The Lancet Series on Alzheimer's Disease 2

Treatment for Alzheimer's disease

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This is the second in a Series of three papers about the new clinical landscape in Alzheimer's disease. All papers in the Series are available at https://www.thelancet.com/series-do/alzheimers-disease

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Over the last three decades, the evidence on how to best treat the cognitive and non-cognitive symptoms of patients with Alzheimer's disease has increased. Although these pharmacological and non-pharmacological strategies have significantly improved health outcomes for patients with Alzheimer's disease, many lack stringent evidence of efficacy. In this second paper of the Series, we provide practical and realistic advice on how to prioritise pharmacological and non-pharmacological strategies to ameliorate cognitive impairment and behavioural and psychological symptoms of dementia. In this clinical environment, dementia specialists are faced with the challenge of holistically integrating the much anticipated and, in some respects, controversial anti-β amyloid monoclonal antibodies. Here, we present the current approval scenario of monoclonal antibodies, our view on how they might further contribute to improve patients' quality of life, and how they could be seamlessly integrated with existing best care options.

Introduction

The pharmacological treatment of patients with Alzheimer's disease is driven by clinical and scientific, but also social, cultural, and contextual, factors. In many European countries, cholinesterase inhibitors, memantine, and their combination, are used and reimbursed to ameliorate cognitive impairment.[1,2] In Switzerland, either cholinesterase inhibitors or memantine is reimbursed, whereas in France both have been de-reimbursed, leading to an 86% drop in doctors prescribing them from 2009 to 2019.[3] In Germany, even some drugs with weak scientific evidence (eg, gingko) are widely used and reimbursed.[4] In Brazil, cholinesterase inhibitors and memantine are offered by the public health system, but in other low-income and middle-income countries, access is limited, particularly for memantine.[5] Expert guidelines recommend non-pharmacological strategies as first-line interventions in patients with behavioural and psychological symptoms of dementia (BPSD) such as agitation, but psychotropic drugs prone to cause significant side-effects are often used.[6,7] Very few of these drugs are approved by regulatory agencies for the treatment of agitation and other BPSD, and most patients are treated with off-label psychotropic drugs.[8]

In this fragmented scenario, anti-β amyloid monoclonal antibodies are now in clinical use or available in the USA, EU, China, Japan, the UK, South Korea, and Israel, among a growing number of countries. The use of these drugs marks the first time in the history of Alzheimer's disease that its inexorable decline has been slowed. The extent to which monoclonal antibodies will contribute to fight the Alzheimer's epidemic is unclear at this time, adding uncertainty to fragmentation. However, it is possible to identify some evidence-based, common-sense rules for the treatment of Alzheimer's disease that are unlikely to change significantly in the foreseeable future, regardless of the uptake of anti-β amyloid monoclonal antibodies.

Alzheimer's disease varies widely, with early memory loss affecting most individuals with the disease.[9] BPSD (apathy, agitation, aggression, delusions, and insomnia, among others) and physical decline develop over time, often alongside other health issues and social challenges, impacting both patients and caregivers. Treatment prioritises addressing social, somatic, and behavioural problems before targeting cognitive symptoms. The second paper of this Series will address the treatment of behavioural and cognitive symptoms of Alzheimer's disease and the use of anti-β amyloid monoclonal antibodies. Acute confusional state, a frequent cause of BPSD in patients with Alzheimer's disease, is addressed in previous reviews.[10,11]

Finally, the lexicon in Alzheimer's disease can be confusing; therefore, this Series adopts the nomenclature

Search strategy and selection criteria

We conducted a review of published articles from Jan 1, 2020, to March 1, 2025, on the PubMed, Embase, Scopus, and Cochrane databases. The search was restricted to studies published in English with different combinations of the following keywords and medical subject heading terms in PubMed (MeSH) and Embase (Emtree): "Alzheimer's disease", "cognitive impairment", "dementia", "behavio(u)ral disturbances", "BPSD", "agitation", "psychosis", "depression", "anxiety", "hallucinations", "delusions", "sleep", "pharmacologic", "non-pharmacologic", "psychological", "interventions", "neuroleptics", "psychotropics", "SSRI", "benzodiazepines", "hypnotics", "cholinesterase inhibitors", "donepezil", "rivastigmine", "galantamine", "memantine", "anti-amyloid", "monoclonal antibodies", "lecanemab", "donanemab", "symptomatic", "disease-modif*", "amyloid-related imaging abnormalities", "ARIA", "clinical* meaningful*", "discontinu*", and "APOE". We prioritised the most robust evidence from clinical trials, systematic reviews, meta-analyses, and pooled studies. We also reviewed guidelines and position statements from the same period on the diagnosis of Alzheimer's disease, cognitive impairment, and dementia.

proposed by Petersen and colleagues.[12] Specific terms are presented in the first paper of this Series.[13] Here, we will preferentially refer to cognitive impairment and neurocognitive disorders, and confine the use of the term dementia to when it specifically refers to cognitive impairment associated with impairment in activities of daily living or when it is part of current accepted nomenclature and taxonomy (eg, behavioural and psychological symptoms of dementia or dementia with Lewy bodies).

Behavioural and psychological symptoms of dementia

In approximately 100 million people affected by Alzheimer's disease, BPSD are highly prevalent, with over 90% of people estimated to develop at least one BPSD over course of the disease (>50% experience agitation and depression; 45% anxiety; 30–40% apathy, sleep disorder, and psychosis).[14] BPSD can be more evident than cognitive symptoms at the onset of Alzheimer's disease, resulting in a diagnostic challenge.[15] Apathy is present at the onset of Alzheimer's disease in about half of patients, irritability in one-third, and depression, agitation, and sleep disturbances in one-quarter.[16]

BPSD in Alzheimer's disease are loosely linked to disease stages, but tend to fluctuate over time, with cycles of weeks or months, showing spontaneous resolution and relapse. Depression is common early on, whereas psychosis is more frequent in the moderate stage, with insomnia and apathy increasing in severe stages. Disinhibition is typical of frontotemporal lobar degeneration, and visual hallucinations and misidentifications occur in dementia with Lewy bodies.[17]

The pathophysiology of BPSD in Alzheimer's disease differs from that in psychiatric disorders like schizophrenia or bipolar disorder. Treatment involves both non-pharmacological and pharmacological approaches, tailored to severity, risk, and triggers.

Stressor-associated BPSD and BPSD likely due to neurodegeneration

BPSD can be divided into two broad categories according to their pathophysiology, implying different therapeutic approaches (appendix p 2). Stressor-associated BPSD result from a psychological and behavioural reaction to cognitive decline, medical conditions, or interaction with the environment (eg, caregivers or the physical environment), or a combination of these, and are increasingly prevalent from the minimal to the moderate and severe stages of cognitive impairment. The successful treatment of BPSD relies on correctly identifying the relevant stressors; diligently seeking these out is necessary, even if this means delaying the initiation of interventions. The progressively lowered stress threshold model stipulates that cognitive impairment entails a progressive loss of the ability to receive, process, and respond to environmental stimuli.[18] The co-occurrence of visual and hearing impairment increases the risk of visual and auditory hallucinations.[19,20] Stressor-associated BPSD are more often of minimal to moderate severity and the first-line interventions should be aimed at reducing the source of stress (eg, treating chronic pain, teaching carers adaptive patient management behaviours, reducing sedative and anticholinergic medications, reducing environmental noise, or providing reassurance). Only when these strategies are not sufficiently effective or feasible should psychotropic drugs be considered (appendix p 2).

BPSD with no apparent environmental trigger or cause are more likely to result from the neurodegenerative process affecting neuronal networks and neurotransmitter systems (appendix p 2; eg, disinhibition due to involvement of the orbitofrontal cortex,[21] delusions to dorsolateral prefrontal cortex,[22] and insomnia to multiple networks[23]). However, the exact topography of involvement of most BPSD likely due to neurodegeneration is unknown. BPSD likely due to neurodegeneration are generally more severe than stressor-associated BPSD. Although some environmental modulation is possible and environment-based interventions can have a beneficial impact, psychotropic drugs are often necessary for optimal symptom control. In Alzheimer's disease, BPSD likely due to neurodegeneration are more frequent in the severe cognitive stages and can consist of insomnia, motor restlessness, wandering, and vocalisations.

