Alzheimer's Disease Diagnosis and Treatments
ALZHEIMER'S DISEASE DIAGNOSIS
AND TREATMENTS

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ALZHEIMER'S DISEASE DIAGNOSIS AND TREATMENTS

MARISA R. BOYD
EDITOR
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Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. The most common form of dementia among older people is Alzheimer's Disease (AD), which involves the parts of the brain that control thought, memory, and language. Age is the most important known risk factor for AD. The course the disease takes and the speed at which changes occur vary from person to person. On average, AD patients live from 8 to 10 years after they are diagnosed, though the disease can last for as many as 20 years. This book presents research in the study of Alzheimer's Disease, including diagnosis, testing and treatment of this condition.

Chapter 1 - In November 1906, in Tubingen, Germany, Alois Alzheimer (1864-1915) first described his laboratory's clinical and neuropathological findings on a then novel neurological disorder in one of his female cases named Auguste D. Institutionalized by her concerned family at the age of 51, Alzheimer’s first patient died of a progressive dementia just four years later. Although the clinical features of this ‘disease of the aged’ were long known since ancient times, and often referred to as a ‘senile psychosis’, ‘age-related madness’ or ‘old-timer's disease’, Alzheimer was probably the first to correlate senile plaque (miliary foci) and neurofibrillary tangle (fibrils) propensity within the association neocortex with disease diagnosis and severity. It is perhaps less well known that Alzheimer also associated cerebrovascular involvement and angiogenesis with his first description of Alzheimer’s disease neuropathology, features that he termed ‘focal lesions in the endothelium’ and ‘new vessel formation’ in the diseased brain.

Chapter 2 - Over the last two decades studies of patients with Alzheimer’s disease (AD) have made a significant contribution in helping to elucidate the neurological and cognitive bases for controlled and automatic forms of retrieval from long-term memory. These studies show that AD patients demonstrate severe deficits on tasks that involve controlled processes. In contrast, their performance on tasks involving automatic processes is variable. This article reviews experimental studies that have revealed dissociations between controlled and automatic memory processing in AD, and discusses evidence from functional neuroimaging studies which indicate that different forms of retrieval represent distinct aspects of brain activity. Attention is given to the assumption that memory retrieval reflects the operation of a single form of processing (automatic or controlled). The implications of adopting this assumption are discussed within the context of contemporary theoretical perspectives, and recent attempts to understand memory processing in AD and normal ageing by using the process-dissociation approach to memory are described. Finally, the importance of
understanding the status of controlled and automatic memory processing for the diagnosis and management of AD is considered.

Chapter 3 - Clinical presenting symptoms of Alzheimer’s disease vary with age, complicating diagnosis in patients with atypical early onset of disease (age < 65 years). Patients with early onset of Alzheimer’s disease symptoms have greater impairment in language, working memory and visuospatial abilities, and relatively less episodic and semantic memory impairment compared to those with the more typical later onset Alzheimer’s disease. These differences suggest greater involvement of the parietal lobes in patients with early onset Alzheimer’s disease, compared to greater early involvement of the hippocampus and medial temporal lobes in those with later onset Alzheimer’s disease. Neuroimaging studies show greater areas of atrophy and decreased brain activity in the parietal lobes, precuneus regions, and posterior cingulate corticies in early onset patients compared to greater temporal lobe and hippocampal atrophy in those with later onset Alzheimer’s disease. Patients with very late onset of Alzheimer’s disease (age > 84 years) present with greater deficit of frontal lobe functions, consistent with the hypothesis of increased vulnerability of the frontal lobes and frontal-subcortical circuits to decline with age. Comparing the clinical findings of patients with Alzheimer’s disease according to their age of onset highlights the complex relationship between the pathology of Alzheimer’s disease and typical aging related changes that occur in the brain, and may aid clinicians in diagnosing this disease in patients at all ages on onset.

