AD and its comorbidities: an obstacle to develop a clinically efficient treatment?

John Baker, Jonathan M Schott*

Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK

* Corresponding: j.schott@ucl.ac.uk

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Abstract

Whilst the development of new drugs designed for the treatment of Alzheimer's disease (AD) has been widely publicised, we do not yet have treatments that are proven to slow the progression of AD. The decision taken by the US Food and Drug Administration (FDA) to grant a licence for the use of aducanumab, based on the premise that β-amyloid removal would result in downstream benefits rather than demonstration of cognitive efficacy per se contrasts with that made by the European Medicines Agency (EMA), who declined to grant a licence, citing lack of evidence of clinical improvement, and a failure to demonstrate that the treatment was sufficiently safe. Multiple factors have complicated the search for new and effective treatments for the management of AD. It is a complex neurodegenerative condition in which multiple comorbidities are common in the affected population. However, such conditions are commonly exclusion criteria in clinical trials for new treatments. Here we discuss how some of these comorbidities impact the develop of clinically efficient treatments for AD. Firstly, we will examine what is meant by AD, and how definitions of this condition have changed and continue to evolve. Secondly, we describe some of the most important comorbid conditions accompanying and in some cases mimicking AD. Finally, we will examine how the inclusion, or exclusion, of these conditions from AD research may have had an effect on treatment trials, the implications of co-morbidities on "real-life" use of novel therapeutics especially when these have been trialled in patients with relatively pure disease, and how clinical trials may need to adapt to account for comorbidities in the future.

Keywords

Alzheimer's disease, comorbidities, neuropathology, neuropharmacology, clinical trials

Introduction

We are entering an age where new treatments for Alzheimer's disease (AD) and other neurodegenerative disorders are edging closer to reality. However, despite the proliferation of news headlines and articles discussing the latest developments, we do not yet have treatments that are proven to slow the progression of AD. While the US Food and Drug Administration (FDA) controversially granted a licence for the use of Aducanumab – a monoclonal antibody targeting β-amyloid, one of the pathological hallmarks of AD – this decision under an accelerated approvals pathway was based on the premise that β-amyloid removal would results in downstream benefits rather than demonstration of cognitive efficacy per se. The European Medicines Agency (EMA) declined to grant a licence citing lack of evidence of clinical improvement, and a failure to demonstrate that the treatment was sufficiently safe (1-5). While other therapies targeting β-amyloid and a range of other targets are in varying stages of development (Figure 1), the field of AD therapeutics has been littered with developments which have met dead-ends, trials which have not led to significant improvements for patients, and/or side effects which have outweighed any benefits.

(Insert figure 1)

Figure 1. Agents in clinical trials for treatment of Alzheimer's disease in 2021. Reproduced from Cummings et al. (2021) (6)

There are many reasons why the development of effective treatments for AD has proven so difficult. The pathophysiological pathways which lead to the development of AD are yet to be fully elucidated but almost certainly represent a complex interplay of genetic, epigenetic and

environmental elements acting on an ageing brain that, in some people, lead to the accumulation of AD pathologies, which in turn in some individuals will result in cognitive impairment. AD is a condition with a prolonged pre-clinical phase: different pathological processes are likely to dominate at different stages and may respond best to therapies before symptoms start. Despite the development of biomarkers capable of detecting some pathologies during life, we do not yet have diagnostic modalities for all of the relevant processes or the ability to apply these at scale at reasonable cost. Importantly, AD commonly does not occur in isolation: patients with AD frequently have other comorbid conditions which serve to further muddy the diagnostic and therapeutic waters. And as trials of potential therapies for AD commonly exclude individuals with other conditions which may cause cognitive impairment, this further complicates the generalisability of any findings to broader "real-world" populations.

Here we discuss how some of these comorbidities impact the develop of clinically efficient treatments for AD. Firstly, we will examine what is meant by AD, and how definitions of this condition have changed and continue to evolve. Secondly, we describe some of the most important comorbid conditions accompanying and, in some cases, mimicking AD. Finally, we will examine how the inclusion, or exclusion, of these conditions from AD research may have had an effect on treatment trials, the implications of co-morbidities on "real-life" use of novel therapeutics especially when these have been trialled in patients with relatively pure disease, and how clinical trials may need to adapt to account for comorbidities in the future.

What is Alzheimer's Disease?

At first sight a seemingly trivial question, a key initial step for any clinical trial is to determine what is meant by AD – and how differing definitions may impact on who is entered into a clinical trial, the outcomes of that trial, and the wider extrapolation of any clinical trial findings in settings where AD is diagnosed differently, e.g. in memory clinics and in the community.