Non-pharmacological treatments for BPSD

Personalised activities and enjoyable exercise have shown benefits for depression and apathy with effect sizes between 0·2 and 0·5.[24] In stressor-associated BPSD, improved communication, good use of non-verbal skills, and planning to avoid specific trigger situations are usually the most effective approaches. Psychological interventions have been less effective in directly improving psychotic symptoms.[24]

Unfortunately, non-pharmacological strategies are infrequently or suboptimally used in real-world settings[25] due to (1) the absence of training among front-line care providers; (2) the time taken to train care providers and caregivers; (3) an absence of understanding about which BPSD are more likely to benefit from the large palette of individual non-pharmacological approaches; and (4) scarcity of staffing resources to provide appropriate evidence-based care.[26] BPSD for which non-pharmacological strategies should be prioritised are provided in the appendix (p 2). In these cases, operationalised approaches are recommended, such as Brief Psychosocial Therapy[27] or the activity and social interaction programme within Well-being and Health for People with Dementia for nursing home residents.[28] For a full assessment of underlying causes and personalised interventions, the DICE approach (ie, Describe the

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See Online for appendix

problem, Investigate the cause, Create a plan, Evaluate the effectiveness of it; appendix p 3) can be useful.[29]

The DICE approach is for personalised assessment and management of BPSD. It is used to identify underlying stressor-related causes; identify the most effective non-pharmacological intervention per patient; provide evidence-based behavioural and environmental strategies; integrate pharmacological treatments, if needed; and improve caregiver confidence in managing BPSD.[26] Caregiver psychoeducation is essential, as the caregiver is a key determinant of the patient's adaptive or maladaptive behaviours. Practical advice can be found elsewhere.[24,26,29]

Panel 1: **Practical advice for a judicious use of psychotropic drugs in patients with behavioural and psychological symptoms of dementia**

Be aware of the neurochemical properties of prescribed drugs

Most psychotropics target multiple neurochemical systems. At therapeutic doses, the dominant receptor activity drives benefits and adverse effects. For instance, risperidone's strong dopamine blockade causes both its high antipsychotic activity and the high risk of parkinsonism. Quetiapine's milder dopaminergic and stronger antihistaminic effects lead to lower antipsychotic activity and risk of parkinsonism, but more sedation compared with risperidone. Other drugs with antihistaminergic and anticholinergic effects can result in sedation and worsened cognition.[30,56]

Avoid drugs with anticholinergic activity

Tricyclic antidepressants, paroxetine, and olanzapine have high propensity to cause confusion, dry mouth, blurred vision, urinary retention, constipation, and increased intraocular pressure, and should be strictly avoided in older people (>65 years) with cognitive impairment.

Minimise number of psychotropic drugs

Behavioural and psychological symptoms of dementia (BPSD) often occur in clusters; for example, depression and insomnia, agitation and insomnia, or anxiety and depression. Whenever possible, use one drug with dual efficacy rather than two drugs. For instance, in a patient with daytime agitation and insomnia, use trazodone during the day and (at higher dose than in the day) at bedtime, rather than risperidone during the day and a hypnotic or a benzodiazepine at bedtime.

Start low, go slow, prescribe, and revise

Start at one-eighth to one-quarter of the adult dose and titrate gradually over 2–4 weeks. Short-loop follow-up assessments of efficacy and tolerability after every drug increment is ideal. As BPSD are inherently intermittent, treatments should never be carried over indefinitely. A follow-up plan should be decided at the start of treatment, and tapering-off attempts should be carried out after 3 months of stable behaviour.

Switch with a scheme

If a drug is not, or insufficiently, effective after an adequate therapeutic trial (usually ≥6 weeks), discontinuation and switching to an alternative is indicated rather than adding on. Different switch schemes can be considered depending on drugs and BPSD: abrupt switch, taper switch, cross-taper switch, or plateau cross-taper switch.[57]

Pharmacological treatments

In medicine, few areas show as large a gap between evidence and practice as pharmacological treatment of BPSD. Although drugs like antipsychotics, selective serotonin reuptake inhibitors, benzodiazepines, hypnotics, and anti-epileptics are used, supporting evidence is scarce. Numerous guidelines offer expert advice on the use of these drugs,[30] but practitioners often rely on familiar medications regardless of guidelines. Therefore, herein, specific drug indications will be avoided, and simple rules to avoid the most harmful approaches provided.

A detailed review of the pharmacological properties, efficacy, and safety of psychotropic drugs used to treat BPSD is beyond the aim of this Series and can be found elsewhere.[31] The best evidence on the pharmacological treatment of BPSD is for the treatment of agitation with non-opioid analgesics (effect size 0·48)[32] and with the serotonin reuptake inhibitor citalopram (effect size 0·3).[33,34] The evidence is less clear for pharmacological treatments of other BPSD. Only the atypical antipsychotics risperidone (Europe and Canada) and brexpiprazole (USA, Canada, and Switzerland), and the typical antipsychotic haloperidol (Germany), are licensed for the treatment of agitation aggression for people with dementia.

Personal experience and evidence from the literature suggest that citalopram and atypical antipsychotics, such as quetiapine, confer small, but significant, benefits for agitation, at least for the first 3 months of treatment,[35] and even smaller benefits are found for psychosis.[36] Mirtazapine is not effective for agitation.[37] Clinical trials indicate that selective serotonin reuptake inhibitors are ineffective for the overall treatment of depression in people with Alzheimer's disease,[38,39] but clinical experience suggests otherwise, at least in the more severe cases, at the cost of acceleration of cognitive decline.[33] The treatments with the most persuasive evidence of a favourable benefit-to-risk ratio for sleep disturbances are trazodone and orexin antagonists, whereas evidence in favour of melatonin is poor.[40] There are very few treatment studies regarding the pharmacological management of anxiety in Alzheimer's disease, which is a significant gap in current treatment, and non-pharmacological approaches are the preferred treatment option.[41] Benzodiazepines should be avoided because of the substantial risk of falls and increased confusion.[42]

Although typical antipsychotics are generally contra-indicated in the treatment of BPSD in Alzheimer's disease outside emergency conditions for their

cognitive, functional, and motor adverse effects,[43,44] atypical antipsychotics are associated with mild but detectable functional decline, particularly in the first few weeks after treatment initiation,[45] and a small increased risk of death.[46] For this reason, best practice guidelines encourage sparing and judicious use, regular review, and discontinuation of antipsychotics in Alzheimer's disease, as soon as possible.[44,47] Traditional neuroleptics and other drugs with dopamine-blocking activity (eg, amisulpride and related agents, domperidone, and flunarizine) are strictly contraindicated in patients with dementia with Lewy bodies, for whom they can cause severe extrapyramidal reactions and even death.[48]

Cholinesterase inhibitors have very modest benefits in the overall reduction of BPSD in Alzheimer's disease and there is no specific benefit in the treatment of agitation.[49] Memantine reduces the emergence of BPSD with long-term treatment.[50] There is some indication that both stimulants, such as methylphenidate, and cholinesterase inhibitors might improve apathy in people with Alzheimer's disease,[51,52] whereas agomelatine, a melatonin receptor agonist and serotonin receptor blocker, might be useful for treating apathy in people with frontotemporal dementia. However, the evidence for these treatments is mainly from case series,[53] and pharmacological therapy should probably be reserved for severe cases of apathy.[51,52] The benefit of cholinesterase inhibitors for managing BPSD is greater in biomarker-confirmed mild cognitive impairment and dementia due to Alzheimer's disease,[54] and a review of their efficacy for BPSD in this context is required.

More details on the diagnosis and treatment of BPSD in Alzheimer's disease and other neurocognitive disorders can be found in a recent review.[55] Practical advice is provided in panel 1. Given the potential risks and scarce evidence for most current psychopharmacological treatments, even when they are indicated, it is often helpful to think about how benefits can be augmented with concurrent non-pharmacological approaches. Some of these principles are highlighted in three case examples provided in panel 2.

