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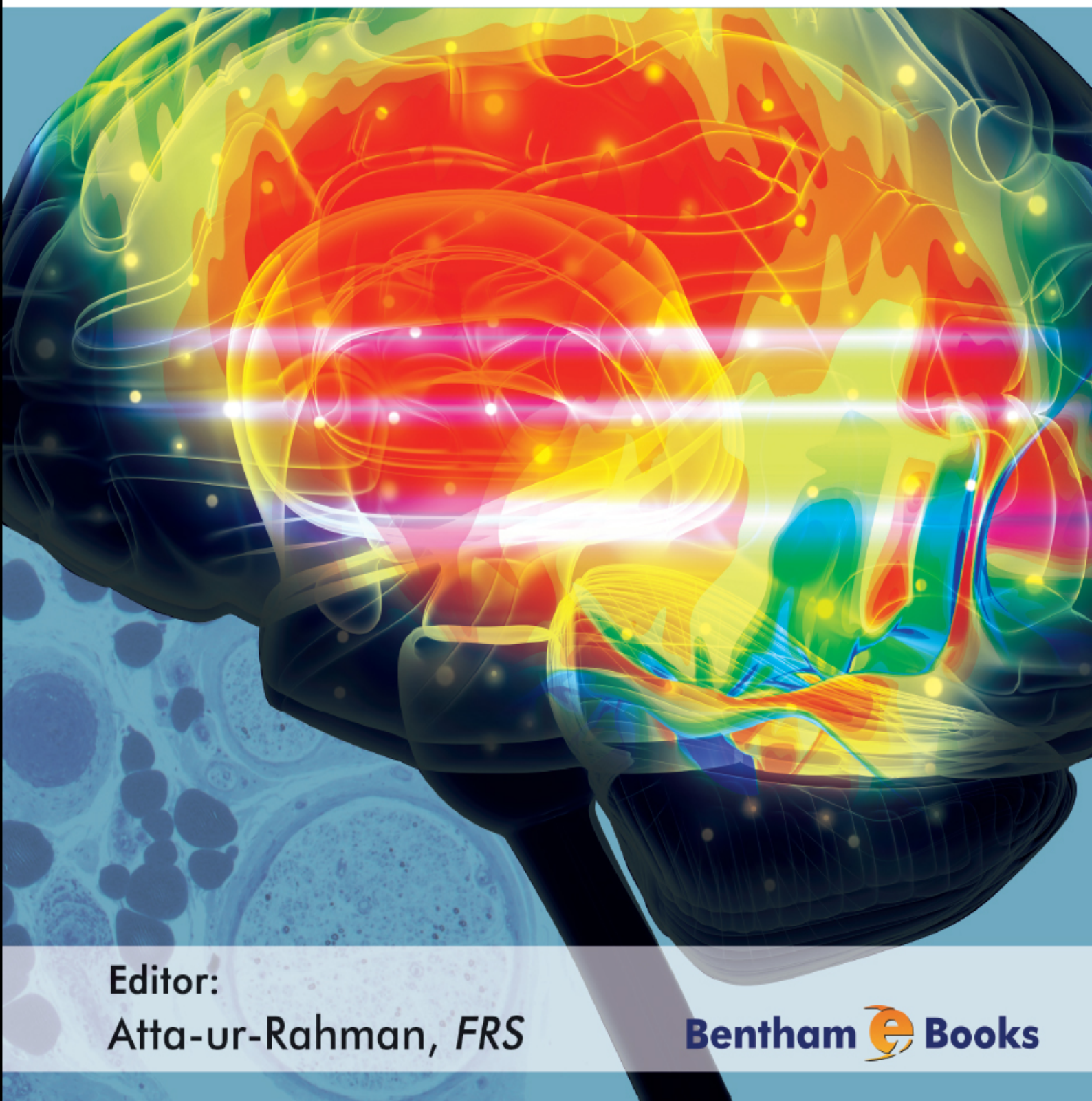
Frontiers in Clinical Drug Research

(Alzheimer Disorders)

Volume 4



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Frontiers in Clinical Drug Research

Alzheimer Disorders

(Volume 4)

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PREFACE

Alzheimer's disease (AD) is the most common age-related multifactorial neurodegenerative disease which is described as the failure of cognitive performance and behavioral capabilities. The clinical features of Alzheimer's disease (AD) are worsening cognition with progressive discrepancy in recovery of memory. The book series, "***Frontiers in Clinical Drug Research – Alzheimer Disorders***", is intended to present the most important advancements in the field in the form of cutting edge reviews written by experts in this field of research. ***Volume 4*** of this eBook series is a compilation of five well written chapters contributed by prominent researchers which include topics such as, the role of melatoninergic pathways, investigational drugs and nutritional approaches in the prevention and treatment of Alzheimer's disease.