Early criteria for AD were based on typical symptoms, the presence of dementia, and exclusion of other causative pathologies (7). These clinical criteria had limited accuracy – with sensitivities of between 70.9% and 87.3% and specificities ranging from 44.3% to 70.8% compared to gold standard pathological diagnoses (8). Clinical trials relying on these criteria would, naturally, therefore recruit significant numbers of patients without AD pathology both limiting the chance of success and risking exposing individuals unlikely to be benefit from treatment to potential side-effects. This was demonstrated in the (negative) anti-amyloid bapineuzumab and solanezumab Phase 3 trials which did not require evidence for β-amyloid deposition for entry: of those with mild AD who *did* have amyloid PET imaging, ~25% did not have evidence for brain amyloid deposits, and so almost certainly did not have AD (9).

In the last decade, several different criteria for AD have been proposed – some have already entered clinical practice; others are limited to research settings. In general, these have attempted: (1) to move the diagnostic phase back from requiring patients to be demented, allowing for individuals to have milder and sometimes isolated cognitive deficits (mild cognitive impairment – MCI) and in some (research) cases allowing for preclinical (asymptomatic) diagnosis; and (2) to increase the specificity of an AD diagnosis through the use of supportive biomarkers, reflecting various aspects of AD pathology. As our

understanding both of the pathogenesis of AD and of neurodegenerative biomarkers continues to evolve, it appears likely that these definitions will see further iterations.

The National Institute on Aging (NIA) diagnostic guidelines for Alzheimer's Disease (2011) were developed at a time when the use of molecular biomarkers for the diagnosis of AD was in a relatively embryonic stage (10). As a result, biomarkers are largely considered as supportive of, rather than a requirement for, diagnosis. In this system, where a diagnosis of possible AD or probable AD is considered based on the clinical presentation, additional subcategories of probable and possible "AD dementia with evidence of the AD pathophysiological process" are proposed, where the options for evidence include measures of key aspects of AD pathology, i.e. β-amyloid accumulation, measured using cerebrospinal fluid (CSF) analysis or β-amyloid PET; tau accumulation assessed by CSF measures of phosphorylated tau or tau PET; and "biomarkers of downstream neuronal degeneration or injury" – assessed using structural MR imaging or FDG-PET imaging. These diagnostic criteria also acknowledge the potential for co-pathologies and comorbidities, recognising that the label of "probable" AD dementia should not be applied where there is substantial concomitant cerebrovascular disease, or core/prominent features of other neurodegenerative dementias e.g. dementia with Lewy bodies, behavioural variant frontotemporal dementia, variant primary progressive aphasia, or nonfluent / agrammatic variant primary progressive aphasia; evidence for another concurrent, active neurological disease; or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition. Instead, it is recommended that such cases be classified as "possible" AD dementia (10).

The International Working Group (IWG)-2 criteria (2014, updated in 2021) further develop the AD diagnostic process by giving equal weight to the clinical phenotype and in-vivo evidence of AD pathology (Figure 2) (11, 12). Separate criteria for atypical AD (posterior variant AD, logopaenic variant AD, frontal variant AD and Down's syndrome variant of AD), mixed AD (cerebrovascular disease and Lewy body disease) and preclinical AD states are also provided.

These criteria recognise the variability of AD presentations – which in themselves might theoretically respond differently to different therapeutics agents – and the possibility of multiple pathologies coexisting within the same patient. The acceptance that AD pathology can occur at the same time as cerebrovascular disease and Lewy body pathology does however pose questions for studies looking to trial treatments for AD: the degree to which these multiple pathologies are responsible for any cognitive impairment or decline in these participants is difficult to quantify, leading many studies to exclude participants where this may occur; conversely some studies may be reticent to include participants with "possible" AD, based on the NIA criteria for the reasons given above.

(Insert figure 2)

Figure 2. IWG-2 criteria for the diagnosis of AD. Reproduced from Dubois et al (2014) (11)

Reflecting the rising use and availability of AD biomarkers and looking to streamline the diagnostic process, the research framework (not currently in clinical use) proposed an A/T/N classification scheme (2016) whereby biomarkers of Amyloid ("A" using PET or CSF), Tau ("T" using PET or CSF p-tau) and Neurodegeneration or neuronal injury ("N" using FDG PET,

structural MRI, CSF total tau) are each classified as positive or negative (+/-) (13). These criteria also allow for a fourth variable ("C") to denote clinical features / clinical status, accepting that these will not fall as neatly into + or – categorisation. Whilst these criteria recognise the utility of biomarker-based tests in identifying cases of AD, and in determining whether a dementia is likely to be due to AD, they do not necessarily identify where multiple pathologies or comorbidities are present. For example, where amyloid exists alongside other pathologies or where age related changes exist *without* underlying dementia (A+/T-/N- is classified as "intermediate likelihood; probable AD dementia; based on clinical criteria", and A-/T+/N- is "probable AD dementia; based on clinical criteria") (13). As a result, it is possible that a treatment study recruiting purely on these criteria, would admit participants with a previous head injury, a history of stroke or epilepsy if a more detailed medical history was obtained, and it is likely that these participants would not respond as well to any treatments designed to target underlying AD pathology.