Panel 2: **Case examples: treatment of behavioural and psychological symptoms of dementia with integrated non-pharmacological and pharmacological interventions**

Person A is a woman, aged 86 years, who has Alzheimer's disease of moderate cognitive and functional severity and who lives in a nursing home. She becomes irritable and verbally aggressive when being helped out of bed in the morning, to move to the dining room for meals, and to go to bed, which has led to frustration among staff. She is prescribed analgesics for arthritis, which she never requests. The irritability and verbal aggression are situational, possibly triggered by pain and exacerbated by interactions with staff. After exclusion of other active medical conditions, regular analgesia is prescribed[32] and staff are trained to develop a non-threatening communication pattern, using soft tones and calming, non-verbal behaviour, and to take more time during interactions. Agitation and aggression resolved within 2 weeks. Person A is regularly monitored for the re-emergence of the symptoms.

Person B is a woman, aged 82 years, who has Alzheimer's disease of moderate cognitive and functional severity and who lives in the community with her daughter. For the past few weeks, when she is alone in the afternoons, about every other day, she starts to become worried that her handbag has been stolen and then shouts to her daughter for help to find the thieves. She usually calms down over about 15 min with a reassuring conversation. After the exclusion of active medical conditions and an ECG to check the QT corrected for heart rate interval, she is prescribed citalopram. Her daughter receives positive reinforcement about the value of what she is already doing. The daughter is also helped to arrange for a friend to visit person B regularly while she is on her own. The frequency of episodes of agitation is significantly reduced after 4 weeks.

Person C is a man, aged 62 years, who has early onset Alzheimer's disease of moderate global severity and who lives in a nursing home. He has been constantly irritable and has hit members of staff and other residents on multiple occasions, despite the staff's kind and understanding behaviour. He has also been tearful and has had low in mood at times, but he is eating and sleeping well. Although irritability happens during interactions, the triggers are not specific. After exclusion of active medical conditions and an ECG to check QT corrected for heart rate, citalopram is prescribed for 4 weeks, but without appreciable effectiveness. Following a risk–benefit assessment, person C is switched to risperidone over 4 weeks with a cross-taper switch scheme. Brexpiprazole would have been equally indicated. Doses of risperidone or brexpiprazole should be started low and increased over 2–4 weeks to identify the lowest effective dose, with careful monitoring for oversedation, reduced mobility, or other adverse effects. As it usually takes at least 4 weeks for the benefits of slow-tapering antipsychotic medication to become evident, it is also important to help to reduce potential triggers—eg, by enabling person C to spend more time in a quiet lounge or his room (with regular interaction). Helping him feel more at home in the nursing home, with more regular personalised interaction with a key member of care staff and increasing the number of personal possessions in his room, might also help. Regular follow-up of treatment is paramount.

Symptomatic treatment for cognitive impairment

Treatment of Alzheimer's disease with cholinesterase inhibitors originated from the idea that the cholinergic system played a key role in cognition—analogous to how the dopaminergic system influences motor control in Parkinson's disease.[58] Donepezil was approved in 1999 in the USA, followed by galantamine and rivastigmine in 2000 and 2001, respectively. Although Alzheimer's disease involves deficits in serotonin, dopamine, norepinephrine, and γ-aminobutyric-acid systems,[59] drugs targeting these neurotransmitters have not shown cognitive benefits. The exception is the glutamatergic system, where memantine is an approved medication that acts by reducing neuronal damage caused by overactivation of N-methyl-D-aspartate receptors.[60]

Initial use of cholinesterase inhibitors was informed by pivotal short-term clinical trials. A review of systematic reviews on the cognitive effects of cholinesterase inhibitors on tests of global cognition (eg, the Mini Mental State Exam [MMSE] or Alzheimer's Disease Assessment Scale cognitive subscale) in double-blind, randomised controlled trials done over a minimum of 12 weeks concluded that efficacy was low.[61] Meta-analyses have estimated the effect of cholinesterase inhibitors on the MMSE at months 3, 6, and 12 at approximately

1 point,[61] and the proportion of responders attributable to treatment between 9% and 20%.[62,63]

Meta-analyses indicate that galantamine (≥24 mg) and donepezil (10 mg) are most effective for mild to moderate Alzheimer's disease, with moderate effect sizes (galantamine 0·5 and donepezil 0·4).[64] Combining memantine (20 mg) with donepezil (10 mg) shows the largest benefit (effect size 0·76) and is recommended for moderate to severe cases. Adding cognitive stimulation to cholinesterase inhibitors might improve outcomes in mild Alzheimer's disease.[65] Cholinesterase inhibitors are also approved for severe stages in several countries.[66]

Side-effects of cholinesterase inhibitor use are due to enhanced muscarinic tone: nausea and vomiting affect one in four to one in seven patients, but the incidence can be reduced by slower titration than that of clinical trials and reported in the instructions for use.[67] Up to one in ten people experience muscle cramps, tiredness, insomnia, loss of appetite, hallucinations, and unusual dreams including nightmares.[68] Caution is advised for individuals with bradycardia, first-degree heart block, and co-prescription of medications that prolong QT corrected for heart rate interval, suggesting pre-initiation ECGs might be useful.[68] The transdermal formulation of rivastigmine reduces the likelihood of nausea and vomiting by three-fold, but at the cost of one in ten patients experiencing skin irritation.[69] Cholinesterase inhibitors might cause urinary urgency resembling overactive bladder; recognising this can prevent unnecessary anticholinergic prescriptions and avoid harm.[70]

A meta-analysis of patients with Alzheimer's disease treated with cholinesterase inhibitors suggested a reduction of progression to severe cognitive and functional impairment,[71] all-cause mortality,[72] and stroke.[72] The prescription of cholinesterase inhibitors to patients with Alzheimer's disease has also been associated with a lower likelihood of antipsychotic prescription compared with patients who were not given the same treatment.[73] Given the well known mortality risks associated with antipsychotics,[74–77] these longitudinal long-term data add dimensionality to the risk-benefit discussion when prescribing cholinesterase inhibitors, and suggest that these agents should remain part of the Alzheimer's disease pharmacotherapeutic armamentarium moving forward.

Long-term efficacy data of cholinesterase inhibitors in non-randomised studies show MMSE decline of 0·2–1·4 points per year in patients who were treated versus 1·1–3·4 points in patients who were not treated, with a reduction in relative risk of mortality of 27–42% over 2–8 years.[78] Despite limitations, these effects are similar to treatments for other chronic diseases.[78] Continued donepezil use is linked to cognitive and functional benefits, and less nursing home placement.[79]

Absence or loss of treatment response is the most common guideline-recommended reason for discontinuation,[80] but rigorous discontinuation trials are needed. The expected response to cholinesterase inhibitors is such that determining absence or loss of treatment response can be difficult. A Cochrane review cautiously stated that discontinuing cholinesterase inhibitors in patients with Alzheimer's disease might result in worse cognitive, neuropsychiatric, and functional status than continuing treatment, and suggested a cautious and individualised approach to discontinuation based on patient and caregiver preference and clinical judgement.[81] There is currently no evidence to guide decisions about when to discontinue memantine.[81]

Cholinesterase inhibitors are also useful in diseases other than Alzheimer's disease, such as dementia of Parkinson's disease,[82] and dementia with Lewy bodies. In patients with dementia with Lewy bodies, rivastigmine has shown remarkable efficacy on cognitive and behavioural outcomes,[83] such that it is considered the drug of first choice for the treatment of apathy, anxiety, delusions, and hallucinations.[84] Alzheimer's disease co-pathology denoted by cerebrospinal fluid (CSF) biomarkers of amyloid PET (see paper 1 in this Series)[13] is associated with poorer outcomes compared with dementia with Lewy bodies without Alzheimer's disease co-pathology, such as institutionalisation and mortality, and a less marked response to cholinesterase inhibitors.[85]