Anderson and Maes in Chapter 1 review the role of melatoninergic pathways in Alzheimer's disease. They also discuss the influence of primary and secondary sites of infection in the etiology and course of AD. In chapter 2, they describe the role of melatonin in more detail with respect to the changes and interventions relevant to AD.

Many researchers are aiming at understanding, preventing and curing AD. Several strategies are being studied for developing therapies against this disorder. Esiri and Wilcock, in Chapter 3 discuss the various approaches for the treatment and prevention of Alzheimer's disease. This review also describes the primary and secondary prevention of AD and the links with cardiovascular disease, diet and other lifestyle-related risks.

Neuritic plaques containing β-amyloid and neurofibrillary tangles containing tau are the two key targets of drugs under investigation that could prevent or slow down the progress of Alzheimer's disease. Pamela E. Potter, in Chapter 4, comprehensively explains the mechanism of action and results of clinical trials for the drugs that have been recently used or that are in development for the treatment and management of Alzheimer's disease.

The role of adequate nutrition in the management of mild cognitive impairment (MCI) and Alzheimer's disease (AD) is extensively reviewed in Chapter 5 by Chen *et al.* This review also discusses the role of several natural products including micronutrients in the nutritional prevention of AD.

The 4th volume of the book series presents important recent researches that have been reviewed comprehensively by eminent researchers. I wish to express my gratitude to the contributors as well as the editorial staff, particularly Mr. Mahmood Alam (Director Publication), Mr. Shehzad Naqvi (Senior Manager Publications) and Ms. Fariya Zulfiqar

(Assistant Manager Publications) for their hard work and persistent efforts.

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CHAPTER 1

Melatoninergic Pathways in Alzheimer's Disease

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Abstract: The utilization of tryptophan for the synthesis of serotonin, allows some of this serotonin to be broken down into N-acetylserotonin (NAS) and melatonin, forming the melatoninergic pathways. Many of the changes and susceptibility factors associated with Alzheimer's disease (AD) regulate, and can be regulated by, the melatoninergic pathways. Melatonin is well known for its night-time release by the pineal gland, which contributes to entraining the circadian rhythm. Decreased pineal melatonin and disruption of the circadian rhythm is common in AD, with melatonin supplementation affording significant protection against cognitive deficits and circadian disruption in most clinical trials. Melatonin is also a significant regulator of the immune system, where its effects afford protection against immuno-senescence and associated alterations in immune responses in AD patients. Being a significant antioxidant, anti-inflammatory and optimizer of mitochondrial functioning, melatonin has many benefits in AD.

Recent data shows that melatonin is produced by many other, if not all, human cells, including astrocytes and immune cells. The release of melatonin by these cells allows for autocrine and paracrine effects that decrease the reactivity of glia and immune cells. Given the role of heightened glia and immune cell reactivity in AD, local melatonin synthesis by these cells is a significant pharmaceutical target.

NAS may be more than simply the immediate precursor of melatonin. NAS is also a powerful antioxidant as well as being a brain derived neurotrophic factor (BDNF) mimic. Given the general protective effects of BDNF and its decrease in AD, NAS is likely to afford protection in AD patients, with effects not necessarily the same as those of melatonin.

In this chapter, we review the role of the melatoninergic pathways in AD, highlighting its usefulness in managing this devastating, and still poorly treated, disease.

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Keywords: Alzheimer's Disease, Glia, Immunity, Inflammation, Melatonin, N-acetylserotonin, Nitrosative stress, Oxidative stress, Pineal, Treatment.

1. INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative condition associated with extensive neuronal loss, driven in part by increased amyloid-β plaques and neurofibrillary tangles. Genetic susceptibility factors, including the E4 variant of the apilopoprotein gene, (Apo)E4, increase AD risk across different ethnic groups [1]. The biological underpinnings of AD are being extensively investigated and include changes in the circadian rhythm, mitochondrial dysfunction, and heightened immune inflammatory activity [2], which all contribute to driving wider behavioural and cognitive manifestations including memory loss, sleep disruption and frequently emergent seizures [3]. Heightened immune inflammatory activity also associates with a more rapid dementing process in AD, as well as in other neurodegenerative conditions [4].