Chapter 4 - The presence of A\(\beta\)-positive neuritic plaques with dense cores is considered an essential pathological marker of Alzheimer’s disease (AD). However, there are atypical cases that have abundant non-cored plaques with surrounding minor dystrophic neurites. The atypical plaques are called ‘cotton wool plaques‘, and AD with cotton wool plaques is thought to be one of the variants of AD. Cotton wool plaques are usually large, round, and eosinophilic, and appear to displace surrounding normal structures. Inflammatory glial response is mild. We here describe two autopsy cases of early-onset dementia with abundant eosinophilic non-cored A\(\beta\) plaques, the histopathological features of which are different. Patient 1 was a 44-year-old man at the time of death, with a clinical course of 8 years. Nine relatives in three generations had died in their thirties to forties, and some of them were verified to have had dementia. The proband presented clinically with spastic paraparesis at age 36 prior to the development of dementia. The brain weight was 1330 g. Macroscopically, only mild atrophy was found in the frontal, temporal, and parietal cortices. Histopathological examination revealed abundant, large, eosinophilic, non-cored plaques having the typical appearance of cotton wool plaques. The plaques were more strongly immunopositive for A\(\beta\)-42 than A\(\beta\)-40. A moderate number of neurofibrillary changes were found in the hippocampus and parahippocampal gyrus, but only a few in other anatomical regions, including the neocortex. The pyramidal tract was degenerated. Although moderate neuronal loss was found in the insular and entorhinal cortices, the other cerebral cortices were relatively spared. Genetic analysis demonstrated the G384A presenilin-1 gene mutation. Patient 2 was a 46-year-old man at the time of death, with a clinical course of 8 years. His family had no history of neurological diseases in the previous three generations. He presented with memory impairment at the age of 39. Subsequently, he showed disinhibition, impulsiveness, and paranoid ideation, but no neurological abnormality. The brain weight was 1700 g. Macroscopically, neither brain atrophy nor edema was observed. Histopathological
examination disclosed abundant eosinophilic non-cored plaques in all cerebral cortices. The diameters were 40-100 μm, including plaques smaller than those in patient 1. The plaques showed little tendency to displace normal structures, but did not contain neurons. Intriguingly, the plaques in this case were more strongly immunoreactive for Aβ1-40 than for Aβ1-42. In the cerebral cortex including the hippocampus, neurons were well preserved, and glial response was slight. In the pyramidal tract, glial proliferation was evident, although loss of myelin was not noted. No tau-positive lesions were found in any region. No mutations in presenilin-1, presenilin-2, or amyloid precursor genes were revealed by genetic analysis using formalin-fixed paraffin-embedded tissue. These findings suggest that factors besides neuritic plaques, neurofibrillary tangles, and severe neuronal loss play a pivotal role in the occurrence of cognitive decline in AD patients.

Chapter 5 - Protein aggregation is the basis for many of the common human neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease and a family of disorders that includes Huntington’s disease. In AD the aggregatory species is termed amyloid β (Aβ), a peptide derived from the proteolytic cleavage of amyloid precursor protein (APP), a ubiquitous transmembrane protein. The aggregatory properties of Aβ are determined by variations in the position of the proteolytic cleavage that generates the C-terminus. In healthy elderly individuals the ratio of the 40 amino acid peptide (Aβ1-40) to the 42 amino acid species (Aβ1-42) favours the less aggregatory Aβ1-40 resulting in effective clearance of the peptide from the brain. In contrast, individuals who go on to develop the common sporadic form of AD have elevated Aβ1-42 concentrations, or have a molar ratio of Aβ1-40 to Aβ1-42 that favours aggregation. In the five percent of AD cases that are inherited as an autosomal dominant trait all the causal mutations have been shown to favour Aβ aggregation, mostly by altering APP processing, either increasing Aβ1-42 in absolute terms or in comparison to Aβ1-40. In rare examples, where Aβ1-42 levels are not elevated, mutations are found within the Aβ sequence that accelerate the intrinsic rate of peptide aggregation and stabilise particularly toxic subpopulations of aggregates, a clear example of this is the Arctic APP mutation.