Treatment with memantine, an N-methyl-D-aspartate receptor antagonist, has also shown a small beneficial effect on cognition in patients with Alzheimer's disease who have moderate to severe cognitive impairment,[86] but not mild cognitive impairment.[87] The number needed to treat for memantine is as low as between three and eight patients for global, cognitive, and functional outcomes,[88] whereas for cholinesterase inhibitors it is between four and 14 patients for cognitive outcomes.[89] Memantine is frequently used in combination with donepezil, and observational and network meta-analytical data have found better outcomes over monotherapy for cognition, global assessment, and daily activities, albeit with lower acceptability than monotherapy.[90,91] From a pooled analysis of Alzheimer's disease registration trials, the incidence of agitation was significantly lower in memantine (8% of patients) versus placebo (12%), with possibly just a minor increase of the incidence of hypertension, somnolence, constipation, vomiting, and abnormal gait (about 3–4% with memantine *vs* 2–3% with placebo).[92–94]

Although cognition and function have been the primary outcomes in phase 3 trials, quality of life (QoL), caregiver, and health outcomes are also important. Notwithstanding the challenges of measuring QoL by self-report in dementia, especially at severe stages, cholinesterase inhibitors and memantine have shown

modest direct patient-reported effects on QoL.[50,95] Indirect effects on QoL might be evident through delayed decline in cognition, behaviour, and function, and reduced hospitalisation or nursing home placement.[73,96–98] Similarly, the use of cholinesterase inhibitors and memantine has shown to improve caregiver burden and caregiver QoL.[50,97]

The use of cholinesterase inhibitors in patients with mild cognitive impairment has been controversial. A meta-analysis of 14 randomised controlled trials found no significant difference in cognitive function scores between cholinesterase inhibitors and placebo groups, but cholinesterase inhibitors were associated with a lower progression rate to dementia.[99] Although cholinesterase inhibitors were associated with fewer falls than placebo, all-cause discontinuation was also higher with the drug than placebo.[99] The challenge with interpreting historical trial results for cholinesterase inhibitors in mild cognitive impairment is that Alzheimer's disease was not confirmed with biomarkers. A systematic review of predictors of response to cholinesterase inhibitors in mild cognitive impairment and dementia found that amyloid positivity conferred greater likelihood of cognitive stabilisation and reduction in neuropsychiatric symptoms.[54] Given the benefit–risk ratio of cholinesterase inhibitors, their use might be considered in mild cognitive impairment for those patients with biomarker confirmation of Alzheimer's disease pathology.

Anti-β amyloid monoclonal antibodies

Symptomatic therapies versus anti-β amyloid monoclonal antibodies

Cholinesterase inhibitors and memantine have shown symptomatic efficacy, but do not alter β-amyloid or tau pathology, metabolism, deposition, or toxicity (table 1). A major development was the successful completion of phase 3 trials for lecanemab and donanemab, reported in 2023, and the subsequent market authorisation (as of Aug 1, 2025, lecanemab or donanemab have been approved by 45 countries, including the USA, the UK, the EU, China, and Japan). A review on the pharmacology of anti-β amyloid monoclonal antibodies has been previously published.[100]

These agents are humanised IgG-1 monoclonal antibodies targeting aggregated β-amyloid species, the underlying neuropathology of Alzheimer's disease. Lecanemab targets β-amyloid 42 protofibrils and donanemab targets a N-terminal pyroglutamate β-amyloid epitope present in established plaques. Both drugs met primary and secondary endpoints (cognition, function, and carer burden) in phase 3 trials up to 18 months. Donanemab has shown a more marked efficacy in patients in the milder biological stages as defined by tau pathology on PET compared with patients with the more severe biological stage.[101] Lecanemab and donanemab require specific considerations for eligibility and safety monitoring, which poses substantial challenges for health-care system implementation, discussed later. The efficacy of these drugs on markers of tau phosphorylation (plasma tau phosphorylated at Thr 181 [p-tau181] and plasma tau phosphorylated at Thr 217 [p-tau217]),[101,102] glial reactivity (GFAP),[103] and neurodegeneration (total tau, neurogranin and neurofilament light polypeptide)[102] support the validity of the amyloid cascade as a clinically meaningful, although probably not unique, pathway to cognitive impairment in Alzheimer's disease.

A fundamental difference between disease-modifying therapies and symptomatic treatments is the effect of initiation on benefit. With disease-modifying therapies, there is benefit in initiating therapy as soon as possible, and any delay cannot be recovered later on. With symptomatic therapies, their benefit depends less critically on when they are started. In theory, the benefit of symptomatic treatments and disease-modifiers should

	Symptomatic drugs	β-amyloid immunotherapies
Molecules	Cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) and memantine	Anti-β amyloid monoclonal antibodies (donanemab or lecanemab)
Mechanism of action	Receptor agonist or antagonist	Microglia-mediated removal of aggregated β-amyloid
Administration route and frequency	Oral (once or twice a day) or transdermal (once a day, twice per week, or weekly)	Donanemab intravenously every 4 weeks; lecanemab intravenously every 2 weeks; and subcutaneous formulations under development
Indication	Clinical diagnosis of Alzheimer's disease with mild to moderate (cholinesterase inhibitors) and moderate to severe (memantine) cognitive impairment; biomarkers not mandatory	Diagnosis of early Alzheimer's disease evidenced by amyloid biomarkers, cognitive impairment of at least mild severity, and no or only mild functional impairment
Efficacy	Cognitive benefit while on therapy equivalent to ~6 months of decline; improved cognitive function can be appreciated within 12 weeks from treatment inception	27–35% less compared with untreated decline in global cognitive or functional endpoints at 18 months from treatment inception; longer term outcomes currently unknown; and no improvement of cognitive function to be expected
Tolerability	Good with appropriate titration (occasional side-effects of nausea, vomiting, diarrhoea, dizziness, headache, or bradycardia)	*APOE*-dependent local brain oedema and bleeding (ARIA); infusion-related reactions; and better tolerability with slow titration
Monitoring of efficacy	Clinical assessment, cognitive tests, and functional scales	Clinical assessment, cognitive tests, and functional scales
Monitoring of adverse events	Clinical follow-up every 6–12 months	Typically, three brain MRI scans in the initial 12 months of treatment and clinical monitoring for symptoms attributable to ARIA, which determines if treatment needs to be paused or discontinued, and prompts additional MRI until ARIA resolution
Discontinuation	When reaching severe or very severe cognitive or functional impairment; intolerance or adverse events; or difficulties in administration of the drug (eg, dysphagia)	Donanemab when amyloid negative on amyloid PET; lecanemab unknown, trials ongoing

ARIA=amyloid-related imaging abnormalities.

Table 1: **Features of symptomatic therapies and β-amyloid immunotherapies**

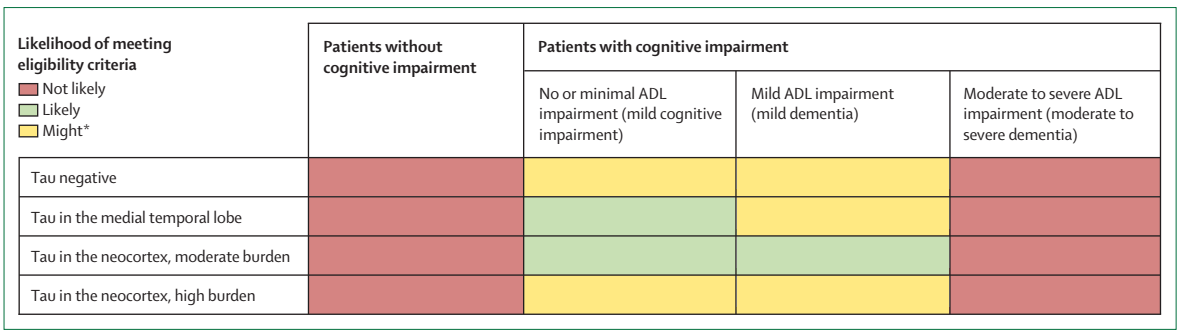

Figure 1: **Current clinical eligibility for anti-β amyloid monoclonal antibody treatment for patients at memory clinics with positive biomarkers for brain beta amyloidosis**

Patients without cognitive impairment includes patients with or without cognitive complaints (subjective cognitive decline). This representation was adapted from Jack and colleagues[109] and simplified for patients at memory clinics. Terms are defined in the appendix (pp 7–9). ADL=activities of daily living. *Patients have a greater likelihood of meeting exclusion criteria, or the risk or burden of treatment might outweigh potential benefit.

be additive, and the two types of drugs should be prescribed in association for maximal benefit–risk ratio. Although lecanemab and donanemab fulfil widely accepted definitions of disease-modifying drugs,[104] we acknowledge that definitive evidence of disease modification would require specifically designed trials and discuss in subsequent sections.