All three sets of criteria outlined above recognise that a diagnosis of AD is not always straightforward, that AD pathology can often coexist with other neurodegenerative conditions, and that the presence of other comorbidities can lessen the degree to which we can be sure of an AD diagnosis. However, as we will see, these comorbidities are common, and complicate a significant proportion of the AD burden in the community. These criteria are also premised upon the fact that the increasing availability of biomarker evidence gives further confidence in a diagnosis of AD, but importantly none of the biomarkers are 100% sensitive or 100% specific. This becomes a particularly thorny issue when it comes to binarizing individuals as "positive/negative" based on quantitative biomarkers (such as CSF Aβ and tau), where decisions have to be made on cut-off points to decide what is "normal"

and what is not. This leaves those looking to establish treatment trials with a difficult conundrum – include only those in whom a diagnosis of AD is *most* certain and where comorbidities are not present, potentially reducing heterogeneity and increasing the power to detect efficacy, but inevitably excluding a proportion of the AD population; or have a broader definition of AD, accepting that cases of 'pure' AD are rare, but in doing so potentially limit the efficacy of potential treatments through their inability to resolve non-AD pathologies.

Comorbidities in the AD population

In order to understand whether comorbidities in people with AD have been an obstacle in the development of effective treatments for it, we must look more closely at what these comorbidities are: what other conditions commonly occur in patients with AD?

Vascular disease

It has long been understood that a range of cerebrovascular changes not only can be found in the brains of those with AD (14-16), but in fact are the rule rather than the exception. A developing understanding of the relationship between cardiovascular disease and neurodegeneration has shown that midlife hypertension is a modifiable risk factor for the development of dementia (17, 18). The extent to which this relationship is driven by AD pathology or through separate vascular pathways that act synergistically with "conventional" AD pathology to impact on cognition is unclear: significant vascular pathology can be evident without leading to AD, and many patients with AD will have neither significant evidence of vascular changes nor risk factors for cardiovascular disease when their history is explored.

Determining the degree to which vascular changes found on the scans of people with concomitant AD pathology impact upon their cognitive function and the decline in this over time has proven difficult and remains unclear (19).

A broad range of cognitive impairments have been described in the setting of stroke, with an expected increase in the severity of cognitive impairment relative to the degree of vascular injury observed, and the regions affected (20, 21). Moreover, rather than purely a cause of static cognitive impairment, stroke has been shown to be a risk for ongoing cognitive decline in some (22, 23). In their study of 1488 patients (mean age 66.3 years) Lo et al., describe significantly faster cognitive decline in the post-stroke setting, vs controls in terms of global cognition and all cognitive domains except executive function (23). As both stroke and AD risk are age associated, it is inevitable that the two conditions will commonly overlap in the community, if not in clinical trials.

The spectrum of vascular changes seen in patients with AD includes not only conventional small vessel disease but also microbleeds, and other features of amyloid angiopathy (24). Increasingly, vascular dysfunction is recognised as a core feature of AD, and a potential driver of cognitive dysfunction in AD patients and is related mechanistically to the deposition of amyloid and tau in affected areas (25). Interactions between vascular dysfunction and conventional AD pathologies may occur through several pathways including altered levels of vascular endothelial growth factor (VEGF) (26, 27), and other alterations to the blood brain barrier and neurovascular unit (16, 28, 29). The presence of microbleeds is also related to the incidence of potential side effects associated with amyloid targeting antibodies - ARIA-E (Amyloid Related Imaging Abnormalities -Edema) and ARIA-H (Amyloid Related Imaging

Abnormalities – Haemorrhages. ARIA-E and ARIA-H are commonly observed in amyloid immunotherapy trials including in the EMERGE and ENGAGE phase 3 studies of aducanumab where 41.3 percent of patients experienced ARIA during the placebo-controlled period, with the risk highest in APOE-ε4 carriers (30). Whilst ARIA-H was less common, brain microhaemorrhages were seen in an increased rate in those treated at high dose (19.1%) vs the placebo group (6.6%). Symptoms associated with ARIA ranging from headache to epileptic seizures and encephalopathy (30, 31). While there is ongoing debate as to the safety or otherwise of ARIA, the potential for side effects related to amyloid removal remains a significant cause for concern both in clinical trials, and perhaps even more so as/when these medications are used in a clinical setting where more comorbidities are to be expected.

Other neurodegenerative pathologies

Post-mortem studies of patients with a clinical diagnosis of AD made during life have frequently identified other neurodegenerative pathologies, that may either co-occur with AD pathologies (32, 33), or in some cases, e.g. Limbic-predominant age-related TDP-43 encephalopathy (LATE), mimic AD (34). In terms of coincidental or concurrent pathologies, it is well known that Lewy Bodies are very often seen in patients with AD: Hamilton et al found Lewy bodies in 50-60% of cases of sporadic AD (35), and Lewy body pathology is also observed in some patients with "pure" autosomal dominant familial AD (36). The reverse is also true – patients diagnosed with other neurodegenerative diseases including dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration, often have a degree of Alzheimer's pathology when their brains are examined post-mortem (37); this is particularly the case in DLB, where in one series 80% of patients with DLB had increased amyloid load (37). The existence of co-pathologies inevitably complicates trials of potential treatments for AD

particularly when, and in contrast to AD, we do not have biomarker that can reliably identify the presence of most non-AD neuropathologies, including a-synuclein and TDP-43. This makes it difficult to know whether any trial participant has 'pure' AD (if this even exists) or not. And as/when this were possible, it remains uncertain how to determine the relative contributions of each pathology to the patient's clinical presentation, and to know if data in relatively selected clinical trial populations can be extrapolated to real world populations where multiple pathologies are more likely to coexist.