In the context of cognitive decline, the demonstration of Aβ deposition in the brain in combination with intraneuronal aggregates of a microtubule-associated protein, tau, comprise the diagnostic criteria for AD. Mature deposits of Aβ are composed of ordered amyloid fibrils and it is their distinctive microscopic appearance and their affinity for dyes such as Congo red that favoured their early characterisation. However there is a poor correlation between the burden of amyloid plaques and the degree of cognitive impairment, indeed elderly individuals may have many plaques without showing signs of cognitive impairment. In contrast, it is the intracellular tau pathology that has been shown to correlate more closely with clinical deficits. The location and progression of the tau lesions correlates well with the brain areas, such as the hippocampus, that are particularly impaired in AD.

The poor correlation between extracellular amyloid plaques and dementia has been used to detract from the significance of Aβ in the pathogenesis of AD. However recent evidence has clarified the situation, emphasising the toxic role of small Aβ aggregates rather than the amyloid fibrils. The finding that soluble Aβ correlates better with synaptic changes and cognitive deficits than plaque count has prompted the investigation of soluble aggregates of Aβ. These small aggregates can be purified by column chromatography and are composed of as few as 4 or as many as 180 Aβ molecules. When applied to cell cultures the oligomers are
toxic whereas in most cases amyloid fibrils and Aβ monomers are not. When oligomers are visualised under electron or atomic force microscopes they are heterogeneous, including spheres, beads-on-a-string and doughnuts, but it seems that the spherical species are most toxic. Toxic oligomers may also be specifically detected, in vitro and in vivo, using rabbit antisera raised against Aβ immobilised on gold beads. The antiserum, described by Kayed and colleagues, binds specifically to small toxic aggregates of Aβ and neutralises their toxicity, in contrast the serum fails to detect monomeric or fibrillar forms of Aβ. Subsequent work has shown that the antiserum recognises an epitope on Aβ oligomers that is common to the oligomeric aggregates of a range of pathological proteins. The interesting corollary of this observation is that a common structural motif predicts a common mechanism of toxicity. This prediction is supported by work by Bucciantini et al. showing that oligomeric aggregates of a non disease related protein can elicit toxicity similar to that of Aβ oligomers in cell culture. Further work done in cell culture by Demuro and colleagues has shown that a shared ability to disturb membrane conductivity may underlie at least part of the toxicity of soluble protein aggregates.

However the hypothesis that soluble aggregates of Aβ represent a stable neurotoxic species has had to be reconsidered in the light of recent work showing that it is the ongoing process of aggregation that is toxic. It seems now that the soluble aggregates may simply be an efficient seed that can promote further addition of Aβ monomers. In their recent study, Wogulis and colleagues showed that, as expected, neither monomeric nor fibrillar Aβ were toxic to human or rat neuronal cell cultures. Their novel observation was that pre-treatment of cells with fibrillar Aβ, followed by a wash to remove unbound fibrils, primed the cells to die when they were subsequently treated with monomeric Aβ. The stability of the interaction of the fibrils with the cells was a surprise; following exposure to fibrils for only one hour the cells were still sensitized to the toxic effects of monomeric Aβ one week later.

With emphasis being placed on the oligomeric aggregates and the initial stages of the aggregation process, the mature plaques and tangles are increasingly being viewed as tombstones of pathological protein aggregation. Indeed there is evidence from cell-based models of Parkinson’s disease that inclusions may be protective, reducing the rate of apoptosis possibly by providing a sink for the disposal of toxic oligomers.

Chapter 6 - The spatial patterns of β-amyloid (Aβ) deposits and neurofibrillary tangles (NFT) were studied in areas of the cerebral cortex in 16 patients with the late-onset, sporadic form of Alzheimer’s disease (AD). Diffuse, primitive, and classic Aβ deposits and NFT were aggregated into clusters; the clusters being regularly distributed parallel to the pia mater in many areas. In a significant proportion of regions, the sizes of the regularly distributed clusters approximated to those of the cells of origin of the cortico-cortical projections. The diffuse and primitive Aβ deposits exhibited a similar range of spatial patterns but the classic Aβ deposits occurred less frequently in large clusters >6400 μm. In addition, the NFT often occurred in larger regularly distributed clusters than the Aβ deposits. The location, size, and distribution of the clusters of Aβ deposits and NFT supports the hypothesis that AD is a 'disconnection syndrome' in which degeneration of specific cortico-cortical and cortico-hippocampal pathways results in synaptic disconnection and the formation of clusters of NFT and Aβ deposits.