Eligibility and exclusion

Several national dementia specialists have issued guidelines for lecanemab use,[105–108] with more expected soon. Key considerations include confirming early Alzheimer's disease-related cognitive impairment and assessing contraindications or conditions that affect the treatment's risk–benefit balance.[105] Additionally, patients need to be aware of the (current) requirements for frequent intravenous infusions, regular MRI monitoring, and risk of side-effects—all much less likely to be tolerated by those with greater frailty or poor caregiver support. As treatments move into clinical practice there will inevitably be a wider range of patients with multiple comorbidities and medications seeking therapy—clinicians will need to be careful and holistic to minimise risk of harm and inappropriate treatment. Trials of anti-β amyloid monoclonal antibodies that have shown clinical benefit only included individuals with Alzheimer's disease in the mild cognitive impairment to mild dementia stages.[101,102] Trial requirements, mirrored by market labels, included a diagnosis of cognitive impairment with no to mild activities of daily living impairment and evidence of cerebral amyloid pathology based on CSF biomarkers or amyloid-PET. Therefore, patients with cognitive impairment due to alternative clinical diagnoses or more advanced Alzheimer's disease with moderate to severe ADL impairment should be excluded.

Patients without cognitive impairment, but with positive amyloid biomarkers, either with or without subjective complaints (ie, subjective cognitive decline and worried well), should at present not receive anti-β amyloid monoclonal antibodies (figure 1). These patients are a key target population for current ongoing trials (eg, TRAILBLAZER-ALZ3 [NCT05026866] and AHEAD 3-45 [NCT04468659]) aiming to prevent the onset of cognitive impairment and other prevention approaches.[110]

Five factors should be considered as unfavourably altering the benefit–risk ratio. First, advanced Alzheimer's disease pathology. Patients complying with indication criteria (table 1), but at a later pathological stage, as evidenced by high neocortical tau burden on tau-PET, should not necessarily be excluded from treatment; however, this subpopulation showed less benefit than those with low-to-medium tau-PET burden in a donanemab phase 3 trial[101] (figure 1). Unfortunately, tau-PET is not commonplace in the clinic, and this stratification is currently unfeasible in practice. The second factor is incomplete expression of the amyloid cascade. Patients with cognitive impairments who have amyloid positivity, but are negative on tau markers, were excluded by the donanemab trial (figure 1). The third factor is situations in which cognitive impairment results from the convergence of Alzheimer's disease and non-Alzheimer's disease pathology (eg, cerebrovascular or chronic psychiatric diseases, other proteinopathies, or frailty). Here, altering the component of cognitive decline amenable to amyloid removal will have lower-than-average benefit on cognitive and functional outcomes. The next factor are those that might interfere with treatment tolerability, safety, or efficacy (eg, patients who are unable to have MRI, have active behavioural symptoms, or have immunological diseases requiring immunosuppression.[105] Finally, the fifth factor is increased risk of amyloid-related imaging abnormalities (ARIA; figure 2).

The risk of ARIA is a key eligibility consideration specific to anti-β amyloid monoclonal antibodies as it decreases the benefit–risk ratio and can contraindicate anti-β amyloid monoclonal antibodies in patients who are otherwise eligible. ARIA consist of cerebral oedema or sulcal effusion (ARIA-E); or haemorrhagic manifestations (ARIA-H), such as cerebral microbleeds, cortical superficial siderosis or,

rarely, lobar intracerebral haemorrhage (defined as >1 cm). Patients at higher risk of ARIA are those with markers of cerebral amyloid angiopathy (cerebral microbleeds or cortical superficial siderosis), and those carrying the ε4 allele of *APOE* gene, with a dose-dependent (number of alleles) increased risk.[111] Due to this risk, *APOE* genotyping is strongly recommended or (in the UK and the EU) required, and a baseline MRI with appropriate blood-sensitive sequences (T2*-weighted imaging or susceptibility-weighted imaging) is mandatory for all patients being considered for anti-β amyloid monoclonal antibodies.

Current appropriate use recommendations suggest that an MRI is required within the last year and that the following findings are exclusions to treatment: current or previous acute or subacute cerebral haemorrhage; superficial siderosis; more than four microhaemorrhages; severe white matter disease; anticoagulant treatment; and any condition that could prevent a satisfactory MRI evaluation for safety monitoring.[105] Antiplatelet drugs are allowed while additional safety data are collected. In the EU, the UK, and Australia, patients who are homozygous for *APOE* ε4 are not eligible for anti-β amyloid monoclonal antibodies due to the higher ARIA incidence. In the USA, the FDA has authorised lecanemab and donanemab irrespective of *APOE* geneotype.

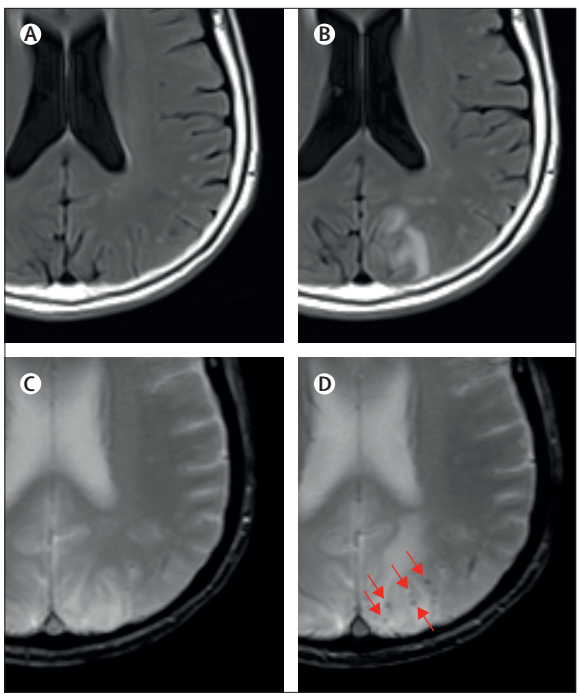

Figure 2: **ARIA-E and ARIA-H**
(A) Baseline brain MRI of a patient treated with an anti-β amyloid monoclonal antibody. Radiologically mild left parietal ARIA on fluid-attenuated inversion recovery (B) and T2*-weighted MRI (C). The patient was asymptomatic and the ARIA was detected during a routine follow-up scan. Immunotherapy was continued according to recommendations.[105] (D) After 1 month, microbleeds (ARIA-H) were detected on T2*-weighted MRI in the region of ARIA-E. ARIA=amyloid-related imaging abnormalities. ARIA-E=amyloid-related imaging abnormalities with oedema. ARIA-H=amyloid-related imaging abnormalities with microhaemorrhages.

Efficacy and clinical meaningfulness

In pivotal phase 3 clinical trials, lecanemab and donanemab both drastically cleared amyloid from the brains of patients with Alzheimer's disease, with donanemab reducing PET-detected levels on average by over 80% after 18 months of treatment.[101] However, in contrast to the striking biological effect, the clinical benefit was more limited. Lecanemab and donanemab slowed cognitive and functional decline by 27% and 36%, respectively, equating to about 0·5–0·7 points less decline at 18 months, on a 0 to 18 points combined cognitive and functional scale (Clinical Dementia Rating-Sum of Boxes, CDR-SB), and 38% to 40% on a purely functional scale (Alzheimer's Disease Cooperative Study–Activities of Daily Living for Mild Cognitive Impairment scale). The benefit of donanemab was greater in patients with milder disease severity on tau PET.[101]

The small effect size on cognitive and functional endpoints has led to substantial debate over whether this effect is clinically meaningful.[112–114] In addressing this point, it is important to consider the difference between the mode of action of the current standard of reference (symptomatic therapies with cholinesterase inhibitors and memantine) and putative disease-modifying therapies (appendix p 4). Comparing the two therapies in terms of meaningful difference over a fixed period might not be appropriate. Symptomatic therapies provide improvement over a short period of time, after which the effect is likely to either stabilise or wane; disease-modifying therapies might provide a cumulative benefit over time, with diverging slopes between drug and placebo over a period of years (appendix p 4). Importantly, this is a hypothesis that is yet to be validated.