To complicate matters further, the direct relationship between Alzheimer's pathology (the demonstrable evidence of amyloid-β and tau deposition, in a characteristic distribution) and the clinical manifestation of AD is less clear than it once was. We now recognise the existence of a number of non-AD tauopathies which may influence cognition, including Primary Age Related Tauopathy (PART) (38), Aging Related Tau Astrogliopathy (ARTAG) (39) , Chronic Traumatic Encephalopathy (CTE), Globular Glial Tauopathy (GGT) and Argyrophilic Grain Disease (AGD) (figure 3); and that a significant proportion of healthy elderly individuals accumulate Aβ pathology (40). Taken together, these findings challenge the concept of a homogeneous group of individuals with a single form of "AD" and underscore the complexities of AD therapeutics, and the challenges associated with recruiting to, and interpreting the results of, clinical trials.

(Insert figure 3)

Figure 3: primary tauopathies. Slide courtesy of Dr Zane Jaunmuktane, UCL Queen Square Brain Bank for Neurological disorders

Epilepsy

Much like AD, the prevalence of epilepsy increases in later life (41). Moreover, extensive research has identified bidirectional links between dementia and epilepsy, such that patients affected by epilepsy commonly report memory impairments and have an increased risk of developing dementia, and those with dementia have an increased risk of developing epileptic seizures. The reasons for these associations are becoming increasing understood (42-44).

People with AD have an increased risk of developing epilepsy. The degree of this increased risk remains unclear and has been widely debated, with studies estimating the prevalence of seizures in AD varying anywhere from 0.5% to 64% (45-48). There is extensive evidence of a relationship between AD pathology and epileptic seizures. Originating from animal models of AD pathology, it has been shown that the deposition of amyloid is associated with neuronal hyperexcitability, in some cases leading to epileptic seizures (49, 50). Epileptic seizures accelerate the propagation of tau pathology throughout the brain, hastening the cognitive decline in those affected (51, 52). Whilst historically epileptic seizures had been considered to be a manifestation of advanced AD, occurring only where extensive neuronal loss and atrophy had already taken place, more recent evidence has shown that seizures can occur early in the clinical course of disease; and in some patients, before cognitive symptoms develop, or a diagnosis of AD is made (53, 54).

Although both epilepsy and dementia increase in prevalence with increasing age, evidence has shown that it is the youngest patients with Alzheimer's disease who are most at risk of developing epilepsy (55). Although the prevalence of seizures in the Familial Alzheimer's

Disease (FAD) population varies depending on the underlying genetic mutation, all mutations have been shown to have an increased risk of seizures (56-58).

That cognitive complaints are among the most common symptoms reported by patients with epilepsy is well-established (59-61). In this population, these difficulties can occur for multiple reasons: as a consequence of the seizures themselves, the causes of them (tumours, hippocampal sclerosis etc.), the medications being used to treat them (particularly older treatments such as phenobarbitone and phenytoin, the use of which is more likely in older patients who may have been taking them for decades), and finally as a result of the psychological and social implications of living with a chronic and often unpredictable condition – which can result in persistent signs of both anxiety and depression, themselves causes of cognitive impairment (62, 63). Patients with longstanding epilepsy are more likely to have an increased deposition of tau identified post-mortem (64) or in surgically removed lesions in those with medically refractory epilepsy (65, 66). In many cases the hyperphosphorylated tau seen here is the same as that seen in AD, although often intermixed with other forms, such as that seen in chronic traumatic encephalopathy (66).

Head Injury

Head injury is common and often benign. Major head injury can lead to acute brain damage with longstanding cognitive sequelae, but it is likely that repeated relatively minor head injuries can induce downstream neurodegeneration, being linked both to AD and to the development of other neurodegenerative disease, most notable chronic traumatic encephalopathy (CTE) (67). In the absence of *in vivo* biomarkers of CTE, this remains a controversial and difficult diagnosis; and while major head injuries are often exclusion criteria

for clinical trials, the possibility of non-AD pathologies related to head injury is not often considered.