Chapter 7 - Disorder of consciousness is not an all-or-none phenomenon but it rather represents a continuum. Alzheimer’s disease (AD) is the most common cause of dementia
Preface

among people aged 65 and older, and patients are frequently unaware of the importance of their cognitive deficits. Vegetative state (VS) is a clinical entity with a complete lack of behavioural signs of awareness, but preserved arousal. Both clinical entities share a certain level of consciousness alteration, and a certain similarity in brain metabolic impairment. Here, we review differences and similarities in brain function between these two types of disorders of consciousness, as revealed by functional neuroimaging studies.

Chapter 8 - Mild Cognitive Impairment (MCI) describes older adults whose cognitive and functional status is considered in-between normal cognitive aging and dementia. MCI is an heterogeneous entity with a number of subtypes each with a different neuropsychological profile. The MCI amnestic type is the better known of the subtypes and many patients with this clinical and cognitive profile will develop Alzheimer’s disease. Although the amnestic MCI concept emphasizes memory loss, other cognitive functions are frequently affected, namely semantic fluency, attention/executive functions, visuo-spatial abilities and language comprehension.

MCI criteria make use of scores in delayed recall of episodic memory tasks to establish the presence of memory impairment. Poor delayed recall can, however, reflect deficits in distinct memory processes. Difficulties in the learning process of MCI patients have also been documented. During the acquisition of semantically structured lists of words, these patients employ less semantic clustering strategies than controls. However, if attention is called to the semantic structure, they can make use of it on subsequent trials in order to improve learning.

Detailed knowledge of the memory processes disturbed in MCI should contribute to the understanding of the pathophysiology of MCI, allow a more precise identification of patients with high probability of progression, and help to delineate future rehabilitation interventions in these patients.

Chapter 9 - There is substantial evidence of morphological, biochemical and molecular abnormalities in mitochondria of patients with neurodegenerative disorders, including Alzheimer’s disease (AD). The functions and properties of mitochondria might render subsets of selectively vulnerable neurons intrinsically susceptible to cellular aging and stress. However, the question “is mitochondrial dysfunction a necessary step in neurodegeneration?” is still unanswered.

This chapter presents how malfunctioning mitochondria might contribute to neuronal death in AD. Moreover, we will investigate the cause and effect relationships between mitochondria and the pathological mechanisms thought to be involved in the disease.

Chapter 10 - The improper regulation of calcium levels in neurons is proposed as a primary regulatory impairment that underlies the onset of Alzheimer’s Disease (AD). Calmodulin is a primary target of calcium ions in all human cells but has essentially been ignored as a downstream target in the onset of AD. Our lab previously has theoretically implicated calmodulin as an interacting protein for of a number of upstream proteins involved in the production of amyloid-beta peptide (Aβ), a pathogenic marker of Alzheimer’s disease (AD) and the primary element of the “amyloid hypothesis”. The first enzyme in the proteolytic processing of amyloid precursor protein (APP1) into Aβ is β-secretase (β site-amyloid converting enzyme 1 or BACE1) which was one of the enzymes identified as a putative calmodulin-binding protein. In this study we tested the effects of calmodulin, calcium and calmodulin antagonists on the in vitro activity of BACE1 to determine if it is potentially regulated by calmodulin. BACE1 enzyme activity was dose-dependently increased
by calmodulin reaching a maximum ~2.5-fold increase at 3\mu M calmodulin. Calcium (1.0mM) enhanced BACE1 activity while the calcium-chelator EGTA (10mM) inhibited it supporting a role for calcium in regulating BACE1 activity. In keeping the role of calmodulin as a regulator of BACE1 activity, five different calmodulin antagonists (trifluoperazine, W7, W5, W12, W13) each differentially inhibited BACE1 activity in vitro. The binding of BACE1 to calmodulin-agarose in the presence of calcium ions but not EGTA further supports the concept of BACE1 as a potential calcium-dependent calmodulin-binding protein.

