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CONTENTS

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Cover Picture

Carl Wilhelm Scheele (1742 – 1786)

Greatest of pharmacist – chemists, Scheele experimented constantly in Swedish apothecary shops, gave the world many chemical discoveries, including oxygen, chlorine, fruit acids and glycerin that contribute to today's industry and daily life.

The Sri Lanka Prescriber

Management of childhood epilepsy

Introduction

Childhood epilepsy is a chronic neurological condition characterized by recurrent, unprovoked seizures in children. It affects approximately 0.5–1% of children globally [1], making it one of the most common neurological disorders in paediatric populations. Sri Lankan data describes a prevalence of 5.7 per 1000 in children below 16 years [2]. The condition can manifest at any age during childhood, highest incidence being in infancy. Early diagnosis and appropriate management are critical to improving the quality of life and developmental outcomes for affected children.

The causes of childhood epilepsy can be multifactorial. The common causes are related to structural abnormalities of the brain and genetic factors. These account for 21% and 10% in children and youth with epilepsy [3]. Another 24% is considered to have a presumed genetic aetiology. Metabolic disorders, inflammation and infection as aetiologias affect only a minority. There is a sizable proportion of children with epilepsy with no identifiable cause even following extensive investigation including neuroimaging, genetic testing, and metabolic evaluations. This proportion varies according to age; those children less than 2 years are more likely to have a known aetiology.

Epilepsy is considered to be a system disorder, hence the impact of epilepsy extends beyond seizures, affecting cognitive development, behavior, and psychosocial well-being. Children with epilepsy often face academic challenges, social stigma, and emotional difficulties. Therefore, caring for such a child requires a comprehensive input from the neurologist/ paediatrician/ physician. There may be requirement for additional input from other disciplines such as psychologists, educators, and social workers.

Treatment of childhood epilepsy primarily involves anti-seizure medications (ASMs), which aim to control seizures while minimizing adverse effects. The choice of ASM depends on the seizure type, underlying cause, age of the child, and potential adverse effects. In drug-resistant epilepsy, where seizures remain uncontrolled despite appropriate medical therapy, alternative treatments such as ketogenic diets, vagus nerve stimulation or epilepsy surgery may be considered. Early intervention, individualized treatment, and ongoing support can significantly improve outcomes for children with epilepsy. This article discusses a rational approach to treatment and management of childhood epilepsy.

Rational approach to treatment of epilepsy

The first step in understanding epilepsy is making an accurate diagnosis. This begins with a clear understanding of the definition of epilepsy. The practical clinical definition and pragmatic approach for the diagnosis of seizures and epilepsy outlined by the ILAE Task Force on Classification and Nosology in 2014 provide a framework for clinicians [4] . According to this framework, a diagnosis of epilepsy is made if at least one of the following criteria is met: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure with a high probability of recurrence (at least 60%) over the next 10 years; or (3) the diagnosis of an epilepsy syndrome (Box 1). These criteria are essential for guiding clinicians toward an accurate diagnosis and facilitating the development of a tailored treatment strategy [4].

Box 1: Diagnostic criteria for epilepsy (any one of below)

(1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart

(2) one unprovoked (or reflex) seizure with a high probability of recurrence (at least 60%) over the next 10 years

(3) the diagnosis of an epilepsy syndrome

Subsequent to diagnosis of epilepsy, the main determinant of the best approach to therapy is guided by understanding the type of epilepsy. This concept was established in the position paper on classification of epilepsies again by the ILAE Task Force on classification in 2017 in their position papers on classification of seizures and epilepsy [5]. The clinician is encouraged to identify the seizure type as the first step in the evaluation. Based on the seizure type, the epilepsies are divided as being a focal epilepsy, generalised epilepsy, focal and generalised epilepsy. This is based on whether the seizures are originating from a focus (focal) or due to rapid activation of neuronal networks bilaterally (generalised). The fourth group known as unknown is considered if the clinician is unable to clearly identify whether the seizures are focal or generalised. This pragmatic approach to establish the epilepsy type is illustrated in Figure 1.