Many of the biological changes occurring in AD, including increased oxidative and nitrosative stress (O&NS) and decreased mitochondrial functioning, as well as increased indoleamine 2,3-dioxygenase (IDO) and immune inflammatory activity [5], are associated with lower levels of peripheral and cerebral spinal fluid melatonin [6]. Melatonin is a powerful anti-oxidant, anti-inflammatory, immune regulator and entrainer of circadian rhythms [7, 8]. Melatonin also increases mitochondrial oxidative phosphorylation and function. Most work on melatonin, including in AD, has focussed on its production by the pineal gland, along with its precursor N-acetylserotonin (NAS). Recent data shows that melatonin and NAS can also be produced by astrocytes [9], and many other cell types [10], suggesting that local astrocyte, and possibly microglia and leukocyte, melatonin may be significant treatment targets in AD [11]. Following an overview of the biological underpinnings of AD, we propose a role for local NAS and melatonin production in the etiology, course and treatment of AD, as well as highlighting how the melatoninergic pathway may be intimately involved in determining the effects of factors known to modulate AD susceptibility and course. We then look at the implications of this for future research.

2. ALZHEIMER'S DISEASE OVERVIEW

2.1. Classical Alzheimer's Disease Pathophysiology

The biological underpinnings of AD are classically attributed to increased production of amyloid-β and hyperphosphorylated tau, which increase amyloid-β plaques and neurofibrillary tangles respectively [12]. Amyloid-β is produced by the beta cleavage of the amyloid precursor protein (APP), predominantly by beta-site amyloid precursor protein-cleaving enzyme (BACE1), in both neurons and astrocytes. The over-production of amyloid-β leads to its fibrillization and oligomerization, which produce the amyloid-β plaques that are highly evident in the AD brain. Amyloid-β induces apoptosis in neurons, possibly by many different means, including increasing the activation of the L-voltage gated calcium channel, in turn leading to toxic levels of Ca2+ influx [13]. Increased oxidative and nitrosative stress (O&NS) and immuno-inflammatory processes, as indicated by increased pro-inflammatory cytokines, occur prior to significant amyloid-β plaque formation [14] and contribute to BACE1 activation and amyloid-β production [15].

Amyloid-β may interact with a number of plasma membrane receptors and channels, including the alpha 7 nicotinic acetylcholine receptor (a7nAChr) on astrocytes, with detrimental effects on neuronal functioning, at least in part *via* increased astrocyte glutamate efflux and extrasynaptic neuronal N-methyl-D-aspartate (NMDA) receptor activation [16]. As well as being neurotoxic, amyloid-β also has significant impacts on astrocyte functioning and releases [17, 18]. Given the powerful astrocytic regulation of neuronal functioning and survival, such amyloid-β modulation of astrocyte reactivity and fluxes are important to neuronal survival and functioning, with astrocytes being a significant AD treatment target [19].

A loss in basal forebrain cholinergic neurons and functioning also occurs in AD, contributing to cognitive deficits, partly *via* the loss of ACh effects on arousal associated cognition. The long-standing cholinergic hypothesis of AD is based on this, including in its recent revised form [20]. The loss of cholinergic neurons alters several other proteins involved in cholinergic activity, including

CHAPTER 2

Pharmaceutical and Nutritional Benefits in Alzheimer's Disease *via* Convergence on the Melatoninergic Pathways

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Abstract: As reviewed in the previous chapter above, tryptophan utilization for serotonin synthesis increases the necessary precursor for the melatoninergic pathways. The changes and susceptibility factors associated with Alzheimer's disease (AD) regulate, and can be regulated by, the melatoninergic pathways. In this chapter we look at the role of the melatoninergic pathways in more detail in relation to changes and interventions relevant to AD.

Many pharmaceutical and dietary factors, with efficacy in AD and/or AD models, regulate the melatoninergic pathways, either directly or indirectly. As such, much of the experimental data pertaining to regulators of the etiology, course and treatment of AD, such as zinc, selenium, acetylcholinesterase inhibitors and valproate, may be intimately intertwined with the melatoninergic pathways.

In this chapter, we review the role of the melatoninergic pathways in AD, highlighting its previously little recognised involvement in a host of susceptibility factors and treatment approaches. More insight as to the relevant changes occurring in AD should allow treatments to better target relevant biochemical targets, thereby improving the management of this poorly conceptualized, and therefore poorly treated, disease.

