Pharmacological treatments for alzheimer’s disease

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Development of Pharmacological Treatments for Alzheimer’s Disease: A literature review

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Abstract

Alzheimer’s disease (AD) is the most common causes of dementia in people over 65 years old. Scientists have been working on exploration and understanding of the pathophysiological processes for decades. However, the lack of currently available therapies reflects the uncertainties in AD. There are abundant studies on treatment for AD underway. Various mechanisms of etiology of AD and pharmacological medications have been examined for years. Several medications (e. g., ChEIs and memantine) have been used as symptomatic treatments. However, it seems still far away from obtaining a disease-modified medicine for treatment of AD. This review aims not only to discuss the currently available treatment, but also emerging treatment, practical issues, and non-pharmacological treatments.

Development of Pharmacological Treatments for Alzheimer’s disease: A literature review

Dementia is a progressive, irreversible decline in cognition that impacts on a patient’s functioning. It is inextricably linked to the ageing process. The increasing number of patients with dementia is estimated to double within 20 years. Dementia also devastates families and is increasingly costly for society. It is the main cause of disability in those over 65 and the strongest health predictor of dependency. The clinical syndrome of dementia has several etiologies with overlapping pathological and clinical features.

Alzheimer’s disease is the most common causes of dementia in people over 65 years old. Scientists have been working on exploration and understanding of the pathophysiological processes for decades. However, the lack of currently available therapies reflects the uncertainties in AD. Although cholinesterase inhibitors ChEIs (donepezil, galantamine and rivastigmine) and the NMDA receptor antagonist (memantine) have been shown to be effective on providing modest symptomatic benefit, until now, there are no treatments proven to slow or cure any of the dementia processes. The exploration of etiologies and the establishment of effective drugs for AD is therefore a global priority.

Pathological Features of AD

Drug development in AD is based on evolving pathophysiological theory (Massoud, & Leger, 2011). The accumulation of amyloid plaques and neurofibrillary tangles of tau is still central to the pathological cascade since decades ago (Cunningham, & Passmore, 2013). Amyloid precursor protein (APP) is cleaved to smaller β-amyloid (Aβ) peptides. Part of Aβ exerts its malign inï¬, uence via a tendency to aggregate into the hallmark insoluble amyloid plaques (Cummings, Gould, & Zhong, 2012). Tau protein is another protein get involved in the etiology of AD. These processes act synergistically to disrupt cell function and architecture. There are a number of hypotheses, such as oxidative damage, mitochondrial dysfunction, neurotoxic excitation, aberrant insulin signaling, disruption of intracellular calcium homeostasis, neuroinï¬, ammation and endothelial pathophysiological mechanisms (Cunningham, & Passmore, 2013). Cerebrovascular damage comprises an untangled pathophysiological web.

Synapse loss and neurotransmitter reduce are the neurological symptoms of AD. These are interacting processes, with activating and inhibiting effects and the exact mechanisms remain unclear (Cunningham, & Passmore, 2013). Therefore, this review aimed to discuss current pharmacological treatments, practical issues, emerging treatments, and dietary approaches for AD.

Current Pharmacological Treatment

Vascular Prevention

The most studied vascular risk factors related to cognitive outcomes are hypertension and dyslipidemia (Massoud, & Leger, 2011). Studies have shown that treatment for high blood pressure in people was associated with better cognitive outcomes (Massoud, & Leger, 2011). However, the treatment of hypertension did not result in a reduction of AD incidence. Two major primary prevention studies evaluating the benefits of cholesterol-lowering medications showed statistically significant benefits on cardiovascular and cerebrovascular outcomes in treated people, while there were no benefits on cognitive outcome measures used in these studies (Massoud, & Leger, 2011). These counterintuitive results can be explained by the relatively crude cognitive measures used and by the short duration of follow-up. A longitudinal observational study in a tertiary memory clinic showed that treatment of vascular risk factors is associated with a slower decline on cognitive measures in people with AD (Massoud, & Leger, 2011). Sánchez-Ferro et al. (2013) also explains that major concerns with statin research are the methodological issues that could influence the results. Sánchez-Ferro (2013) further suggested that an additional possibility for the

lack of consistent results is that statins may have a negative impact on cognition. Food and Drug Administration has warned about this potential adverse outcome. Therefore, although a potential role of cholesterol in the pathogenic process of AD has been proved by different models, statin therapy has failed to show the effect on neither the treatment nor the prevention of this disease (Sánchez-Ferro, 2013).