Chapter 11 - As a result of advances in molecular biological techniques, the first mice overexpressing mutated genes associated with familial Alzheimer’s disease (AD) were engineered ten years ago. Most of the transgenic murine models replicate one key neuropathological sign of AD, namely cerebral amyloidosis consisting of parenchymal accumulation of amyloid-beta (A\beta) peptides that subsequently form plaques. Major research efforts today focus on the use of sophisticated transgenic approaches to discover and validate drugs aimed at reducing the brain amyloid load (e.g., recent immunotherapeutical attempts).

However, since the initial publications, the limitations associated with classic transgenic (APP and APP/PS1) models have become apparent. First, induction of AD-related brain lesions in genetically modified mice mimics, through parallel causal mechanisms, the physiopathology of familial forms of AD; however, the relevance of such transgenic mice in modeling the most prevalent forms (sporadic late-onset) of AD remains largely uncertain. Second, the neuropathological phenotype of mice bearing human mutated transgenes is largely incomplete. In particular, neurofibrillary alterations (tangles) are not reported in these models.

Transgenic mice nonetheless provide a unique opportunity to address different questions regarding AD pathology. Since these models do not replicate classic neurofibrillary lesions they can be used to specifically investigate and isolate the impact of the remaining brain injuries (A\beta deposition) on different aspects of the mouse phenotype. In addition, comparisons can be made between A\beta-induced alterations in mice and known features of the human pathology.

The present review questions the specific impact of A\beta brain lesions at different levels. First we describe macroscopic and microscopic neuropathological alterations (neuritic dystrophy, inflammation, neuronal loss) associated with amyloid deposits in transgenic mice. Then, modifications of the behavioral phenotype of these animals are listed to illustrate the functional consequences of A\beta accumulation. Next we describe the non-invasive methods that are used to follow the course of cerebral alterations. Finally, we discuss the usefulness of these models to preclinical research through examples of therapeutical trials involving AD drug candidates.

Chapter 12 - Cyclooxygenase 2 (COX-2) is one of the main enzymes involved in inflammation and a major player in prostaglandin synthesis. There exists data that suggest a potential role of COX-2 in Alzheimer’s disease (AD) pathogenesis. AD is the most prevalent form of dementia affecting 10% of individuals over the age of 65 and 50% of individuals over 85 years of age and is characterized by the presence of beta-amyloid (A\beta) deposits and neurofibrillary tangles (NFT) comprising of hyperphosphorylated tau. A\beta peptides have been shown to trigger inflammation and to stimulate COX-2 activity in various cell types including neurons, glia (microglia and astrocytes) and cerebrovascular cells. Several epidemiological studies have shown that the use of non-selective COX inhibitors are associated with reduced
risk of developing AD. COX-2 inhibitors have also been shown to alter AD pathology and ameliorate some behavioral impairment in transgenic mouse models of AD. Furthermore, in these mouse models, it has been shown that COX-2 inhibitors may influence APP processing. More studies are required to determine whether COX-2 inhibitors have beneficial or detrimental effects on the treatment of AD.

Chapter 13 - Abnormalities of brain metal homeostasis in Alzheimer’s disease (AD) could contribute to set up chemical conditions where β-amyloid (Aβ) toxicity and deposition are promoted. Recent studies, some also in vivo, have shown the possible implication of copper in AD pathogenesis. In particular, evidence collected in the last five years showed that abnormalities in copper distribution deriving from blood stream variations, or as a consequence of aging, correlate with functional or anatomical deficits in AD. Serum copper increases specifically in AD and its assessment may help to non-invasively discriminate AD from normalcy and vascular dementia. Moreover, changes in distribution of the serum copper components, consisting of an increase of a copper fraction not related to ceruloplasmin, seem to be characteristic of AD and possibly implicated in the pathogenesis of the disease.

