological process in AD. One proposed hypothesis is that, in addition to acting as an NMDA antagonist, it might prevent the expression of amyloid precursor protein and tau by inhibiting the internal ribosome entry site (Wu & Chen 2009). Imaging studies looking at the effect of memantine on neuronal loss in AD used the N-Acetyl Aspartate (NAA) to Creatine (Cr) ratio as an indicator (Ashford et al. 2011). This failed to show a benefit of memantine although this was in mild to moderate AD. A more recent trial (Wang et al. 2013) used fluorodeoxyglucose positron emission tomography (FDG-PET), which monitors disease-modifying effect, to study the effect of memantine in moderate to severe AD and found an association between its clinical benefit and FDG-PET measurements in AD-affected brain regions. Larger-scale and more longitudinal studies are required to confirm these findings and evaluate the various indicators of pathological decline in AD.

Combination therapies

There is limited evidence about the efficacy of combining pharmacological treatments in AD dementia. One critically appraised topic concluded that adding memantine to donepezil in patients suffering moderate to severe AD did result in a statistically significant improvement for a number of AD-oriented outcome measures (Riordan et al. 2011). Comparisons of memantine-donepezil therapy with placebo-donepezil and memantine-only therapies revealed significantly greater clinical benefits when utilisng the combination (Atri et al. 2015). Data was pooled from four 6-month randomized controlled trials and subjected to an area-under-the-curve analysis on measures of cognition, function, behavior and global status. A very recent meta-analysis (Matsunaga et al. 2015) included 7 studies and found that combination therapy provided more benefit than monotherapy for moderate-to-severe Alzheimer's in the areas of cognition, behavioural disturbance, activities of daily living and global assessment.

From an economic perspective, an analysis of long-term health costs and outcomes was performed using an individual patient simulation with data input based on patient-level trial data and published literature (Saint-Laurent Thibault et al. 2015). This concluded that, in the US, combination therapy for moderate-to-severe AD

provides better clinical outcomes at lower cost than acetylcholinesterase monotherapy.

However, a recent trial assessing the effects of donepezil when AD progresses, from a mild/moderate to a moderate/severe stage, demonstrated that continued treatment was associated with cognitive benefits yet there was no significant advantage to the combination of donepezil and memantine over donepezil alone (Howard et al. 2012).

DISCUSSION

Future therapies

There is a medical requirement for novel therapies that have an impact in the early stages of AD as current treatment has relatively weak beneficial effects on cognitive function in sufferers with negligible effect on disease progression (Mancuso et al. 2011). The development of effective management must be based on an understanding of the underlying pathology of AD, namely the amyloid hypothesis. Histopathologically, this consists of amyloid plaques, tau tangles and neuronal loss, which present a number of targets for potential therapies. Associated pathogenic mechanisms include oxidative damage (Reddy et al. 2009), inflammation (Griffin 2006), cholesterol metabolism (Stefani & Liguri 2009) and iron deregulation (Adlard & Bush 2006). This review will focus on treatments modifying the primary disease mechanisms. Emerging evidence suggests that neurofibrillary tangles and senile plaques may even be interconnected at a molecular level (Lloret et al. 2015), which would support the use of combination therapies.

Modulation of amyloid deposition

This is based on the principle that aggregation of Aβ forms toxic oligomers causing neuronal damage (Golde, 2005). Tramiprosate (3APS) is an inhibitor of Aβ aggregation, operating by interfering with the binding of Aβ and glycosaminoglycans (Gauthier et al. 2009). Results of the North American phase III trial were discouraging and so further trials were discontinued (Aisen et al. 2011). Additionally, there was data to suggest that tramiprosate causes abnormal aggregation of tau protein in neuronal cells and thereby worsening the other primary lesion in AD (Santa-Maria et al. 2007). Scyllo-insitol (ELND005) is a compound able to stabilize Aβ aggregates and inhibit their toxicity in mouse models, however, an 18-month randomized controlled trial in people with mild to moderate AD showed no significant evidence for any benefit at long-term follow up. Further trials are planned with the aim of intervening at earlier stages of AD (Salloway et al. 2011). Further evidence demonstrates that scyllo-insitol prevents changes induced by Aβ plaques in a dose and steroisomer-specific manner (Jin & Selkoe 2015). Drugs that interfere with the copper and zinc mediated toxic-oligomerisation of Aβ show promise also and will progress to further testing such as PBT2, which is a second-generation 8-OH quinolone metal-protein-attenuating compound (Faux et al. 2010).