Keywords: Antioxidants, Alzheimer's disease, Glia, Immunity, Inflammation, Melatonin, N-acetylserotonin, Oxidative stress, Pineal, Treatment.

1. INTRODUCTION

The modelling of a significant role for glia and immune cell melatoninergic

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pathways in Alzheimer's disease (AD) and wider neurodegenerative and psychiatric conditions, provides a new frame of reference as to their relevant, and overlapping, biological underpinnings, in turn providing a basis for the reconceptualization of how different medications and food related risk factors and treatments modulate the biological underpinnings of apparently diverse disorders. We now look at how a variety of factors that have been utilized or proposed for treatment in AD, as well as for wider AD-associated neurodegenerative and psychiatric disorders, may have their biological effects, at least in part, *via* the regulation of the serotonin and melatonin pathways.

Initially, we reviewed the literature for pharmaceutical and dietary factors that have been shown to have efficacy in delaying AD symptomatology and/or in slowing its course. We detail as to how the serotoninergic and melatoninergic pathways may be a point of convergence for such a wide array of pharmaceutical and dietary factors.

1.1. Methods

Firstly, we look at the some of the pharmaceutical treatments of AD, followed by the nutritional factors that have been shown to influence the etiology and course of AD. As to how each of the pharmaceutical and nutritional factors may impact on the serotoninergic and melatoninergic pathways in mediating their effects is detailed. Following this, we look at how such pharmaceutical and dietary factors may be integrated into a model of wider relevant processes in AD that emphasize the importance of the melatoninergic pathways. This is then followed by a section on the future research directions that such a conceptualization would indicate.

2. PHARMACOLOGICAL AND DIETARY TREATMENTS

2.1. Overview

A wide range of pharmaceuticals and nutritional products have shown efficacy in decreasing AD susceptibility in epidemiological studies, with these being biochemically supported by experiments in AD models.