Chapter 14 - Neurodegenerative diseases, such as Alzheimer’s disease (AD) and prion diseases (PDs), are among the most serious threats to human health. Although the pathogenetic mechanisms of these diseases are not very clear, it is widely accepted that transition metal ions (e.g., copper ions) and reactive oxidative species (ROS) are implicated in the pathogenesis of AD and PDs. As a result, there is growing interest in using metal chelators and antioxidants to combat both diseases. Some metal chelators have showed promising preventive effects on AD and PDs. For instance, desferrioxamine, clioquinol and D-( -)-penicillamine are effective to prevent AD in vitro and/or in vivo and D-( -)-penicillamine can delay the onset of PD in mice. As to antioxidants’ effects, although convincing clinical evidence is still lacking, some modest therapeutic effects on AD and PDs have been observed for antioxidant combinations.

Considering the preliminary success of metal chelators in treating AD and PDs and the fact that some superoxide dismutase (SOD) mimics are metal chelates, we proposed a new strategy to combat these diseases. That is, using SOD-mimetic ligands to chelate copper ions, then the chelates will hold radical-scavenging potential, which may lead to better clinical effects than pure metal chelators. It is interesting to note that this strategy is supported by recent in vitro experimental findings that copper chelators whose copper complexes have high SOD-like activity are potential anti-prion drug candidates. To evaluate the potential of existing copper chelators as anti-Alzheimer and anti-prion drug candidates, we attempted to compare the copper-binding ability and SOD-like activity of various chelators and derived chelates by theoretical calculations. The results may help screen new anti-Alzheimer and anti-prion drugs.

Chapter 15 - Psychosis and behavioral problems are very common in patients with dementia and the burden this causes caregivers cannot be overstated. Behavioral problems in dementia are the leading reason that families place dementia patients in facility settings, yet facilities themselves are often overwhelmed by such behaviors. No less important, patients suffer when they feel agitated, psychotic or combative and the humane treatment of dementia patients includes treating their symptoms for quality of life.

Currently, there are no FDA approved treatments for dementia with psychosis or behavioral disturbance. Atypical antipsychotics have been prescribed for these behaviors. They had been considered to have a better side effect profile compared with typical
antipsychotics, with lower rates of adverse effects such as tardive dyskinesia, extrapyramidal symptoms and orthostasis. However, recent concerns including increased risk of cerebrovascular adverse events and death have resulted in an FDA warning, bringing into question their use in the demented population.

However, the research examining efficacy and safety of treatment of such patients has been fraught with difficulty. The main problem is that dementia with psychosis and behavioral disturbance is a heterogeneous group of patients, not a single disorder. Treating dementia patients with behavioral problems as if they have a single diagnosis that can all be treated by a single type of medicine is a mistake. Unfortunately, most studies examining treatment of behavioral disturbance in dementia have been designed in this way.

Chapter 16 - Immunization strategies which aid in the clearance of beta-amyloid (Aβ) plaques have raised new hopes for the treatment of Alzheimer’s disease (AD). Two particularly promising passive immunization therapies currently being investigated include intravenous immunoglobulins (IVIG) containing Aβ antibodies and specifically developed monoclonal antibodies for Aβ. These Aβ antibodies may reduce amyloid accumulation in the brain by binding to the amyloid peptide and drawing it in through the blood-brain barrier for subsequent removal from the capillaries. However, as this strategy aims at removing extracellular amyloid through cerebral vessels, a redistribution of amyloid pathology may manifest as increased cerebral amyloid angiopathy (CAA). CAA occurs when Aβ becomes embedded in the walls of cerebral vessels associated with weakening of the vessel walls. Antibody mediated Aβ clearance from the parenchyma could significantly increase the Aβ burden in the vessel lumen and wall, therefore increasing the risk of vessel rupture and hemorrhage. This chapter will review the current literature on Aβ immunotherapy for AD and explore the mechanisms as well as possible risks of amyloid clearance treatment, particularly cerebral amyloid angiopathy.

Chapter 17 - Aims: The objective of the study was to provide observational clinical data on psychotropic drugs used in older people with mental illness.