Depression and Anxiety

Cognitive impairments occurring in those affected by depression are common and well described (68-70). The strength of this association is sufficient that depression in later life may be a potentially modifiable risk factor for the development of dementia (18). Investigation of the pathways that lead from depression to dementia have identified several possible mechanisms including accelerated brain ageing (71), reduced functional connectivity (72) and immune dysregulation (73). This relationship is also bidirectional. Incident depression is more common in many chronic diseases, and in this respect, AD is no different. Several studies have reported that people with AD have an increased risk of developing depression (74-76). However, despite this close relationship, randomised controlled trials frequently exclude patients where depression is present (77).

Functional cognitive disorders

Functional cognitive disorders (FCD), for a long time poorly understood and under-represented, have been gaining increased attention. These are conditions which can have enormous impacts on the functional capabilities of sufferers in their daily lives, and which require different approaches to diagnosis and treatment than those used in AD (78, 79). The degree to which FCD and AD overlap in the clinical setting is a particular issue when cognitive symptoms are mild, e.g. in MCI (78) which may be due to AD, FCD, combinations of both, or a range of other conditions (78). Distinguishing the aetiology of MCI is especially important as many clinical trials of potential treatments typically target very early disease in an attempt to

achieve maximal benefit. While targeted investigations (CSF, neuroimaging) can be used to support an underlying diagnosis of AD, their presence does not exclude FCD; and where symptoms of this nature are suspected, these must be explored in more detail and factored into possible treatment responses. Research has also shown a frequent interaction between FCD and depression, further complicating the relationship between both with Alzheimer's disease, and dementia more broadly (80).

Normal ageing

Accepting that Alzheimer's disease is increasingly prevalent in ageing populations it becomes easy to elide the pathological changes seen in the ageing brain with those that occur in the course of AD. However, AD is not 'normal ageing' and the changes which are observed in the brain as it ages are not the well-described changes described in AD, although in some cases there is an overlap. The term 'normal ageing' is often ill-defined and incompletely understood. As global populations continue to age and the proportion of people who live to see their 80^{th}, 90^{th} or even 100^{th} birthdays increases, our knowledge of ageing processes changes and the concept of what constitutes 'normal' ageing continues to evolve. The variability of brain health as we age, and the impact that this can have on cognitive performance suggests that brain ageing is a further comorbidity that should be considered in the development of clinical trials in AD.

Several long-running birth cohort studies have played a fundamental role in clarifying how cognition changes with age, and what life course factors impact on these changes (81, 82). Through their work on the NSHD 1946 birth cohort Lu et al., have shown that childhood cognitive performance (at age 8), level of educational attainment and socioeconomic position

remain predictors of cognition at age 70. However, their findings also identify an independent association of later life cognition with both amyloid deposition and white matter hyperintensity volume, confirming that cognitive decline in ageing is both multi-factorial and influenced by a range of life course factors (81). Further understanding of the trajectories of cognitive ageing has been facilitated by work with the 1936 Lothian birth cohort, in whom declining cognitive performance has been linked with declining physical performance (82), and exposure to air pollution over the life course (83). Whilst a link between mid-life hypertension and increased WMHV and smaller brain volumes at 69-71 years of age has been reported in the 1946 cohort (84), this finding had not been identified in the 1936 cohort. Although in that population higher cognitive performance in women was associated with lower blood pressure in later life (85). Ultimately it is clear that brain health in later life is a reflection of multiple factors including late life pathologies but also early life influences – some dating back as far as childhood and that these factors and the changes associated with them, have a variable impact upon cognitive performance as we age. These issues are important when it comes to clinical trials of AD, and particularly when cognitive measures are used as outcomes measures: the best that can be hoped for is to attenuate rates of cognitive decline to those of normal ageing.

Obstacles to the development of effective treatments

Having established that multiple comorbidities and multiple neurodegenerative pathologies are common amongst individuals diagnosed with clinical AD population, how might these impact the development and validation of novel treatments?

<u>Animal models</u>

Drug development is a long pathway that takes many years, involves multiple stages, and typically starts with the use of cellular and animal models of the disease in question. The complexity of AD even before the ageing brain and myriad comorbidities are considered means that it is inevitable that cellular and animal models can at best approximate rather than recapitulate the human disease. Commonly used mouse models for FAD have often resulted in (often extreme) isolated amyloid or purely tau pathology (86, 87), although latterly mouse models which exhibit multiple pathologies (such as "triple transgenic" models), have been developed to better reflect the complexity of AD (87).

Animal models of AD are typically based on FAD, harnessing the common genetic mutations responsible. FAD represents a very small minority of the total AD population, and whilst the pathology of FAD is very similar to that observed in sporadic disease, the pathophysiological processes that lead to disease in these two groups are not the same; and patients with FAD are typically younger and have fewer comorbidities. It follows that animal or cellular models produced via induction of FAD pathophysiology may differ (and potentially underestimate) the complexity of sporadic disease occurring in the milieu of an ageing human brain. Similarly, it would be impossible, in mouse models of AD to replicate the decades-long preclinical phase seen in human disease, as well as the years of disease progression, life course exposures and brain ageing which are clearly important features of disease in humans. This is not to say that these models of disease are wholly inaccurate or unhelpful. Such models have played vital roles in our understanding of AD and the development of new treatments; however, their limitations may also explain some of the many failures to convert promising treatments in animals into real-world benefits for patients.

