

# What advancements in clinical neurosciences need to occur in the next 10 years?

## DISCUSSION STARTERS

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### ABSTRACT

From the inception of clinical neuroscience, scientific breakthroughs have enhanced our knowledge of how certain pathologies impair the function of the nervous system. Alzheimer's disease (AD) is a perpetual challenge in modern clinical neuroscience due to the ageing population which makes individuals increasingly susceptible to AD. AD is the most common form of dementia globally and the number of people living with dementia worldwide has more than doubled from 1990 to 2016 which warrants prompt advancements in clinical neuroscience to develop effective interventions that may halt or delay disease progression. This narrative review recommends further investigation into the effectiveness of monoclonal antibody treatment in patients with early AD and the utilisation of optogenetics to understand the complex aetiology of AD. In the next ten years, it is hoped that the recommendations in this article will come to fruition and facilitate further advancements in clinical neuroscience to develop therapies that delay the onset and even reverse the somatic manifestation of AD that currently has a poor prognosis.

## INTRODUCTION

From the inception of clinical neuroscience, scientific breakthroughs have enhanced our knowledge of how certain pathologies impair the function of the nervous system. Clinical neuroscience now plays a pivotal role when informing the scientific community about the developments in diagnosis, prognosis, and treatment of neurological disorders.

Alzheimer's disease (AD) is a perpetual challenge in modern clinical neuroscience due to the ageing population which makes individuals increasingly susceptible to AD. The non-clinical sequelae of AD is considerable. AD is the most common form of dementia globally and the number of people living with dementia worldwide has more than doubled from 20.2 million in 1990 to 43.8 million in 2016. (1) This increase can be explained by the rise in population ageing and growth. The World Health Organisation also forecasts that the total number of people with dementia will reach 82 million by 2030 and 152 million by 2050, which highlights the exponential scale of this condition. (2) In 2019, 16 million family members and other unpaid caregivers provided an estimated 18.6 billion hours of care in the United States alone. (3) There is also a great economic cost associated with AD estimated at £23 billion a year, which is predicted to triple by 2040, and as such, (4) AD warrants prompt advancements in clinical neuroscience to develop effective interventions that may halt or delay disease progression.

The aetiology of AD is multi-faceted and not completely understood. An expanding body of evidence shows that plaque deposition is not the sole cause of AD, and instead, AB oligomers (ABOs) are the main toxins responsible for synapse dysfunction and cognitive deficits. (5) The precise mechanisms of how ABOs elicit excitotoxic effects remain indeterminate. Binding of AB aggregates to various receptors may disrupt integral neuronal activity. Though, the nature of the receptors to which they bind, and the underlying signalling pathways remain to be ascertained. (6)

This narrative review focusses on three important aspects in which major advances in clinical neurosciences are anticipated to occur within the next 10 years: The history of key discoveries relating to AD will be reviewed and the underlying pathophysiology. Most importantly, this review will explore the likely advances to occur in the understanding and management of AD.

### KEY PAST DISCOVERIES IN ALZHEIMER'S DISEASE

In 1973, AD was principally thought to be a disorder of cortical and hippocampal origin. During this period, fluctuations in acetylcholine levels were found to be significantly reduced in the cerebral cortex and subsequently in the basal ganglia neuro-circuitry of individuals with AD. (7) Cholinesterase inhibitors were predicted to be beneficial in patients with AD and are currently used as a pharmacological agent which displays mild to moderate effectiveness. The study of protein aggregates reached important milestones between 1977 and 1984 when tau, the phosphorylated protein of which constitutes neurofibrillary tangles, and the first purification of the AB-amyloid protein were identified by Cleveland et al and

Glennier et al, respectively. (8,9) Modern clinical neuroscience has established that the magnitude and locality of neurofibrillary tangle formation are highly correlated with the severity of dementia, to a greater extent than the absolute number of amyloid plaques.

In 1996 further progress was made with development of cholinesterase inhibitors which were finally approved for the management of AD. (10) From this milestone to the present day, the management of AD still involves symptomatic treatment with either cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in mild to moderate AD, or N-methyl-d-aspartate receptor antagonists (memantine) in severe AD. (11) These pharmacological agents elicit moderate benefit in cognitive function and activities of daily living in some patients, but also cause side effects in a substantial number of treated patients. It is apparent that the main limitation of these pharmacological agents is their inability to halt or slow down the underlying pathological processes in AD.

In more recent times, there has been great interest in developing novel disease modifying drugs for the management of AD. Such disease modifying drugs differ to symptomatic measures such as cholinesterase inhibitors and N-methyl-d-aspartate receptor antagonists in that they aim to disrupt specific components of the pathological processes in AD which then limits disease progression. There are currently three main classes of therapeutic intervention that target AB: 1) Inhibiting AB generation, 2) facilitating AB clearance, and preventing AB aggregation. These interventions have been tested in several clinical trials using the following modalities: modulation of B- and B-secretase to reduce AB production, passive immunization with monoclonal antibodies and active immunization to stimulate clearance of AB, and finally preventing AB aggregation with B-sheet breakers and pathological chaperone inhibitors. (12)

### CURRENT CHALLENGES IN ALZHEIMER'S DISEASE

The amyloid cascade theory suggests that neurotoxic amyloid plaques are the earliest manifestation of pathological change in AD. Current evidence shows that these aberrant amyloid plaques initiates tau protein phosphorylation, which then disseminates in an infectious manner by virtue of microtubule transport to adjacent neurons, which then culminates in neuronal death. (13) The amyloid cascade theory provides the foundation for the development of novel interventions. If correct, the theory will prove that disrupting cascade would avert neuronal loss and cognitive decline.