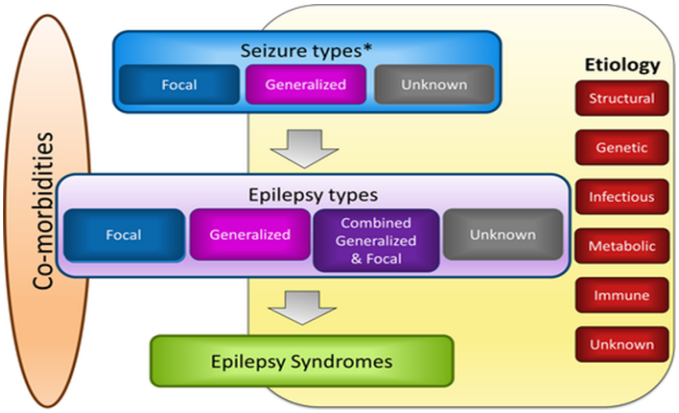

Figure 1: ILAE framework for classification of the epilepsies [5]

In children particularly, the epilepsy together with accompanying electroclinical characteristics determine the underlying epilepsy syndrome. Though not possible to diagnose a syndrome in every epilepsy patient, in most instances, it facilitates an understanding of the specific age of presentation, electroencephalographic findings, underlying aetiology, response to therapy and long-term outcome. Therefore, trying to identify the epilepsy syndrome helps the clinician to optimise the plan on investigations, choice of therapy and long-term follow up.

Pharmacological management

Diagnosis of epilepsy does not necessarily mean need for medication. There are many instances, when despite the diagnosis a conservative approach of observation is possible, particularly when the paediatric epilepsy syndrome has a self-limited course.

In others the cornerstone of epilepsy management is the use of ASMs**.** The selection of ASMs depends on several factors, including:

- Seizure type (i.e. focal, generalized or unknown onset)
- Epilepsy syndrome (e.g., Lennox-Gastaut syndrome, Dravet syndrome)
- Patient's age, sex, and co-morbidities
- Potential side effects and interactions with other medications
- Cost of medication and availability

Of these the most important single factor that governs the choice of medication is the efficacy of each medication in controlling the specific seizure type i.e. focal or generalised or both.

The last three decades witnessed a massive expansion of the number of available ASMs resulting in the total number of ASMs approved by FDA exceeding 30. They are categorized as first generation (Old), second generation (new) and third generation (newer) ASMs. (Table 1). The choice of appropriate ASMs is governed by many factors, but as stated above, the most important factor is the

efficacy of each ASM towards the specific seizure type or epilepsy syndrome.

Table 1: Classifications of anti-seizure medicines according to generation (the year of introduction of each drug is given in parentheses)

First-Generation ASMs (Older)	Second-Generation ASMs (Newer)	Third-Generation ASMs (Newest)
Phenobarbital (1912)	Gabapentin (1993)	Perampanel (2012)
Phenytoin (1938)	Lamotrigine (1994)	Brivaracetam (2016)
Trimethadione (1946)	Topiramate (1996)	Cannabidiol (2018)
Primidone (1952)	Tiagabine (1997)	Cenobamate (2019)
Ethosuximide (1960)	Levetiracetam (1999)	Fenfluramine (2020)
Carbamazepine (1963)	Oxcarbazepine (2000)	Ganaxolone (2022)
Valproic Acid (1967)	Zonisamide (2000)	Stiripentol (2018)
Clonazepam (1975)	Pregabalin (2004)	Everolimus (2018)
Diazepam (1963)	Rufinamide (2008)	Midazolam Nasal Spray (2019)
Lorazepam (1972)	Lacosamide (2008)	Diazepam Nasal Spray (2020)
	Eslicarbazepine Acetate (2009)	
	Vigabatrin (2009)	
	Clobazam (2011)	

The first generation ASMs were introduced to the market before 1990, and to date remain the most commonly used ASMs globally. They include valproic acid; the drug of choice for absence epilepsy and juvenile myoclonic epilepsy, carbamazepine; the first line for focal epilepsy, ethosuximide; another drug of choice for absence epilepsy as well as clonazepam, phenobarbitone, and phenytoin. The second line medications introduced from the 1990s onward, have improved tolerability, fewer drug interactions, and better pharmacokinetics. However, they do not show a superiority over the first line medications for efficacy. The third generation ASMs were introduced to the marked after 2020. These are mostly reserved for refractory patients and offer refined mechanisms and improved tolerability. However, the cost of these medications is substantial. The first line ASMs are both effective and cost effective and are ideal for a resource limited country like Sri Lanka,

The general strategy in treating epilepsy involves starting with monotherapy: using a single ASM, at a low dose and gradually increasing the dosage until seizure control is achieved or side effects occur. Monotherapy is typically preferred to minimize side effects, and dosage adjustments are made based on seizure control and tolerability. If seizures persist, another ASM is introduced as a monotherapy.

In drug-resistant cases, defined as seizures remaining uncontrolled despite trials of two appropriate ASMs, polytherapy (combining two or more ASMs) may be considered. Polytherapy is also considered early when the initial seizure load is high or when the patient experiences different types of seizures.