Which therapeutic target?

The choice of model for research purposes is likely to have affected the identification of therapeutic targets and the treatments that have been developed. FAD is associated with over-production of β-amyloid and therefore animal models based on FAD demonstrate over-expression of this protein. As a result, treatments are designed to target the clearance of amyloid, and are deemed to be effective when that goal is achieved. This is at least partly true for Aducanumab, where evidence shows this has been done successfully (4). However, clinical trials have demonstrated that this change does not necessarily correlate with a commensurate degree of cognitive improvement, or even slowed decline. This is a point acknowledged by the US FDA, who conclude in their decision to approve Aducanumab, that "approval is based upon the drug's effect on a surrogate endpoint … where the drug's effect on the surrogate endpoint is expected, but not established, to predict clinical benefit" (4). In the case of solanezumab, a humanized monoclonal IgG1 antibody directed against the mid-domain of the Aβ peptide, evidence of a biomarker-targeted effect (an increase in CSF Aβ42) was again described, but again did not lead to a significant cognitive improvement within the cohort (88). Several different approaches to drug development have had a similar focus on tau deposition, on neurodegeneration, on altered neuronal excitability and on neuro-inflammation. Single target treatments such as these are unlikely to address the complexity of AD patients with multiple medical comorbidities and multiple pathologies, particularly as determining the predominant pathology can be difficult in post-mortem, let alone at the onset of a clinical trial.

Polypharmacy

Multiple medical comorbidities become increasingly commonplace in an ageing population, accompanied by a commensurate increase in polypharmacy. The nature of clinical trials in any population means that potential study participants with multiple conditions, and often taking multiple medications, are often excluded, despite representing a significant proportion of the real-world cohort. Where patients are already taking medications for which ongoing monitoring is required, such as anticoagulants, anti-diabetic treatments and thyroid medications or where a treatment effect or level can be monitored, such as antihypertensives and anti-seizure medications, it is often unclear how these treatments may be affected by a new treatment, or where they may affect the efficacy of this new treatment. This is particularly true for the use of anti-platelet and anti-coagulant treatments, in light of the increased risk of ARIA in amyloid immunotherapy studies. Polypharmacy therefore represents a significant issue in recruiting suitable patients for clinical trials and may also mean that drug effects seen in trials may not be the same when applied in real life settings when polypharmacy is likely to be much more common.

Monitoring

It is certainly possible, should it be determined that a new treatment is safe to use in the AD population, that extensive monitoring may be required, particularly in the early stages of its use. What is less clear is how well-equipped memory clinics are to adapt to these changes when they come along, as new treatments and the monitoring of them are likely to require significant increases in time and manpower to do this effectively. Given both treatment effects (reduction in amyloid load) and the potential risk factors (such as ARIA) would both require monitoring with MRI / PET-MRI there will likely need to be significant changes in how memory services are structured in order to achieve this. As we have seen, the majority of

patients with AD will have multiple medical comorbidities. This is one reason why study populations may need to be compared to real-world populations with some caution, and why comorbidities may have proven an obstacle to the development of effective treatments for AD. It remains to be seen whether this will also prove a barrier to the utilisation of new treatments as and when they become available. This is particularly the case if the licence for clinical use is broader than that used as an entry criteria for the clinical trials, as is the case for the FDA licence for Aducanumab which did not specify what, if any specific confirmatory evidence was required to determine a diagnosis of AD (biomarker or otherwise), other than to advocate its use in a patient cohort reflecting those recruited to the studies (patients with confirmed presence of amyloid pathology, and MCI or mild dementia (4). Such an approach may ensure that this medication is provided to a larger population of patients but runs the risk of diminishing (any) observed treatment effect, through its use in patients who may be less likely to benefit from the amyloid clearance that it achieves, and potentially increasing the risk of side-effects.

Conclusion

The journey towards new and efficacious treatments for Alzheimer's disease continues to be long and fraught with difficulties, resulting from the complexities of both the pathophysiology of the disease and the nature of the population that it affects. That improved treatments may be on the horizon is a testament to the hard work and dedication of those working in this field, but a number of significant barriers remain. This, in part, is a result of the frequency with which those diagnosed with AD commonly have other conditions, which may or may not also affect their cognition; may be on other treatments which may influence treatment response and side-effects; may, even in the best centres, be misdiagnosed; and that co-

pathologies are the rule rather than the exception. In order for the most effective treatments to be developed, for the largest population of patients, it is likely that future AD treatments will need to consider these issues when developing trials and therapeutic approaches, and importantly when drugs leave the clinical trials pipeline and become used in real world settings.