To counteract this pathophysiological mechanism, monoclonal antibodies have been developed as one class of therapeutic intervention. Monoclonal antibodies are synthetic antibodies made by identical immune cells that are all clones of a unique parent cell and have affinity for a single antigen. (14) Administration of monoclonal antibodies involves injection of an antibody that targets abnormal AB amyloid plaques and facilitates its removal from the brain. It has been theorised that antibody binding to amyloid leads to macrophage phagocytosis and complement activation. (15) However, this theory presupposes that enough antibodies cross the blood-brain-barrier to enter the central nervous system and bind

to the amyloid to instigate this phagocytic activity of either local microglia, or infiltrating macrophages.

The main challenge with monoclonal antibody therapy is the absence of significant clinical improvement. Numerous studies have trialled different monoclonal antibody preparations, all of which failed to improve cognitive scores in patients with mild-to-moderate disease. (16,17). It is therefore logical to suggest that monoclonal antibody therapy may display clinical benefit in the early stage of mild cognitive impairment. Despite the unfavourable clinical findings, at the molecular level biomarker results showed that bapineuzumab reduced phosphorylated tau proteins in the cerebrospinal fluid (CSF) which supports the validity of the amyloid cascade theory. (16)

There are also several adverse events of note associated with monoclonal antibody therapy. In a double-blind study by Rinne et al, they reported that 8 (22%) participants experienced headache, confusion, neuropsychiatric and gastrointestinal symptoms after taking 6 separate infusions of bapineuzumab over a period of 78 weeks. (16) However, these adverse events were typically mild to moderate in severity and transient. Given the extended duration of treatment, these adverse events may limit treatment compliance in patients with AD which in turn limits the effectiveness of monoclonal antibody therapy.

Another prominent challenge with monoclonal antibody therapy is the development of vasogenic oedema which presents clinically as amyloid-related imaging abnormalities (ARIA) during magnetic resonance imaging in several patients during the course of treatment. The exact cause of ARIAs is not completely understood but the latest data suggests that vascular amyloid protein increases cerebral vascular permeability. (18) ARIAs are strongly correlated with drug dose and apolipoprotein E e4 carriers but is also largely (approximately 78%) asymptomatic and self-limiting in approximately 78% of cases and may not require temporary treatment cessation. (19,20)

#### IMPLICATIONS FOR FUTURE RESEARCH

On the topic of monoclonal antibodies, future interventions in this promising domain should focus on investigating if the commencement of an amyloid cascade means cognitive deterioration can no longer be inhibited, or whether, in cases of advanced AB deposition, moderate AB clearance, through monoclonal antibody therapy, would be rendered ineffective. If the latter is true, then clinical neuroscientists will need to ascertain if higher doses of monoclonal antibodies would yield significant improvements in clinical outcomes whilst simultaneously limiting adverse events such as ARIAs. As such, monoclonal antibody therapy trials should be undertaken amongst patients with AD in the preclinical and prodromal phases of the disease. Yet, this recommendation is not without its own challenge as recruitment of patients in this phase is dependent on accurate and prompt diagnosis from clinicians.

The pathogenesis of AD involves progressive inflammation in the brain leading to neurodegeneration and propagation of the

metabolic abnormalities that exhibit a positive correlation with cognitive impairment. (21) A deeper understanding of the complex processes underlying the behavioural, inflammatory, and metabolic disturbances observed in AD, may promote the development of novel and effective therapies. Due to the heterogeneous prevalence of AD between men and women, gender discrepancies should also be considered when researching AD pathophysiology, as this disparity may necessitate the need for distinct treatment approaches for both cohorts. The utilisation of optogenetics, which involves the combination of both optical and genetic techniques to activate or inhibit the activity of specific cells or tissues, (22) may lead to advancements in our understanding of AD from both an exploratory and interventional perspective. Optogenetics can be employed to investigate the consequence of neuronal activity on behaviour and cognitive performance as well as to selectively regulate temporal neuronal activity with high precision for neuromodulation.

An animal study by Yang et al demonstrated that optogenetics up-regulated GluR2, NMDAR1, and mGluR5 receptors, which have a critical role in long-term potentiation and depression, resulting in neuroinflammatory inhibition and attenuation of neuronal loss in the dentate gyrus caused by AB plaques. (23) This physiological response ultimately improved working and short-term memory in the test subjects. The technique is, however, invasive and neuro-trauma is probable during the injection procedure. Hence, there is an urgent need to develop a minimally invasive procedure that exhibits acceptable safety before large scale clinical application.

#### CONCLUSION

In the next ten years, it is hoped that the recommendations in this article will come to fruition and facilitate further advancements in clinical neuroscience to develop therapies that delay the onset and even reverse the somatic manifestation of AD that currently has a poor prognosis. The prevalence and morbidity associated with AD warrants extensive research to develop treatments that improve patients' quality of life and reduce the financial burden on healthcare services worldwide. Significant progress has been made in clinical neuroscience within the past decade, yet with the exponential evolution of technology, researchers and clinicians must endeavour to transcend the current frontiers of knowledge on the diagnosis, prevention, and treatment of AD through international research collaboration and transparent dissemination of newfound knowledge to make today's research, tomorrow's standard of care.

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