Given the nature of the effect of anti-β amyloid monoclonal antibodies (slowing of cognitive and functional decline) and the heterogeneity of disease progression in Alzheimer's disease, translating the benefits of clinical trials to an individual patient context in the clinic is challenging.[112] The definition of clinical meaningfulness varies for each person, dependent on their values and priorities, and attitudes towards risk and medical treatment. In any case, a drop of 0·5 on the CDR-SB score can mean the difference between being able to drive independently or only being able to go out with supervision (table 2). It should be noted that the benefit of about 0·5 points on the CDR-SB score shown in the phase 3 clinical trials of lecanemab and donanemab is the sum of changes across all six CDR domains shown in table 2.

Time-saved with treatment has been proposed as an alternative method to quantify the benefits of these therapies, with these treatments representing 5–6 months extra time compared with placebo over an 18-month

	Very mild impairment	Mild impairment
Memory	Consistent slight forgetfulness; partial recollection of events; or benign forgetfulness	Moderate memory loss; more marked for recent events; or interferes with everyday activities
Orientation	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; or might have geographical disorientation
Judgement and problem solving	Slight impairment in everyday problems (business and financial affairs); or slight impairment in judgement of past performance	Moderate difficulty in handling problems, similarities, and differences; or social judgement usually maintained
Community affairs	Slight impairment; or still able to work and drive	Unable to function independently; might engage in some activities; appears normal to casual inspection; or can no longer work, but can walk around local area
Home-life and hobbies	Life at home; or home-life, hobbies, and intellectual interests slightly impaired	Mild, but definite, impairment of function at home; more difficult chores and interests abandoned; or more complicated hobbies and interests abandoned
Personal care	Fully capable of self-care	Needs prompting

Very mild impairment refers to a score of 0·5 on CDR-SB scale, whereas mild impairment refers to a score of 1. The effects of donanemab and lecanemab consist of around 0·5 points less progression on the CDR-SB scale over 18 months. We illustrate how this amount of benefit might translate in a patient's daily life when, for example, transitioning from very mild to mild impairment in one of the scale domains. The benefit of about 0·5 points on the CDR-SB scale shown in the phase 3 clinical trials of lecanemab and donanemab is the sum of changes across all six CDR domains (memory, orientation, judgment and problem solving, community affairs, home-life and hobbies, and personal care).[101,102] Scores 0, 2, and 3 (no, moderate, and severe impairment, respectively) are not shown as they are not pertinent to patients eligible for treatment with these drugs. Modified from Morris.[115] CDR=Clinical Dementia Rating. CDR-SB=Clinical Dementia Rating-Sum of Boxes.

Table 2: **Clinical meaningfulness of treatment with donanemab and lecanemab on the CDR-SB scale**

period.[116,117] Another way of communicating likely benefits is quantifying the chance of progression with or without treatment—for donanemab, 163 (28%) of 573 patients with low or medium tau burden treated with placebo had worsening on the CDR-Global (CDR-G) score at 18 months, compared with 100 (18%) of 555 patients on donanemab.[101] An alternative way to express these results is the number needed to treat; ie, to prevent progression on the CDR-G scale over 18 months in one patient, 13 patients need to be treated with lecanemab and ten with donanemab.[110] A more in-depth discussion of the clinical meaningfulness of anti-β amyloid monoclonal antibodies in Alzheimer's disease can be found in paper 3 of this Series.[110]

Ultimately, an individualised discussion of benefit, risk, and treatment burden is required, taking into account patient context and preferences, in the context of an evolving relationship between the patient, family, and physician. The public availability of patient-level clinical trial results and longer-term outcomes might crucially boost this process.[118]

Safety and follow-up

Both donanemab and lecanemab can cause acute infusion-related reactions (IRRs), with an incidence of approximately one in 13 patients and one in four patients, respectively,[101,102] and this risk should be taken into account when considering the setting for infusions. Most IRRs are mild-to-moderate, with severe IRRs seen in 1·2% of lecanemab-treated and 0·3% of donanemab-treated patients.[101,102] Three-quarters of IRRs occur during or within 30 min of the first infusion for lecanemab and between the second and fifth infusion for donanemab.[101,102] Rare hypersensitivity reactions, including anaphylaxis and angioedema, have been reported and represent a contraindication to ongoing treatment, but otherwise discontinuation due to IRRs is uncommon (12 [1·3%] of 898 patients treated with lecanemab and 31 [3·6%] of 853 with donanemab). Prophylactic treatment, such as antihistamines or corticosteroids, can reduce the risk of recurrence.[105,119]

ARIA (figure 2) is the major concern with β-amyloid immunotherapies, and clinical and MRI monitoring for ARIA is required during treatment. ARIA rates are higher in *APOE* ε4 carriers than non-carriers, with highest rates in homozygotes—3–6-times higher than in non-carriers (table 3). Donanemab treatment has overall higher rates of ARIA (314 [36·8%] of 853 patients treated with donanemab compared with 193 [21·5%] of 898 with lecanemab), but more gradual titration regimens might drastically reduce their incidence.[120] High blood pressure (mean arterial pressure >107 mm Hg) is the sole modifiable known risk factor.[121] With lecanemab, about two-thirds of patients experience non-focal neurological symptoms (headache, visual disturbances, dizziness, confusion, generalised tonic-clonic seizures, reduced responsivity to stimuli, behavioural disturbances, and hallucinations), about 20–25% experience non-neurological symptoms (tinnitus, retinal haemorrhage, nausea, vomiting, fatigue, muscle weakness, and fall), and 10–15% experience focal neurological stroke-like symptoms (diplopia, amnesia, aphasia, ataxia, paraesthesia, and speech disturbances) and focal seizures with secondary generalisation.[122]

As to the clinical expression of ARIA, 70% of ARIA-E occur in the first 3 months and 90% in the first 6 months of therapy.[121,122] Most ARIA-E resolve spontaneously or within 2 months of pausing treatment (depending on severity), although corticosteroid treatment might be indicated in those with more radiologically severe or symptomatic ARIA. For discussion with patients, it might be helpful to remember that approximately 80% of patients with ARIA are asymptomatic, approximately 80% of ARIA occur in the first 4 months, and approximately 80% of ARIA resolve within 4 months. Clinically serious ARIA have occurred in one in 299 and one in 66 patients treated with lecanemab and donanemab, respectively. Seven deaths attributed to treatment occurred during the phase 3 trials with lecanemab and donanemab in people aged 65–85 years; two were *APOE* ε4 homozygotes, two heterozygotes, and three non-carriers. Five of these seven individuals experienced stroke-like symptoms, and two experienced nausea or vomiting, and headache.[101,102,122] Death was generally considered related to brain haemorrhage associated with ARIA-E.[101,122] The incidence

of ARIA-E in patients with mild cognitive impairment or very mild dementia outside clinical trials seems lower than in clinical trials (three [1·8%] of 164 patients treated with lecanemab at 1 year).[123]

The occurrence of radiological, symptomatic, radiologically severe, and clinically serious ARIA-E increases from *APOE* ε4 non-carriers to heterozygotes and homozygotes (table 3). However, when radiological ARIA-E occur in patients treated with lecanemab or donanemab, the frequency of symptoms of any severity is not different by *APOE* genotype, and those ARIA-E severe on MRI and clinically serious are more frequent in carriers than non-carriers, but equally frequent in heterozygotes and homozygotes (table 3). These data are from a low number of events and accruing additional data in the future will allow for better clarification of the relationship between *APOE* genotype and clinical seriousness of ARIA. At least two deaths have been reported anecdotally in the clinic, both of whom were homozygous for *APOE* ε4.[124]