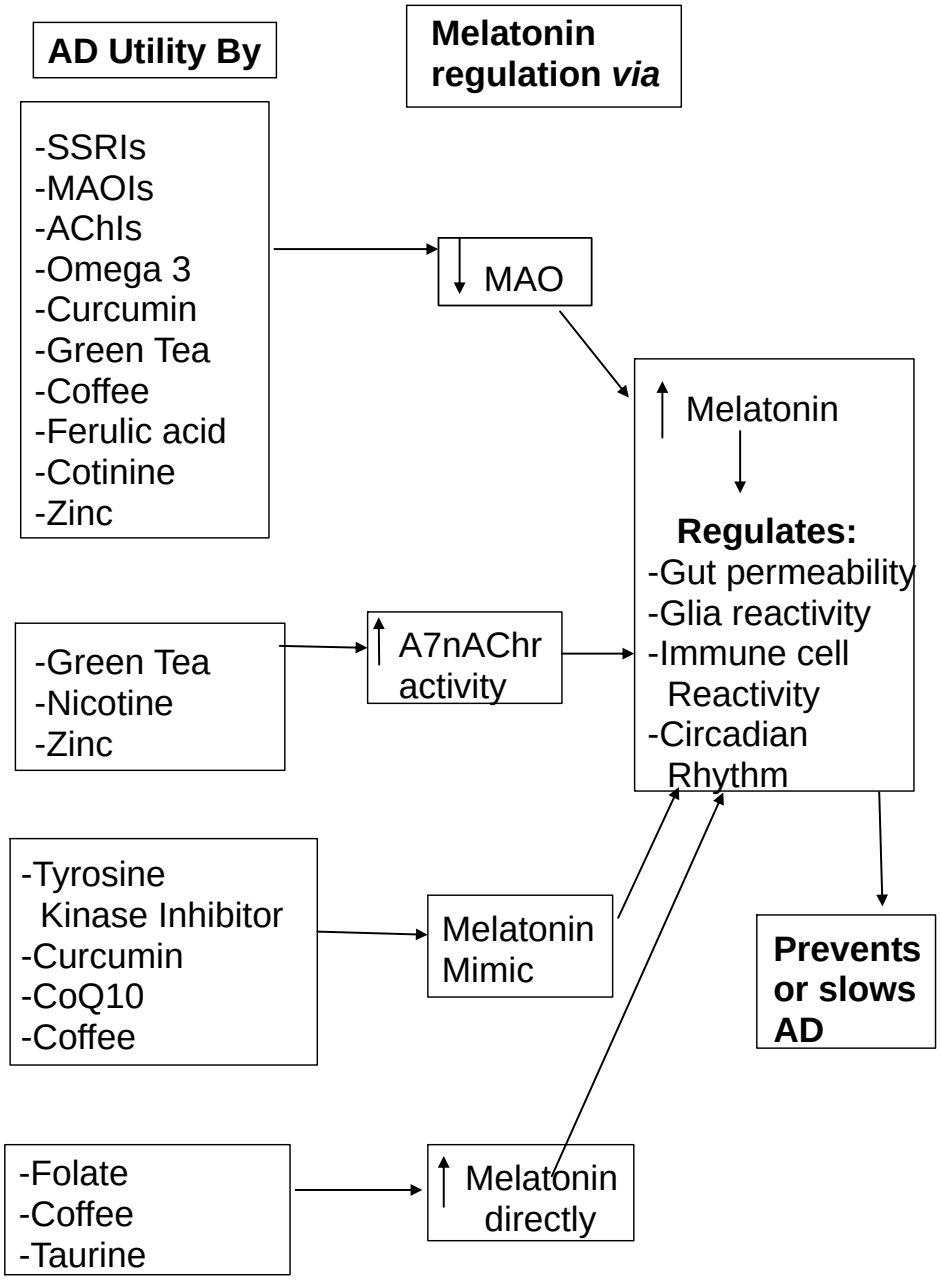

Fig. (1). The summary figure shows the variety of pharmaceuticals and neutraceuticals that have shown utility in Alzheimer's disease (AD) and AD models, with these effects being mediated by a number of means that may increase melatonin, with consequences for biological processes contributing to the etiology and/or course of AD.

CHAPTER 3

Some Questions Posed About the Prevention and Treatment of Alzheimer's Disease

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Abstract: This chapter considers the current state of efforts to develop prevention and treatment strategies for Alzheimer's disease (AD). It takes the form of answers to 12 posed questions on this topic. The urgent need for improved interventions to prevent symptomatic AD is highlighted while the outcome of treatment trials for those who already have developed symptoms is also reviewed. Efforts at primary and secondary prevention are distinguished and the link with cardiovascular disease, diet and other lifestyle-related risks discussed. The need for better understanding of the pathogenesis of sporadic AD is considered crucial since any improved interventions are likely to depend on this. The important role of neuroimaging in extending understanding of the trajectory of pre-clinical AD development is considered as is the importance of developing improved and readily applicable biomarkers for the disease. Approaches to develop further randomised controlled clinical trials for AD and the formidable costs that these entail are discussed together with the contribution of epidemiological studies as an adjunct to trials. Ultimately there needs to be improved education about the risks of AD so that individuals throughout their lives can be encouraged to take better personal responsibility for living well into old age.

Keywords: Alzheimer's disease (AD), Biomarkers, Cardiovascular disease risks, Diet, Lifestyle-related risks, Neuroimaging, Pathogenesis of sporadic AD, Primary prevention, Randomised controlled trials for AD, Secondary prevention.

INTRODUCTION

For those at an earlier stage in life, dementia has become the most feared consequence of living into old age [1]. The questions that we attempt to answer below about Alzheimer's disease (AD), the condition that accounts for most cases

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of dementia, are intended to summarise the current position with regard to its treatment and prevention.

AD is a condition that develops through various stages and over a long time scale, usually measured in years. Pathologists have long been aware that some of the structural brain changes that occur in AD can be found at autopsy in some people from middle age. This knowledge has been reinforced and extended by the recent development of means of detecting such changes in living subjects using brain imaging methods [2 - 4]. AD initially affects people clinically by reducing their ability to think, memorise and use language. It can also change their behaviour and eventually destroys their ability to lead an independent life. Psychological tests and assessment of activities of daily living can document deterioration in these functions when they reach a certain level of severity but usually more subtle alterations that are subjectively detectable to some occur earlier than this. Thus, an initial state of 'subjective cognitive impairment' is recognised to occur first [5]. This is followed by a stage when objective evidence of cognitive impairment can be established using psychological tests [6]. This is termed 'mild cognitive impairment' (MCI) and at this stage there is little if any loss of functional ability. Some people stabilise and show no further objective deterioration in their cognition beyond this but in others full-blown dementia develops and progresses so that they eventually become dependent on others for their day-to-day care. They may become unable to recognise close friends and family members and lose the elements of their lives that made their existence meaningful. The aim of those who carry out research on AD is to find ways to halt or at least slow this sequence of deterioration.