Inhibition of beta secretase and gamma secretase or the potentiation of alpha secretase can reduce Aβ production. There are a number of problems with beta secretase enzyme (BACE1) inhibition. BACE1 has other physiological functions, inhibition of which would cause adverse effects and also the enzyme has a large active site so any compound produced to inhibit it would not be able to cross the blood-brain barrier. The compounds developed so far have issues with their CNS penetration and oral bio-availability yet some such as CST-21166 have been shown to reduce human plasma Aβ in phase I trials (Ghosh et al. 2012). Efforts continue to develop agents with superior pharmaceutical properties. Similar issues arise with gamma secretase as it has a number of other substrates and is particularly important in growth and development. It is the inhibition of Notch processing, which gamma secretase cleaves, and accumulation of Aβ's neurotoxic precursor that leads to the failure of these inhibitors. The aim now is to develop Notch-sparing gamma secretase inhibitors with sufficient brain penetration (Imbimbo & Giardina 2011). Alpha secretase is another target as stimulating this enzyme drives the non-amyloidogenic pathway. Etazolate (EHT0202) has been safe and well tolerated in a randomized controlled trial using 159 patients with mild to moderate AD and may now be tested in a larger group of patients longitudinally (Vellas et al. 2011) although the initial trial was not powered to show drug efficacy.

Finally, it is hypothesized that there may be over 6 different humoral immunological pathways by which amyloid plaques are cleared and these have the potential to be used in immunotherapies for AD (Wisniewski & Konietzko 2008). Active immunisation strategies have been the victim of adverse reactions such as encephalitis and variable antibody response to vaccines. Passive immunisation methods include the monoclonal antibody bapineuzumab, which demonstrated clinically significant benefits in mild to moderate AD. Additionally, solanezumab is an Aβ central domain directed monoclonal antibody that has been declared safe by phase II trials and is currently in phase III studies (Brody & Holtzman 2008). There may also be a role to play for natural antiamyloid antibodies as shown in a phase I trial involving 8 patients with AD given IVIg. At 6 months, all seven patients had halted cognitive decline and 6 actually derived benefits. A more recent strategy involves mucosal immunotherapy where nasal administration of recombinant Sendai virus vector carrying Aβ1-43 and mouse IL-10 cDNA reduced the amount of Aβ on both soluble and insoluble fractions of the brain homogenates of APP transgenic mice and induced good antibody responses (Hara et al. 2011).

Modulation of Tau deposition

Compounds here may target tau deposition or tau phosphorylation and so multiple approaches have been taken. Methylene blue (MB), a phenothiazine, is currently being assessed as a tau aggregation inhibitor. Experimentally, it is not conducive to blinding as it causes urine to be coloured blue, nonetheless, a phase II

trial has demonstrated improvements in the cognitive function of patients suffering AD at 6 months (Gura, 2008). There is a link between tau phosphorylation and pathological effects of tau and while there are many phosphorylation sites, inhibition of glycogen synthase kinase 3 may have therapeutic effect in AD. Recent trials have considered lithium, looking at the cognitive and biological outcomes in people with mild cognitive impairment and there may be some disease-modifying impact (Forlenza et al. 2011).

CONCLUSION

Alzheimer's dementia is one of the most significant health problems in the elderly, with rapidly increasing prevalence as life expectancy continues to rise. Typically, it is characterized by progressive and profound cognitive deficits in memory, orientation, judgment, language and other areas, becoming a major contributor to morbidity and loss of function. The current licensed treatments (rivastigmine, donepezil, galantamine and memantine) offer symptomatic therapy. While they have consistently shown beneficial effects on cognition, behaviour, function and global status, these are modest and they have no disease-modifying effect.

Developing agents that can alter the course of AD has relied on our current knowledge of its underlying pathological processes, which we have not fully elucidated. This lack of complete understanding is reflected in the fact that drugs designed to target elements of the Aβ and tau pathway have actually failed to show a demonstrable effect. Therefore, further and more thorough investigation of Aβ, tau and associated disease mechanisms is critical to progressing therapy. Nonetheless, some agents such as scyllo-insotiol, PBT2 and lithium as well as immunotherapy strategies show some promise and are being advanced to further clinical trials.

Another consideration is the design of trials being used to test novel therapies in terms of the population used, the duration and which indicators may be used as outcome measures such as MRI, CSF tau and Aβ amyloid positron emission tomography (Salomone et al. 2012, Vellas et al. 2007). We must establish robust ways to assess the clinical benefit of a drug and evaluate any disease-modifying effect. Finally, the very definition of AD is subject to change as it is currently considered in presymptomatic and symptomatic phases (Dubois et al. 2010, Sperling et al. 2011). New drugs must be deployed in the early presymptomatic stages of AD before neuronal damage is severe and essentially irreversible. Operating alongside this should be the biomarkers that are able to anticipate disease progression and guide therapeutic intervention, as ultimately, the aim is to halt the disease long before it develops into dementia.

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