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Figure 1

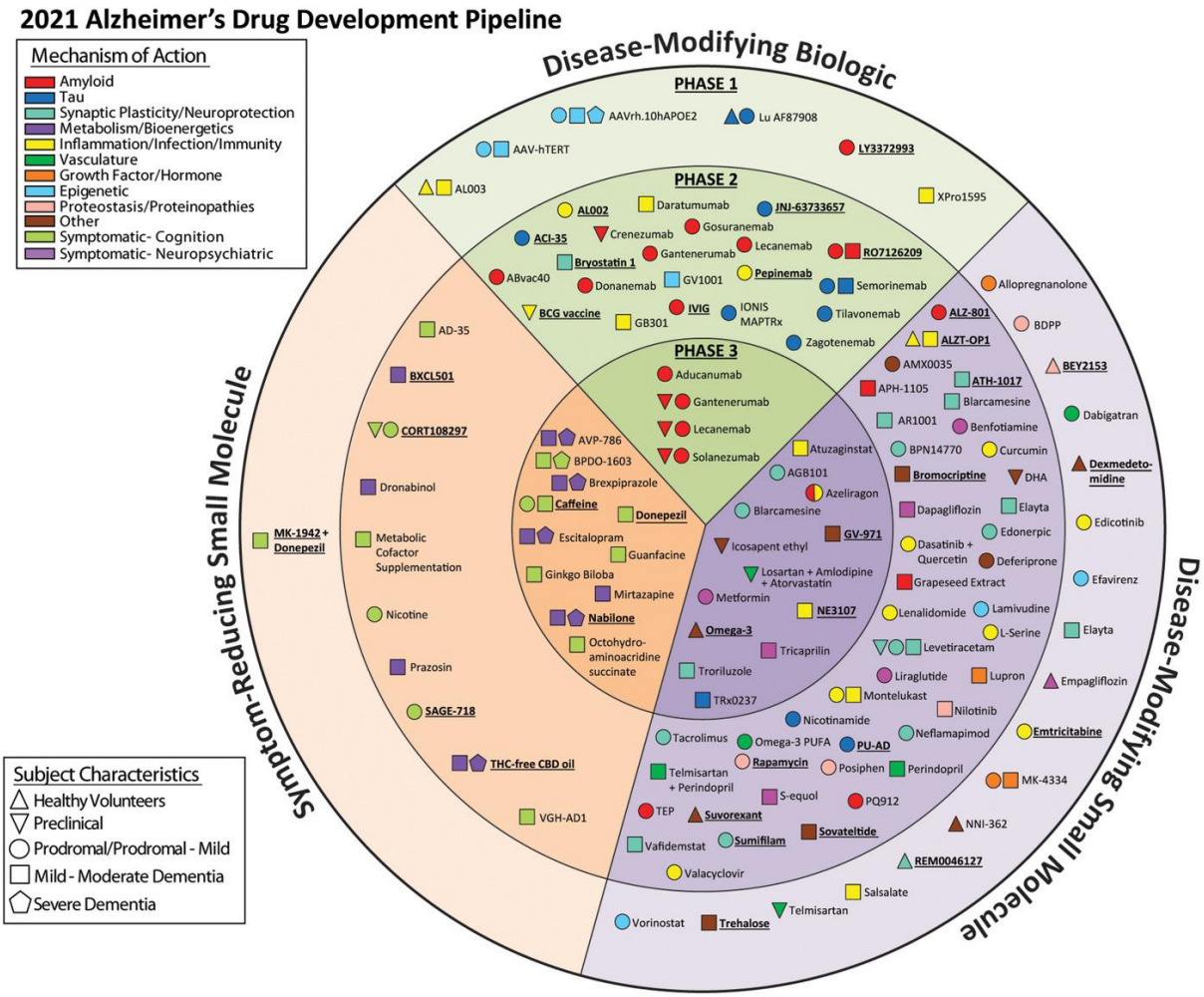

2021 Alzheimer's Drug Development Pipeline
Mechanism of Action
Amyloid
Tau
Synaptic Plasticity/Neuroprotection
Metabolism/Bioenergetics
Inflammation/Infection/Immunity
Vasculature
Growth Factor/Hormone
Epigenetic
Proteostasis/Proteinopathies
Other
Symptomatic- Cognition
Symptomatic- Neuropsychiatric
Disease-Modifying Biologic
PHASE 1
AAVrh.10hAPOE2
Lu AF87908
AAV-hTERT
LY3372993
AL003
XPro1595
PHASE 2
AL002
Daratumumab
JNJ-63733657
ACI-35
Crenezumab
Gosuranemab
Lecanemab
Gantenerumab
RO7126209
Bryostatin 1
ABvac40
Donanemab
GV1001
Pepinemab
Semorinemab
Allopregnanolone
BCG vaccine
GB301
IVIG
IONIS MAPTRx
Tilavonemab
ALZ-801
BDPP
Zagotenemab
ALZT-OP1
PHASE 3
Aducanumab
Gantenerumab
Lecanemab
Solanezumab
AMX0035
BEY2153
APH-1105
ATH-1017
Blarcamesine
AD-35
BXCL501
CORT108297
AVP-786
BPDO-1603
Brexpiprazole
Caffeine
Donepezil
Atuzaginstat
AGB101
Azeliragon
AR1001
Benfotiamine
Dabigatran
BPN14770
Curcumin
Bromocriptine
DHA
Dexmedeto-midine
Dronabinol
Blarcamesine
Dapagliflozin
Elayta
Escitalopram
Guanfacine
Icosapent ethyl
GV-971
Dasatinib + Quercetin
Edonerpic
Edicotinib
Deferiprone
Ginkgo Biloba
Mirtazapine
Losartan + Amlodipine + Atorvastatin
Grapeseed Extract
Efavirenz
MK-1942 + Donepezil
Metabolic Cofactor Supplementation
Nabilone
Octohydro-aminoacridine succinate
Metformin
NE3107
Lenalidomide
Lamivudine
Omega-3
L-Serine
Elayta
Nicotine
Tricaprilin
Levetiracetam
Troriluzole
Liraglutide
Lupron
Empagliflozin
Prazosin
TRx0237
Montelukast
Nilotinib
Nicotinamide
Emtricitabine
SAGE-718
Tacrolimus
Omega-3 PUFA
PU-AD
Neflamapimod
Rapamycin
Posiphen
Perindopril
MK-4334