1. WHAT IS THE NEED FOR PREVENTION AND TREATMENT OF AD?

The rapid improvement in life expectancy throughout the world that has occurred, principally in the twentieth century, has posed a colossal problem in this century: how to deal with the massive increase in prevalence of dementia in the elderly, not only in the developed world but also in the developing one [7]. By far the most important contributing factor to dementia is AD, a condition that has so far resisted attempts to delay its onset or to slow down the deterioration in cognition that it causes. Other ageing changes in the brain also contribute to dementia in old

age, most notably cerebrovascular disease and Lewy body disease. These forms of brain pathology are intricately linked to the ageing process but we do not yet have sufficient understanding either of brain ageing or of these conditions to be able to intervene effectively to ameliorate their effects. However, there are preliminary indications that control of medical and lifestyle risk factors in mid-life, aimed primarily at reducing cerebrovascular disease, may be able to influence cognitive outcomes in late life (see question 2 below). Dementia eventually deprives a person of the ability to live an independent, meaningful life and therefore brings with it a social and financial burden that, without amelioration, will become hard to sustain.

The scale of the problem has been laid out in models that use the evidence provided by estimates of people currently, or in the recent past, suffering from dementia to predict likely numbers further into the twenty first century. The estimate for the global tally of people living with dementia in 2001 was put at 24.3 million and this number was predicted to nearly double every 20 years to reach 81.1 million by 2040 [8]. In 2013 a further review, which had the advantage of a larger and, in part, better quality evidence base (although coverage of different regions still remained patchy), and a detailed analysis of the literature, provided a more detailed assessment as outlined in the next paragraph [7].

In all regions of the world the prevalence of dementia was found to increase exponentially with increasing age from 60 years. Prevalence doubled for every 5.5 year increment in age in North America, Latin America and Asia Pacific regions, for every 5.6 year increment in age for East Asia, every 6.3 year increment in age for Western Europe and South Asia and for every 6.7 year increment in age for South East Asia and Australasia. In most regions of the world dementia was more prevalent in females than males, by 19-29%. For most countries for the population aged >60 years the prevalence Figures ranged between 5-7% but they were substantially lower for West Africa, represented by Nigeria, where a prevalence of 2.07% was recorded and higher in Latin America (8.5%). In this study the world total of dementia sufferers in 2010 was estimated to be 35.5 million and, as in the previous study, the total numbers were estimated to nearly double every 20 years to give a total expected in 2030 of 65.7 million and in 2050 of 115.4 million. Currently, low and middle income countries were estimated to host 58% of all

CHAPTER 4

Current and Investigational Drugs for Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease is characterized pathologically by the presence of neuritic plaques containing β-amyloid and neurofibrillary tangles containing tau. These have become two targets of investigational drugs aimed at preventing or slowing the disease. Early findings of extensive cholinergic degeneration inspired the development of drugs targeting cholinergic function. Cholinesterase inhibitors were the first drugs to be approved for treatment, followed by the NMDA receptor antagonist memantine. This chapter will focus on the development, mechanism of action, and results of clinical trials for drugs currently used or in development for treatment of Alzheimer's disease. Examples of these include drugs targeting cholinergic neurons, such as cholinesterase inhibitors, muscarinic receptor agonists and nicotinic receptor agonists, as well as memantine. Several drugs aimed at reducing levels of β-amyloid or tau are in development and will be addressed. Finally, drugs directed at other targets that may be useful in treatment of Alzheimer's disease will be discussed.

Keywords: Alzheimer's disease, anti-inflammatory drugs, β-amyloid, β-secretase, Cholinesterase inhibitor, Curcumin, Immunotherapy, Insulin, Leukotriene inhibitors, Memantine, Muscarinic agonist, Nicotinic agonist, NMDA receptor, Serotonin receptor agonists, Statins, Vaccine, Tau, γ-secretase.

1. INTRODUCTION

Alzheimer's disease (AD) is characterized by a progressive decrease in cognitive function and loss of short-term memory. Pathological changes include formation of neuritic plaques containing β-amyloid, and neurofibrillary tangles containing

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the protein tau. There is a massive loss of cholinergic neurons, which correlates closely with the decline in cognitive function [1, 2]. Thus, current therapeutic strategies for treating the disease focus on augmenting cholinergic function [3] with cholinesterase inhibitors [4 - 6]. In 2003, the NMDA receptor antagonist memantine became available [7 - 9]. New drugs are currently being tested for possible usefulness in treating symptoms or to delay or reverse the pathology of AD. While in many cases these drugs, alone or in combination, have produced an improvement in symptoms and tests of cognition, their effectiveness wanes as the disease progresses. This review will focus on drugs currently used in the treatment of AD (Table **1**) as well as those that are in the process of being tested (Table **2**), categorized by therapeutic target or mechanism of action.