Isolated microbleeds (ie, participants with ARIA-H who did not also have ARIA-E) are believed not to be causally related to treatment. The incidence of isolated ARIA-H with lecanemab was 9% of patients, versus 13% with donanemab and 12% with placebo.[102,121] The incidence of symptomatic isolated ARIA-H with lecanemab was six (0·7%) of 898 of patients and two (0·2%) of 897, respectively.[102] Major intracerebral haemorrhages were infrequent events, occurring in five participants treated with lecanemab and three with donanemab versus one and two participants treated with placebo, respectively.[101,102]

Monitoring requires regular MRIs, ideally on the same scanner (so as to be most able to detect change from the baseline MRI), and with timing and sequences as specified in the product information for the relevant agent. If ARIA is detected, decision algorithms based on imaging and clinical criteria will lead to a personalised decision as to whether to pause or discontinue treatment.[125] This pause or discontinuation of treatment varies between countries, but in simple terms treatment should only continue if the patient is asymptomatic and the ARIA is radiographically mild (as defined by an ARIA severity scale).[119] Ischaemic stroke unrelated to anti-β amyloid monoclonal antibodies poses a particular challenge due to a likely significant increased risk of intracerebral haemorrhage with thrombolytic therapy.[126]

Several trials of anti-β amyloid monoclonal antibodies (including those of lecanemab and donanemab) have shown greater brain volume reduction and more ventricular enlargement compared with placebo.[127–129] Originally considered paradoxical, these excess volume changes are characteristic of only those immunotherapies that achieve lowering of β-amyloid concentrations and cause ARIA. Evidence suggests that the parenchymal changes are most compatible with plaque removal and regression of plaque-associated inflammation, whereas the ventricular changes might relate to changes in CSF dynamics induced by ARIA-E. Evidence to date does not suggest an association between amyloid-removal-related pseudoatrophy and adverse cognitive or functional outcomes.[127,128] Patient-level data, long-term follow-up, and more autopsy studies will be important for understanding this finding.

Open clinical issues

The benefit–risk ratio of monoclonal antibody treatment of individuals homozygous for APOE ε4 is debated, with the USA taking a liberal, and the EU taking a restrictive, approach. Despite ARIA being more frequent in individuals homozygous for *APOE* ε4, no evidence indicates greater clinical seriousness compared with heterozygotes and non-carriers, and, at least with donanemab, a minimally slower titration (compared with the titration regimen of clinical trials) can decrease

	Lecanemab (n=898)	Donanemab (n=853)	All placebo (n=1771)
Proportion relative to treated or placebo			
Of any severity			
All	12·6% (10·6–14·9); 9 (8–12)	24·0% (21·3–27·0); 5 (4–5)	1·8% (1·3–2·5)
ε4 non-carrier	5·4% (3·3–8·7); 20 (13–43)	15·7% (11·7–20·7); 7 (5–10)	0·6% (0·2–1·6)
ε4 heterozygous	10·9% (8·4–14·0); 11 (8–17)	22·8% (19·2–26·9); 5 (4–6)	1·9% (1·2–3·0)
ε4 homozygous	32·6% (25·4–40·7); 3 (3–5)	40·6% (32·9–48·8); 3 (2–4)	3·6% (2·0–6·5)
Symptomatic			
All	2·8% (1·9–4·1); 36 (26–59)	5·8% (4·5–7·4); 18 (14–24)	0·1% (0–0·3)
ε4 non-carrier	1·4% (0·6–3·6); 70 (35–2565)	4·1% (2·4–7·1); 24 (16–54)	0% (0–0·7)
ε4 heterozygous	1·7% (0·8–3·3); 60 (36–191)	6·1% (4·4–8·5); 16 (12–25)	0% (0–0·4)
ε4 homozygous	9·2% (5·5–15·1); 11 (7–23)	7·7% (4·6–12·8); 14 (9–34)	0·3% (0·1–1·8)
Severe on MRI			
All	1·0% (0·5–1·9); 100 (60–285)	1·6% (1–2·7); 61 (40–126)	0% (0–0·2)
ε4 non-carrier	0% (0–1·4); infinity	0·4% (0·1–2·2); 255	0% (0–0·7)
ε4 heterozygous	0·4% (0·1–1·5); 240	2·0% (1·1–3·7); 50 (31–142)	0% (0–0·4)
ε4 homozygous	5·0% (2·4–9·9); 20 (12–73)	2·8% (1·1–7·0); 36 (18–1057)	0% (0–1·4)
Clinically serious			
All	0·3% (0·1–1·0); 299	1·5% (0·9–2·6); 65 (43–142)	0% (0–0·2)
ε4 non-carrier	0% (0–1·4); infinity	0·4% (0·1–2·2); 255	0% (0–0·7)
ε4 heterozygous	0·4% (0·1–1·5); 240	1·8% (0·9–3·5); 57 (34–180)	0% (0–0·4)
ε4 homozygous	0·7% (0·1–3·9); 141	2·8% (1·1–7·0); 36 (18–1057)	0% (0–1·4)

(Table 3 continues on next page)

	Lecanemab (n=898)	Donanemab (n=853)	All placebo (n=1771)
(Continued from previous page)			
Proportion relative to radiological ARIA-E			
Symptomatic			
All	22·1% (15·5–30·6); NA	23·8% (18·8–29·5); NA	2·9% (0·5–14·9)
ε4 non-carrier	26·7% (10·9–52); NA	27·9% (16·7–42·7); NA	0% (0–56·1)
ε4 heterozygous	15·4% (8–27·5); NA	25·4% (18·6–33·6); NA	0% (0–16·8)
ε4 homozygous	28·3% (17·3–42·5); NA	18·6% (11·2–29·2); NA	9·1% (1·6–37·7)
Severe on MRI			
All	8·0% (4·2–14·4); NA	6·8% (4·1–11·1); NA	0% (0–10·7)
ε4 non-carrier	0% (0–20·4); NA	2·5% (0·4–12·9); NA	0% (0–56·1)
ε4 heterozygous	3·8% (1·1–13); NA	8·7% (4·7–15·8); NA	0% (0–17·6)
ε4 homozygous	15·2% (7·6–28·2); NA	6·9% (2·7–16·4); NA	0% (0–27·8)
Clinically serious			
All	2·7% (0·9–7·5); NA	6·3% (3·7–10·5); NA	0% (0–10·7)
ε4 non-carrier	0% (0–20·4); NA	2·5% (0·4–12·9); NA	0% (0–56·1)
ε4 heterozygous	3·8% (1·1–13); NA	7·8% (4–14·6); NA	0% (0–17·6)
ε4 homozygous	2·2% (0·4–11·3); NA	6·9% (2·7–16·4); NA	0% (0–27·8)

Data are % (95% CI); number needed to harm (95% CI). Number needed to harm data are number of people who are expected to be treated for one adverse event to occur. The method for calculating number needed to harm is provided in the appendix (p 5). As the inclusion criteria for the trials were largely similar, placebo groups are merged. Data on the incidence of symptomatic ARIA by *APOE* ε4 genotypes were not available in the donanemab placebo-controlled phase 3 trial.[101] Rates have been computed based on pooled phase 2 and phase 3 placebo-controlled trials.[120] ARIA-E=amyloid-related imaging abnormalities with oedema. NA=not applicable.

Table 3: **Incidence of ARIA-E in randomised controlled trials of lecanemab and donanemab and number needed to harm**

ARIA by three-fold in homozygotes and by 40% in heterozygotes.[120]

A pressing question is whether the separation between placebo and treatment curves widens progressively, supporting the claim of disease modification. Trials with a follow-up longer than the 18 months of registration trials, ideally with a staggered start or staggered withdrawal design, would help to provide an answer. Allied to this question is whether any benefits will translate into longer preserved independent function and then compressed morbidity—the biggest driver of economic cost being the care needed in later stages. Also unanswered is at which stage treatment is best started to maximise benefit.