When an epilepsy patient does not respond to two correctly chosen ASMs of adequate dosage given for an adequate duration, they are considered to have drug resistant epilepsy[6]. Usually this may account for about 30% of childhood epilepsies. These children may be offered different combinations of ASMs (often not more than three at any given time) or referred for non-pharmacological treatment options. These include:

- Ketogenic Diet: A high-fat, low-carbohydrate diet that has shown effectiveness in reducing seizure frequency, especially in refractory cases.

- Vagus Nerve Stimulation (VNS): An implanted device that delivers electrical impulses to the vagus nerve, reducing seizure frequency in some children.
- Epilepsy Surgery: Recommended for children with focal epilepsy arising from a specific brain region. Surgical removal of the epileptogenic zone can result in significant seizure reduction or complete remission.

Other aspects of managements

Children with epilepsy often face challenges beyond seizures, including cognitive difficulties, behavioral problems, and social stigma[7]. Evaluating for these psychosocial and learning issues should be an integral part of assessments of all children with epilepsy. Early intervention with special education services, speech therapy, occupational therapy, and psychological support for those in need is crucial. Together with the family, a multidisciplinary team including the neurologist, physician or paediatrician, psychologists, educators, and social workers, should work together to support the child's developmental and emotional needs.

Monitoring and follow-up

Regular follow-up is essential to monitor seizure control, medication side effects, growth, and developmental progress. Repeat or serial electroencephalography is not indicated in most children. However, they may be repeated, in those suspected of possible worsening or development of new seizure types or evaluated for potential development of an epileptic encephalopathy. Neuroimaging with magnetic resonance imaging is important to identify underlying structural (congenital or acquired) abnormality. Medication adherence and side effects should be closely monitored, particularly during periods of rapid growth or puberty.

Family education and support

Educating families about seizure recognition, first aid, and medication adherence is critical. Families should also be informed about safety precautions, such as avoiding swimming alone and ensuring adequate supervision during activities that pose a risk of injury during seizures. At the same time, advocating to the family and school to support the child in participating in both curricular and extra-curricular activities is vital. Advice on first aid during a recurrence of seizures birth at home and school is also required.

Conclusion

Childhood epilepsy is a common neurological condition affecting 0.5–1% of children globally, with a prevalence of 5.7 per 1000 in Sri Lanka. It is a system disorder which impacts cognition, behavior, and psychosocial well-being. Diagnosis follows the ILAE 2014 framework, requiring either two unprovoked seizures**,** one seizure with a high recurrence risk**,** or an epilepsy syndrome diagnosis. The 2017 ILAE classification further categorizes epilepsy into focal, generalized, combined, or unknown onset types, aiding treatment selection.

Treatment primarily involves anti-seizure medications (ASMs)**,** chosen based on seizure type and epilepsy syndrome. First-generation ASMs (e.g., valproate, carbamazepine) are widely used, while second-generation ASMs (e.g., lamotrigine, levetiracetam) offer better tolerability. Third-generation ASMs (e.g., cannabidiol, cenobamate) are used for drug-resistant cases. Monotherapy is preferred, with polytherapy reserved for refractory epilepsy. For drug-resistant epilepsy, alternative treatments like ketogenic diets, vagus nerve stimulation, and epilepsy surgery are considered. Psychosocial support, regular monitoring, and family education are crucial for optimal outcomes.

References

1. Hauser WA: Epidemiology of epilepsy in children. *Neurosurg Clin N Am* 1995, 6(3):419-429.
2. Wanigasinghe J, Arambepola C, Murugupillai R, Chang T: Age, sex and ethnic differentials in the prevalence and control of epilepsy among Sri Lankan

children: a population-based study. *BMJ Paediatr Open* 2019, 3(1):e000430.
3. Vikin T, Lossius MI, Brandlistuen RE, Chin RF, Aaberg KM: Incidence of childhood and youth epilepsy: A population-based prospective cohort study utilizing current International League Against Epilepsy classifications for seizures, syndromes, and etiologies. *Epilepsia* 2025.
4. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Jr., Forsgren L, French JA, Glynn M *et al*: ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014, 55(4):475-482.
5. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL *et al*: ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017, 58(4):512-521.
6. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J: Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010, 51(6):1069-1077.
7. Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC: Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. *Nat Rev Neurol* 2016, 12(8):465-476.

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Optimizing Parkinson's Disease Management: A Comprehensive Approach

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting millions of adults worldwide. It is primarily characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. However, PD also encompasses a spectrum of non-motor manifestations, including cognitive impairment, mood disorders, autonomic dysfunction and sleep disturbances, which significantly impact patients' quality of life. Given its multifaceted nature, effective management of PD necessitates an integrated approach that combines pharmacological therapy, non-pharmacological strategies, surgical interventions, and multidisciplinary care.