THC-free CBD oil
Telmisartan + Perindopril
S-equol
PQ912
TEP
Suvorexant
NNI-362
VGH-AD1
Sovateltide
Vafidemstat
Sumifilam
REM0046127
Valacyclovir
Salsalate
Telmisartan
Vorinostat
Trehalose
Symptom-Reducing Small Molecule
Disease-Modifying Small Molecule
Subject Characteristics
Healthy Volunteers
Preclinical
Prodromal/Prodromal - Mild
Mild - Moderate Dementia
Severe Dementia

Figure 2

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion criteria† for typical AD

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes

Clinical features

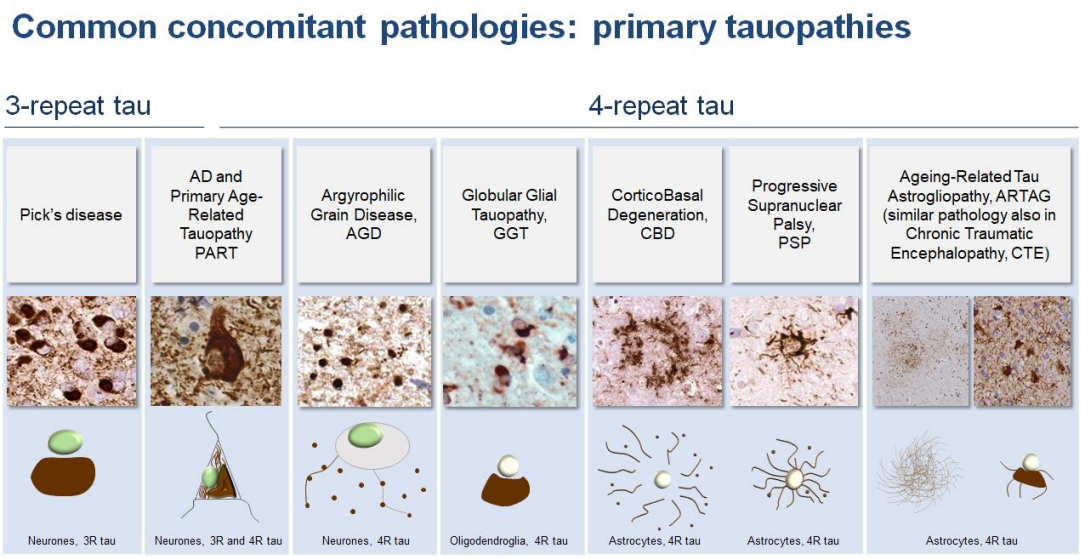
- Focal neurological features
- Early extrapyramidal signs
- Early hallucinations
- Cognitive fluctuations

Other medical conditions severe enough to account for memory and related symptoms

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults

AD=Alzheimer's disease. *Hippocampal amnestic syndrome might be difficult to identify in the moderately severe to severe dementia stages of the disease, in which in-vivo evidence of Alzheimer's pathology might be sufficient in the presence of a well characterised dementia syndrome. †Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

Figure 3


Common concomitant pathologies: primary tauopathies
3-repeat tau
4-repeat tau
Pick's disease
AD and Primary Age-Related Tauopathy PART
Argyrophilic Grain Disease, AGD
Globular Glial Tauopathy, GGT
CorticoBasal Degeneration, CBD
Progressive Supranuclear Palsy, PSP
Ageing-Related Tau Astrogliopathy, ARTAG (similar pathology also in Chronic Traumatic Encephalopathy, CTE)
Neurones, 3R tau
Neurones, 3R and 4R tau
Neurones, 4R tau
Oligodendroglia, 4R tau
Astrocytes, 4R tau
Astrocytes, 4R tau
Astrocytes, 4R tau