Method: This was an observational, single-centre, one-week prevalence study of psychiatric symptoms, disorders and psychotropic/antidepressant drug use in older people with mental illness cared for by the South West people Yorkshire Mental Health NHS Trust (Wakefield Locality), UK. The clinical assessment included completion of the Psychosis Evaluation Tool for Common use by Caregivers.

Results: A total of 593/660 older patients with mental illness (mean±SD age, 76±8.1 years) were assessed). 44.5% had dementia (excluding vascular dementia) and 33.7% had a mood disorder. Of the total, 20.4% did not receive CNS active medication and 46.2% of patients were prescribed an antidepressant. Antidepressants were commonly prescribed where the primary diagnosis was not depression including vascular dementia (31%), dementia (26.1%), schizophrenia and related disorders (26.2%) and anxiety disorders (51.5%). SSRIs were the most commonly prescribed drugs (63.2%) followed by TCAs (22.4%), venlafaxine (9%), mirtazapine (3.2%), reboxetine (1.8%) and phenelzine (0.36%). The single most commonly prescribed drug was paroxetine (n=77) which accounted for 27.7% of all prescriptions. Medications were well tolerated but some patients prescribed a TCA received relatively small doses. Patients with non-vascular dementia received a significantly lower dose of paroxetine compared with other diagnostic groups (F=3.14, p<0.02) though this was still within the recommended/therapeutic range.
Conclusions: Antidepressants are commonly used in older people with mental illness including dementia, schizophrenia and anxiety disorders as well as for patients with a primary diagnosis of depression. Antidepressants are generally well-tolerated and patients were broadly satisfied with their medication. The evidence for the use of low dose TCAs in older people remains controversial and further work is needed in this area.

Declaration of interest: None.

Chapter 18 - In the brain cystatin C is synthesized by the choroid plexus and leptomeningeal cells, and it is localized in glial cells and in neurons. Its physiological high concentration in the cerebrospinal fluid (CSF) of the central nervous system and its proliferative effect on neural rat stem cells strongly suggest that cystatin C could exert a trophic function in the brain. Acute and chronic neurodegenerative processes induce an increase of cystatin C expression levels, mainly in activated glial cells. In brains from Alzheimer disease (AD) patients neuronal concentration of cystatin C protein is increased and its association to beta-amyloid peptide (A-beta) was revealed. A direct interaction of cystatin C and A-beta, resulting in an inhibition of amyloid formation, was demonstrated. An involvement of cystatin C in the pathogenesis of AD was further suggested by genetic studies in which the allelic haplotype B in cystatin C gene (CST3), determining an Ala25Thr substitution in the signal peptide, was associated with risk to develop late-onset AD. The B/B haplotype is specifically associated to highly reduced levels of extracellular cystatin C. In this view, the molecular correlate of the genetic risk conferred by cystatin C B variant could be the reduction in cystatin C secretion, which may result in A-beta formation and deposition. Alternatively, a reduced secretion of this protein could cause an impairment in neuroregeneration in response to brain damage.

Chapter 19 - One century has passed since the discovery of Alzheimer’s disease (AD), however, there has been no effective therapeutics to the disease. Since multiple factors are involved in the pathogenesis of AD, finding multipotent agents that can hit the multiple targets implicated in the disease is attracting more and more attention. Recently, accumulating evidence indicated that quercetin, a flavonoid abundant in fruits and vegetables, is a multipotent anti-AD agent. It can block Aβ- or τ-aggregation with IC_{50}s of < 1 μM and inhibit monoamine oxidases A and B (MAO A and MAO B) with IC_{50}s of 0.01 μM and 10.89 μM, respectively. Besides, quercetin is an efficient inhibitor for butyrylcholinesterase (BChE, a recently recognized potential target for treating AD) with an IC_{50} of 1 μM. Of course, quercetin is also an excellent antioxidant, both as reactive oxygen species (ROS) scavenger and transition metal chelator. As quercetin is highly bioavailable and can pass through the blood-brain barrier (BBB), it is highly possible to be responsible for the benefits of fruit and vegetable juices to AD. However, considering the fact that the current strategy in the fight against AD depends largely on inhibiting acetylcholinesterase (AChE), it is of interest to explore the AChE- inhibitory potential of quercetin.