Pharmacological Management

Levodopa and Dopaminergic Therapy

Levodopa remains the gold-standard therapy for PD due to its potent symptom relief. It is administered in combination with a peripheral dopa decarboxylase inhibitor such as carbidopa or benserazide to enhance central bioavailability while minimizing peripheral side effects like nausea and hypotension. With advanced PD where motor complications such as motor fluctuations and dyskinesias are likely to occur, levodopa needs careful dose titration along with adjunctive therapies.

Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) are often used in early PD, particularly in younger patients, to delay levodopa initiation. However, they are associated with side effects such as somnolence, impulse control disorders and peripheral edema, which must be monitored carefully. Monoamine oxidase-B (MAO-B) inhibitors (e.g., selegiline, rasagiline, safinamide) provide mild symptomatic relief by inhibiting dopamine breakdown, whereas catechol-O-methyltransferase (COMT) inhibitors (e.g., entacapone, opicapone) extend the half-life of levodopa and reduce wearing-off phenomena.

Addressing Motor Complications

Motor fluctuations, including wearing-off and dyskinesias, often emerge as PD progresses. Strategies to mitigate these include fractionating levodopa doses, introducing extended-release formulations, or employing adjuncts such as COMT inhibitors and MAO-B inhibitors. Amantadine, an NMDA receptor antagonist, is particularly beneficial in managing levodopa-induced dyskinesias. Patients experiencing severe motor fluctuations may benefit from continuous dopaminergic stimulation via subcutaneous apomorphine infusion or intrajejunal levodopa-carbidopa intestinal gel.

Non-Dopaminergic Treatments

In addition to dopaminergic therapy, non-dopaminergic agents play a crucial role in managing PD-related symptoms. Anticholinergics (e.g., trihexyphenidyl, benztropine) can provide relief for tremor-predominant PD but are limited by their cognitive side effects, particularly in elderly patients. Adenosine A2A receptor antagonists, such as istradefylline, offer an emerging alternative for motor symptom control. Treatment of non-motor symptoms such as depression, anxiety, psychosis and autonomic dysfunction require a tailored approach, with selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (e.g., pimavanserin, clozapine), and autonomic modulators (e.g., midodrine, fludrocortisone) playing key roles.

Non-Pharmacological Approaches

Physical Therapy and Rehabilitation

Exercise is a cornerstone of PD management, with substantial evidence supporting its role in improving motor function, balance, and overall wellbeing. Physiotherapy interventions, including resistance

training, aerobic exercise and balance exercises such as tai chi and dance therapy, have been shown to enhance mobility and reduce falls. Gait training, particularly treadmill-based rehabilitation, can improve stride length and walking speed. Occupational therapy assists patients in maintaining independence in activities of daily living (ADLs) by implementing adaptive strategies and use of assistive devices.

Speech and Swallowing Therapy

Hypophonia and dysphagia are common in PD, often leading to social withdrawal and malnutrition. Swallowing assessment and modified diets are essential to mitigate aspiration risk and ensure adequate nutrition. In advanced cases, percutaneous endoscopic gastrostomy (PEG) could be considered.

Cognitive and Psychological Support

Cognitive decline and neuropsychiatric symptoms significantly impact PD patients. Cognitive behavioral therapy (CBT) and structured cognitive training can alleviate anxiety and depression, whereas cholinesterase inhibitors (e.g., rivastigmine) are beneficial for PD dementia. Caregiver education and psychosocial support are vital in maintaining patient well-being and reducing caregiver burden.

Surgical and Advanced Therapies

Deep Brain Stimulation (DBS)

DBS is a well-established intervention for patients with medically refractory motor fluctuations or severe tremor. The procedure involves the implantation of electrodes in deep brain structures, most commonly the subthalamic nucleus (STN) or globus pallidus interna (GPi). While DBS effectively reduces motor symptoms and medication dependency, patient selection is crucial—optimal candidates typically exhibit levodopa-responsive symptoms without significant cognitive impairment or psychiatric co-morbidities.

Infusion Therapies

For patients with advanced PD experiencing severe fluctuations, continuous infusion therapies provide an alternative to oral medication. Subcutaneous apomorphine infusion delivers consistent dopaminergic stimulation, reducing off-periods. Similarly, intrajejunal infusion of levodopa-carbidopa gel offers steady drug delivery, bypassing gastric emptying delays associated with PD.

Multidisciplinary and Supportive Care

Comprehensive Care Teams

Optimal PD management necessitates a multidisciplinary approach involving neurologists, physiotherapists, occupational therapists, speech therapists, dietitians, and psychologists. Coordinated care ensures comprehensive symptom control and maximizes functional independence.