Table 1. Drugs currently approved for treatment of AD in the US.

DRUG	FDA Approval	Remarks
Cholinesterase Inhibitors		
Donepezil (Aricept)	Approved 1996	Improved cognition in most clinical trials, widely prescribed for AD. Now available in combination product with memantine [374]
Rivastigmine (Exelon)	Approved 2000, transdermal patch approved 2007	Patch found to be as effective as capsules in clinical trials Also approved for dementia in Parkinson's disease [374]
Galantamine (Razadyne)	Approved 2001	Brand name changed from Reminyl to Razadyne in US to prevent prescribing confusion [374]
NMDA Antagonist		
Memantine (Namenda; Namenda XR)	Approved 2003; long acting from approved 2010 Combination with donepezil approved 2014	Approved for use in moderate to severe AD but not in mild AD [374]

Table 2. Drugs being investigated or that have been tested for use in AD.

DRUG	Stage in Development	Results
Muscarinic Agonists		
Xanomeline (M1, M4)	Phase II clinical trial halted after 6 months (NCT00744978)	No improvement in cognition and caused psychiatric side effects [114]

(Table 2) contd.....

DRUG	Stage in Development	Results
Muscarinic Agonists		
Talsaclidine (M1)	Phase II clinical trials completed or terminated (NCT02249403; NCT02249351)	Further development not being pursued despite decrease in β-amyloid. Salivation and sweating significant side effects [111, 130]
AC-260584 (allosteric)	Animal model	Increased cognitive performance [139]
TBPB (allosteric)	Animal model	Decreased β-amyloid *in vitro* [137]
BCQA, ML169 (allosteric)	Animal model	Reverses scopolamine-induced cognitive impairment [142]
PQCA (allosteric)	Animal model	Improved cognition in transgenic mouse [143]
Nicotinic Agonists		
ABT-089 (α4β2)	Phase II studies terminated (NCT00555204; NCT00069849)	No improvement in ADAS-cog [153]
Varenicline (α4β2)	Phase II clinical trial (NCT00744978) completed	Did not improve ADAS-Cog and caused psychiatric side effects [154]
ABT-126 (α7)	Phase I, II, and IIb completed (NCT01549834; NCT01676935)	Tested in mild to moderate AD. No results have been published. Ongoing testing for schizophrenia [375]
ABT-107 (α7)	Animal models, Phase I	Improved cognition in animals but was not studied beyond Phase I [163]
Encenicline (EVP-6124; α7)	Phase III trials alone in AD recruiting (NCT01969123; NCT01969136) ; Phase III with memantine (NCT02246075)	Being studied alone or combined with cholinesterase inhibitor for AD and alone for schizophrenia Improved cognition in Phase II [168]
5-HT_6 Inhibitors		
RVT-101 (SB 742457)	Phase II trial (NCT00710684) completed 2011	Improved cognition with donepezil [176, 177]
Ilalopiridine (Lu AE58054)	Phase II with donepezil completed 2011 (NCT01019421; LADDER); Phase III trials combined with donepezil recruiting (NCT02006641; NCT01955161; NCT02006654)	Improved cognition [178, 179]
RVT-101 (SB 742457)	Phase II trial (NCT00710684) completed 2011	Improved cognition with donepezil [176, 177]

CHAPTER 5

Nutritional Approaches in Alzheimer's Disease Prevention

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Abstract: Epidemiological and biochemical studies have confirmed that some nutritional deficiencies (or malnourishment) are risk factors for the development of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Adequate nutrition plays an important role in cognitive-function maintenance. Early nutritional intervention in the preclinical or predormal phases of AD is likely to prevent or arrest the neurodegenerative processes that are involved in both normal elderly and cognitively impaired elderly with prodromal AD. Furthermore, nutritional strategies are relatively safe. Therefore, nutritional intervention is an important approach to prevent or delay the development of AD in the elderly, which would reduce the disease burden

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[#] The authors contribute equally to this work.

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of dementia for the whole society. This review aims to highlight recent developments regarding the values of nutritional intervention in reducing and preventing AD and dementia.

Keywords: Alzheimer's disease, Aβ oligomers, B complex vitamin, Inflammation, Microglial activation, Nutritional prevention, Omega-3 polyunsaturated fatty acids, Oxidative stress, Phospholipids, Polyphenolic compounds, Selenium, Souvenaid, Synaptic dysfunction, Vitamin C, Vitamin E.