Cholinesterase Inhibitors

Use of ChEIs, such as donepezil, rivastigmine, and galantamine, is based on studies showing that people with AD have deficits in ACh production which lead to cortical cholinergic dysfunction (Massoud, & Leger, 2011). Cholinesterase degrades ACh in the synapses. ChEIs act by inhibiting this action and maintain the levels of Ach. ChEIs improve symptoms of AD but not modify its natural course (Takeda, 2012). Donepezil inhibits AChE and analyses have shown statistically significant benefits on cognitive, functional, and behavioral outcome measures (Massoud, & Leger, 2011). There are some dose-dependent side effects of donepezil such as nausea, vomiting, diarrhea, muscle cramps, dizziness, fatigue, and anorexia. Rivastigmine reversibly inhibits both AChE and BuChE and pooled analyses have shown its benefits on cognitive, global, and functional outcome measures; while there are no significant benefits on behavioral outcomes (Massoud, & Leger, 2011). Side effects of rivastigmine include nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain, and dizziness. Galantamine reversibly inhibits AChE and binds to nicotinic receptors which enhance cholinergic transmission. A review showed significant treatment effects on cognitive, global, functional, and behavioral outcome. Typical cholinergic

side effects were reported more commonly in patients on galantamine than placebo group (Massoud, & Leger, 2011).

Memantine

Memantine is an NMDA noncompetitive glutamate receptor antagonist. It is used in treatment of AD is because that glutamate-related cytotoxicity is involved in the pathophysiology of the disease (Cummings et al., 2012). Studies on effects of memantine have shown inconsistent degree in different measures: some showed benefits on measure of cognition and function while some only in cognition (Massoud, & Leger, 2011). Dose-limiting side effects of memantine are rare

Antipsychotics

Until the introduction of the atypical antipsychotics, conventional antipsychotics were the mainstay of pharmacotherapy for the psychosis of AD (Madhusoodanan, 2007). However, conventional antipsychotics have significant risks in the elderly population, including a high incidence of serious cardiovascular and anticholinergic adverse effects, extrapyramidal symptoms and tardive dyskinesia (Madhusoodanan, 2007). Because of these potentially serious adverse effects, the inappropriate use of antipsychotics in nursing homes became a focus of attention. Although atypical antipsychotics have been warned about their side effects, the author suggests that until an useful medication is approved for the indication of the psychosis of AD, clinicians do not have a better choice for the management of the serious psychotic symptoms of AD.

Practical Issues

Massoud and Leger (2011) indicate four clinical issues need to be considered when prescribing ChEIs and memantine for AD: treatment expectations, management of side effects, switching agents, and discontinuation of therapy. Since currently all available pharmacological treatments are only symptomatic, treatment expectations need to be adjusted accordingly (Takeda, 2012; Massoud, & Leger 2011). In clinical practice, patients do not typically show improvement on functional measures. Therefore, clinicians should not expect to improve the symptom of functions lost, such as managing one's finances or driving (Massoud, & Leger, 2011). Regarding behavior problems, ChEIs usually help prevent new neuropsychiatric symptoms in mild-to-moderate AD (Massoud, & Leger, 2011; Fereshtehnejad, Johnell, & Eriksdotter, 2014). Treatment of ChEIs has cholinergic, dose-dependent side effects, which include anorexia, nausea, vomiting, diarrhea, abdominal discomfort, fatigue, and muscle cramps (Massoud, & Leger, 2011). The authors further suggest that it will help to minimize side effects if clinicians start with prescribing these agents at the lowest dose, and then slowly titrating to the minimally effective dose. Besides, in the absence of clear guidelines for the treatment of patients with AD suffering from other comorbidities, Massoud and Leger (2011) recommend prudence and an individualized approach based on clinicians' judgment. The unique pharmacological properties of each ChEIs make switching prescription a feasible option for intolerance or for lack of clinical response. Discontinuing ChEIs or memantine treatments is challenging clinicians especially when there is no guideline from satisfied clinical trial (Massoud & Leger, 2011). The

authors suggest that clinicians should be guided by individualized clinical judgment.