The clinical trials of donanemab and lecanemab allowed co-treatment with cholinesterase inhibitors, memantine, or both. In theory, the benefit of disease-modifying treatments should increase over time and be additive to that of symptomatic drugs (appendix p 4). As both cholinesterase inhibitors, memantine are in routine clinical use in most countries, ethical considerations might make it impossible to test this hypothesis in randomised placebo-controlled trials. Some evidence, albeit less stringent, might be obtained through observational designs with historical controls.[130]

Subgroups with responses higher and lower than average allow for the maximisation of the benefit–risk ratio. Post-hoc analyses with insufficient statistical power have suggested differential effects of lecanemab and donanemab by age, sex, and *APOE* genotype,[101,102] but trials should be designed to answer these questions a priori—at this point we do not have sufficient information to opine. Predictors of greater benefit will need to be weighed alongside the well established predictors of risk for ARIA-E (*APOE* ε4 carrier status and MRI evidence of cerebral amyloid angiopathy)—markers to predict severity of ARIA are absent. As a result, the current regimen (with frequent MRI monitoring) is borne of an abundance of caution. Ongoing work on novel third-generation anti-β amyloid immunotherapies, such as trontinemab, provide promise in reducing side-effects and maximising efficacy (NCT04639050).

Maintenance dosing of lecanemab with monthly infusions has recently been approved by the US Food and Drug Administration (FDA),[131] but when anti-β amyloid monoclonal antibodies should be paused or discontinued, apart from adverse effects, is not clear from the FDA and European Medicines Association (EMA) prescribing information.[119,125,132] The EMA mentions that lecanemab is indicated in individuals with a "clinical diagnosis of MCI [mild cognitive impairment] and mild dementia due to Alzheimer's disease",[132] implicitly implying discontinuation in individuals progressing to more severe stages. The FDA's wording that treatment should be initiated in the mild cognitive impairment and mild dementia stages implies that treatment can be continued in more severe stages.[119]

As with any treatment, if the perceived treatment burden or risks outweigh potential quality of life benefits, discontinuation should be discussed with patients and their families. In patients with serial cognitive assessments before treatment, evidence of no slowing—or even acceleration—of progression might support discontinuation. However, this progression is notoriously difficult to assess in individual patients. Moreover, immunotherapies introduce new considerations, notably whether to continue treatment based on biological markers, such as normalised amyloid levels on PET scans. If amyloid PET scanning is available, showing amyloid burden reduction to normal can justify stopping or reducing treatment to a maintenance dose[101]—akin to reaching remission. Nevertheless, long-term clinical efficacy beyond 18 months is uncertain, and β-amyloid is expected to reaccumulate over time; whether this accumulation will be clinically significant remains unknown. A threshold of biomarker non-response—in terms of amyloid reduction—might eventually guide decisions of continuing treatment. Plasma markers currently under validation for disease tracking might enable single-patient monitoring in the future, aiding discontinuation decisions.[133]

Another challenge lies in the generalisability of the trial results. Current studies involve selected populations, with few comorbidities, and under-represented ethnic groups. International treatment registries will be

essential to gather data on diverse populations. The issue of equity within low-income and middle-income countries remains unresolved—these drugs are often unaffordable in such settings, where nearly two-thirds of individuals with cognitive disorders worldwide live.[5] Cost-effectiveness studies tailored for low-income and middle-income countries are crucial, as clinical trials did not include individuals living in these regions.[134] Populations under consideration for these therapies include individuals with genetically defined early-onset Alzheimer's disease. Early secondary prevention trials of anti-β amyloid therapies in this group have shown biological, but not cognitive, benefits, but clinical trials of lecanemab in combination with an anti-tau therapy are underway.[135] Organisational and pharmacoeconomic issues of monoclonal antibody treatment for Alzheimer's disease and novel drugs and modes of action are addressed in paper 3 of this Series.[110]

Health-care system implementation

In many countries (eg, the UK and most low-income and middle-income countries), most patients with cognitive impairment have CT or no structural scan, and only a minority have MRI as part of their assessment. Routine use of anti-β amyloid monoclonal antibodies will require MRIs to exclude cerebral amyloid angiopathy and assess eligibility, along with additional MRIs (three or four MRIs in the first year) for ARIA monitoring in all patients who receive treatment, plus follow-up in case of ARIA. This approach will necessitate expanding MRI capacity globally.

Anti-β amyloid monoclonal antibodies for Alzheimer's disease will challenge health-care systems worldwide, potentially widening existing disparities in access to diagnosis, care, and support. Facilities and specialised staff will need to be scaled up to administer fortnightly or monthly infusions until subcutaneous formulations are approved outside the USA.[136] Enhanced diagnostic capabilities, particularly to confirm amyloid status via PET CSF biomarkers, are essential. As blood-based biomarkers become standardised, together with normality thresholds, and achieve high predictive value accuracy for Alzheimer's disease pathology,[137] PET and CSF testing could be replaced in up to 90–95% of cases,[138] vastly improving accessibility, particularly in low-income and middle-income countries.

Anti-β amyloid monoclonal antibodies for Alzheimer's disease will create opportunities for cross-specialty collaborations between dementia specialists, neuro-radiologists, general neurologists, emergency departments, nuclear and laboratory medicine specialists, and nurses. Eligibility and adverse events might be discussed at multidisciplinary memory boards, in analogy to the successful model developed in oncology.[139] Standard operating procedures for the emergency management of ARIA should be developed locally and shared among all actors.[140] Several regional working groups have already developed recommendations that should inspire local standard operating procedures.[105–108]

However, there is a wider challenge. Historically, individuals have delayed seeking advice for cognitive concerns, believing there is little that can be done. In the UK, it is estimated that 35% of patients with dementia never receive a diagnosis.[141] Awareness about anti-β amyloid monoclonal antibodies for Alzheimer's disease might lead more patients with cognitive impairment or concerns to seek advice. Clinical services, primary and secondary, will need to change their approach and make diagnoses more swiftly. If not, patients might progress past the point of eligibility while awaiting appointments and diagnostic tests.

These challenges come with opportunities for all patients with cognitive complaints and impairment. Greater societal awareness of the importance of early diagnosis and greater accessibility to diagnostic facilities might translate into timelier diagnoses and better post-diagnostic support. The potential for new effective therapies to drive wide-ranging improvements in services has been seen in many medical conditions.

Conclusions

Knowledge and practice around therapeutical strategies to improve the quality of life of people with Alzheimer's disease have increased dramatically over recent decades. Structured non-pharmacological programmes are being used for the management of BPSDs along with better tolerated drugs than those used previously. Symptomatic drugs for cognitive impairment, although with limited efficacy, have forced health-care systems to organise dedicated expert care networks, thus facilitating access to diagnosis and care. Anti-β amyloid monoclonal antibody treatment for Alzheimer's disease represents the latest tool and promise long-term improvements of patients' quality of life.

Every step of this ever-improving journey has come at a cost for society, and anti-β amyloid monoclonal antibodies will not be an exception. The debate on the clinical meaningfulness of the effect of anti-β amyloid monoclonal antibodies, their cost–benefit ratio, the appropriateness of resource allocation, and the benefit to the quality of life of society at large will engage the community of Alzheimer's disease experts and decision makers for years to come. Data from real life observational cohorts from high-income countries and from low-income and middle-income countries will be key for informed choices. However, the amount of resources to devote to ameliorate the quality of life of people with Alzheimer's disease will ultimately be a political and societal—not a clinical—decision. Insight into some elements of this debate is provided in the third paper of this Series on controversies and the future.[110]

Contributors

GBF drafted the structure of the paper and an early draft of text, tables, and figures with input from NCF. HCK was the main contributor to the section on non-pharmacological treatments for behavioural and psychological symptoms of dementia. CBa was the main contributor to section on pharmacological treatments. ZI was the main contributor to the section on symptomatic treatment for cognitive impairment. CM was the main contributor to the sections on efficacy and clinical

meaningfulness and open clinical issues. NCF and CBe contributed to the sections on current symptomatic therapies versus anti-β amyloid monoclonal antibodies, eligibility and exclusion, and safety and follow-up. NCF revised the final version of the paper for scientific consistency and narrative coherence. All authors did the pertinent literature searches, revised the manuscript one or more times, and contributed important intellectual content. Authors appearing on individual papers of the Series contributed to those papers only and had no contribution to the other papers. All authors had the opportunity to read final drafts of all the Series papers pre-acceptance and agree that the paper they co-authored appears in this Series.

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All other authors declare no competing interests.

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