Chapter 20 - Alzheimer's disease (AD) is a group of disorders involving the areas of the brain that control thought, memory, and language. AD is the most common form of dementia among the elderly. Almost four million Americans and eight million more worldwide suffer from AD; after the age of 65, the incidence of the disease doubles every five years and, by the age of 85, it affects nearly half of the population. Currently approved Alzheimer's therapies primarily treat the disease symptoms but do not reverse or slow down the disease progression. The increasing awareness of the diverse factors involved in the onset of AD has outlined new
paths of research for prevention and pharmacological treatments. A pivot clinical trial using Abeta1-42 immunization (AN1792) on AD patients showed a possible therapeutic effect, in line with previous experiments using animal models; however, the trial was interrupted because of meningoencephalitis probably due to the activation of T-cells and microglia, in 6% of participants. Although no significant amelioration of cognitive dysfunction was observed, CSF tau decreased in anti-AN1792 antibody responder patients. A MRI study on AD patients with immunotherapy demonstrated decreased volume of neuronal tissue including hippocampus, which is unrelated to worsening cognitive dysfunction; this shows a possible amyloid removal by immunootherapy. Another approach to observe the decrease of Abeta-associated amyloidogenesis is the inhibition of Abeta aggregation and its clearance.

In this commentary, the Authors express their opinion regarding the Questio of AZD-103 (scyllo-cyclohexanehexol) and AD concomitantly with the publication of the paper by McLaurin J et al. The findings in the Nature Medicine publication show that oral treatment of AZD-103 (scyllo-cyclohexanehexol) reduces accumulation of amyloid beta and amyloid beta plaques in the brain, and it also reduces, or eliminates, learning deficits in an AD transgenic mouse model. Transition Therapeutics Inc. (Canada) is pursuing the clinical drug development of AZD-103 in an expedited manner and it has also announced that dosing with AZD-103 has commenced in Phase I clinical trial. The Phase I trial is a single blind, randomized, placebo controlled study in which healthy volunteers will receive placebo or increasing acute doses of AZD-103. The primary aim of the trial is to evaluate AZD-103 safety, tolerability, and pharmacokinetics.

Chapter 21 - Brain inflammation is an underlying factor in the pathogenesis of Alzheimer’s disease (AD) and epidemiological studies indicate that sustained use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of AD and may delay its onset or slow its progression. Nevertheless, recent clinical trials have shown that NSAIDs do not alter the progression of AD. Neuroinflammation occurs in vulnerable regions of the AD brain where highly insoluble β-amyloid (Aβ) peptide deposits and neurofibrillary tangles, as well as damaged neurons and neurites, provide stimuli for inflammation. To elucidate the complex role of inflammation in neurodegenerative processes and the efficacy of NSAIDs in AD we developed an animal model of neuroinflammation/neurodegeneration in vivo. An “artificial plaque” was formed by injecting aggregated β-amyloid peptide (Aβ(1-40) or Aβ(1-42)) into the nucleus basalis magnocellularis (NBM) of rats. We investigated several aspects of the neuroinflammatory reaction around the “artificial plaque” such as microglia and astrocyte activation, production of proinflammatory compounds, activation of cyclooxygenase-2 (COX-2), p38 Mitogen Activated Protein Kinase (p38MAPK) and induction of inducible Nitric Oxide Synthase (iNOS). Finally, degeneration of cortically projecting cholinergic neurons was also evaluated by means of immunohistochemistry and microdialysis. We examined whether the attenuation of brain inflammatory reaction by NSAIDs and NO-donors may protect neurons against neurodegeneration. The data reported in this review show that in in vivo model of brain inflammation and neurodegeneration, the administration of NSAIDs and NO-donors prevent not only the inflammatory reaction, but also the cholinergic hypofunction. Our data may help elucidating the role of neuroinflammation in the pathogenesis of AD and the ability of anti-inflammatory agents to reduce the risk of developing AD and to slow its progression.