Emerging Treatments

The amyloid cascade hypothesis suggests that the accumulation of Aβ is the initial trigger to the AD pathological process (Massoud, & Leger, 2011). The authors state that in order to prevent the production, increasing the removal and reducing the toxic Aβ are obvious goals.

The pathological aggregation of tau has also been the focus of therapeutic attempts (Cunningham, & Passmore, 2013). The authors indicate that strategies are based on a shifting pathophysiological understanding, with target pathways including the hyperphosphorylation and aggregation of tau. The authors also suggest that the categorization of drugs by target pathway is an increasingly arbitrary one, as the pathophysiological basis of AD and the various pharmacological effects of candidate drugs remain an untangled web.

Immunological issues such as systemic inï¬, ammation, aberrant function of microglia and astrocytes, dysregulation of the complement system, and generation of detrimental brain-reactive antibodies all contribute to the development and progression of AD (Liu et al., 2013). The authors indicate that age-related immune decline promote the progression of AD, which might be bridged by age-related chronic inï¬, ammation. The authors suggest that the close relation between immune system and AD provides a novel way. This opinion is consistent with Cunningham and Passmore (2013).

The authors state that modifying inï¬¬, ammation is a unifying theme of drug development in AD drugs.

Multi-Target Compound

Several compounds which targeted both the Ab and tau aggregations were reported (Capurro et al., 2013). The authors also note that several dual targeting inhibitors against Ab aggregation and acetyl/butyryl choline esterase have been reported recently. The authors especially take Memoquin (MQ), a multi-target compound, as an example. MQ acts as an acetylcholinesterase and b-secretase-1 inhibitor, and also possesses anti-amyloid and anti-oxidant properties. In the present study, MQ was found to be broadly effective in vivo on memory disturbances. Moreover, MQ can be effective against oxidative stress thus offering a therapeutic benefit over existing treatments. These findings indicate that MQ might be a promising multi-target candidate for addressing the complex nature of AD (Capurro et al., 2013).

Dietary approaches and supplements

Takeda (2012) indicate that due to the limited benefits of the symptomatic drugs, non-pharmacological intervention, integrating social and psychological factors, should be combined with pharmacological intervention in the treatment of Alzheimer patients The author states that the limited efficacy of drug treatment and the plasticity of the human brain are the two main reasons that explain this growing interest in non-pharmacological intervention for patients with AD. Cunnungham and Passmore (2013) indicate a number of dietary approaches which have been considered to fight AD. Although many of these are being studied as preventative

measures, interventional approaches in established disease are being evaluated (Cunnungham, & Passmore, 2013). Studies on caloric restriction, a combination of folic acid/vitamin B12/vitamin B6, a combination of antioxidants, vitamin E/vitamin C/lipoic acid, curcumin, resveratrol, and souvenaid have shown benefits on patients with AD (Cunnungham & Passmore, 2013).

Discussion

There are abundant studies on treatment for AD underway. Various mechanisms of etiology of AD and pharmacological medications have been examined for years. Several medications (e. g., ChEIs and memantine) have been used as symptomatic treatments. However, it seems still far away from obtaining a disease-modified medicine for treatment of AD. Although the side effects of antipsychotics make them controversial, in practice there is no better choice for clinicians. Practical issues on using these symptomatic medication and off-label medications should be noted. Multi-target compound seems to be a promising candidate. Besides pharmacological treatment, non-pharmacological intervention has been noticed recently. Takeda (2012) indicates that there are many complementary and alternative medicines for AD, such as Chinese herbal medicine, natural supplements, food, exercise, leisure activities, and life styles. In addition to the treatment for patients with AD, the burnout of caregiver is another significant issue in Alzheimer’s disease.

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