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most common forms of dementia and mostly affects the elderly, which hinders personal experiences, memory, orientation, judgment, executive function, self-care ability, and social functions [1]. With the inevitability of global aging, the number of dementia and AD patients is estimated to double in the coming 20 years [2]. This will lead to heavy burdens on public health care and social economic systems. AD mostly occurs in the late-stages of human life, while clinical diagnosis usually occurring at the end stages of the disease. This causes untimely and complicated treatments for AD patients [3]. Therefore, an early intervention, and the prevention or delay of disease progression may have a strong impact on clinical outcomes and health care/social systems.

1.1. Disease Progression Delay or Modification

The rate of AD progression is caused by a combination of genetic factors (such as the ε4 variant of the APOE gene), environmental factors (such as nutrition deficiency, lack of exercise, environmental toxins) and interactions with physiological aging processes in the brain [4, 5]. In term of dietary factors, animal models have demonstrated that dietary restriction could extend lifespan and arrest neuronal degeneration [6]. These observations imply a preventive and pathogenic role of dietary factors in AD [7]. Nutritional interventions could be more effective in symptomatic predementia phase of AD, referred to mild cognitive impairment (MCI) [8, 9]. It has been demonstrated that MCI prevalence ranges from 10% to 25% among the elderly, and 12% to 25% of this population will develop AD [10 - 12]. Therefore, an elderly person with MCI is believed to be an appropriate

candidate for early intervention. MCI due to AD can be diagnosed by Amyloid-β (Aβ) and tau/p-tau biomarkers that is a good entity for preventive intervention. Interestingly, postponing AD onset by one year is estimated to reduce the number of AD patients by 9.5 million in 2050 [6]. Therefore, early intervention would be highly significant in AD treatment that could delay and modify disease progression.

1.2. Life Integrity Prolongation for Elderly

AD is one of the most prevalent age-related neurodegenerative diseases and the leading cause of dementia in the elderly. As life expectancy grows, the world has more elderly people and with it, the prevalence of AD is expected to increase. An estimated 700,000 elderly people (aged 65 or older) will die of AD in the United States in 2015. AD is listed as the sixth leading cause of death in the United States [6]. Despite the increasing number of AD cases, there is currently no effective medical therapy confirmed to prevent AD [13]. Interestingly, non-pharmacological attempts and lifestyle modifications have shown to reduce the risk of AD progression, and nutrition has been suggested to influence cognitive function [14]. Therefore, nutritional intervention in early AD treatment have been highlighted recently by scientists and the media.

1.3. Reduction in Disease Burden

The cost of treatment and healthcare services in heart diseases or cancers is high, and the present cost of AD is equally as high or even higher [15]. According to the Alzheimer's disease report from the United States, the cost of care for patients with AD and other dementias increased from approximately $203 billion in 2013 to $226 billion in 2015. Given the large cost of AD worldwide, early intervention has become increasingly necessary and urgent now.

2. PATHOGENESIS OF AD

AD is one of the most common progressive chronic neurodegenerative disorders. Neuropathological hallmarks include neurofibrillary tangles (NFTs), amyloid plaques, dystrophic neuritis and neuropil threads that are accompanied with the activation of astrogliosis and microglial cells [16, 17]. NFTs are the major

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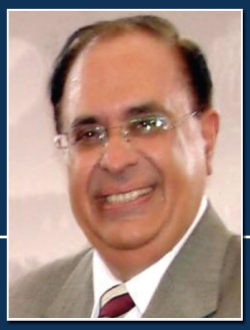

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Prof. Atta-ur-Rahman obtained his Ph.D. in organic chemistry from Cambridge University (1968). He has 974 publications in several fields of organic chemistry including 718 research publications, 37 international patents, 151 books and 68 chapters in books published largely by major U.S. and European presses. He is the Editor-in-Chief of several European Chemistry journals and the Editor of "Studies in Natural Product Chemistry" 43 volumes of which have been published by Elsevier Science Publishers (Netherlands) under his Editorship during the last two decades. Eighty students have completed their Ph.D. degrees under his supervision.

Prof. Rahman was elected Fellow of Royal Society (London) (2006) and won the UNESCO Science Prize (1999). He has been conferred honorary doctorate degrees by Cambridge University and many other universities. He was elected Honorary Life Fellow of Kings College, Cambridge University (2007).