Palliative Care and End-of-Life Planning

As PD progresses, palliative care principles should be incorporated to address pain, dysautonomia, and quality-of-life concerns. Advanced care planning, including discussions about feeding options and respiratory support. End-of-life care empowers patients and families to make informed decisions aligned with their values.

Conclusion

Parkinson’s disease is a complex disorder requiring an individualized and evolving management strategy. Pharmacological treatment remain the mainstay of therapy, but non-pharmacological interventions and surgical options play integral roles in optimizing outcomes. A holistic, multidisciplinary approach that addresses both motor and non-motor symptoms is essential to improving patient quality of life. As research advances, future therapies may offer neuroprotective benefits and alter disease progression.

Key take-home messages:

1. Individualized, Multidisciplinary Management is Key: Parkinson's disease is a complex disorder requiring a personalized approach that integrates pharmacological, non-pharmacological, and surgical therapies, with input from a multidisciplinary team.

2. Non-Motor Symptoms Significantly Impact Quality of Life: Cognitive decline, mood disturbances, autonomic dysfunction, and sleep disorders must be proactively addressed to improve patient outcomes and overall wellbeing.

3. Early Consideration of Advanced and Palliative Care: DBS and infusion therapies should be considered in appropriate candidates with refractory motor symptoms while palliative care planning ensures holistic and patient-centered disease management.

Further reading

1. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386(9996):896-912.
2. Olanow CW, Stocchi F, Lang AE. Parkinson's disease: non-motor and non-dopaminergic features. Mov Disord.2011;26 Suppl 1:S3-S15
3. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284-2303.
4. Espay AJ, Lang AE. Common myths in the use of levodopa in Parkinson disease. JAMA Neurol. 2017;74(6):633-640

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New and emerging drug therapies for Alzheimer disease

SUMMARY

Established drug therapies for Alzheimer disease (cholinesterase inhibitors and memantine) do not modify the disease course and provide only modest clinical benefit. Biomarker measures of amyloid, tau and neurodegeneration have been integral to Alzheimer disease clinical trials for biologic drugs, for patient selection and efficacy monitoring. At the time of writing, two monoclonal antibodies targeting the amyloid-beta protein (aducanumab and lecanemab) have been approved in the USA, and two agents (lecanemab and donanemab) are under evaluation by the Therapeutic Goods Administration in Australia. Clinical trials have demonstrated that monoclonal antibodies are effective at removing amyloid from the brain in people with early Alzheimer disease. Cognitive benefits are statistically significant, but do not achieve the minimal clinically important difference. Amyloid-related imaging abnormalities of vasogenic oedema and microhaemorrhages occur more frequently on treatment; although these are usually asymptomatic or transient, in some people they are serious or fatal. Targeting amyloid as a unimodal strategy is unlikely to be sufficient and future therapies may need to be multimodal, targeting multiple pathogenic pathways. The burden of dementia is greatest in the older population where mixed dementia pathology dominates; the relationship between biomarkers, clinical phenotype and pathology attenuates; and frailty and comorbidity impact cognition. This creates challenges in identifying effective therapies for the group where dementia is most prevalent.

Keywords

Alzheimer disease, amyloid, immunotherapies, dementia, monoclonal antibodies

(Aust Prescr 2024;47:75–9)

Introduction

Introduction Dementia is now the second leading cause of death in Australia and the leading cause of burden of disease in people aged over 65 years.1 Alzheimer disease is the most prevalent of the dementias. Cholinesterase inhibitors and memantine have been the only approved drug therapies for Alzheimer disease for over 20 years, and these provide modest symptomatic relief only. Recent trials showing that monoclonal antibodies can remove amyloid protein from the brain have generated optimism that disease modification may be possible, but clinically meaningful cognitive and functional benefits have not yet been demonstrated. At the time of writing, two monoclonal antibodies (aducanumab and lecanemab) have been approved in the USA by the Food and Drug Administration (FDA), and two agents (lecanemab and donanemab) are under evaluation by the Therapeutic Goods Administration in Australia.

Established drug therapies

Three cholinesterase inhibitors are approved for use in mild to moderate Alzheimer disease: donepezil, galantamine and rivastigmine. They are equally efficacious, with pooled trials demonstrating a 1.4 point improvement (on a 30-point scale) in the Mini Mental State Examination over 6 months.2 However, the response varies significantly, with only one-third of trial participants showing a clinically measurable benefit. Adverse effects are reported in up to one third of patients and include nausea, vomiting, diarrhoea, muscle cramps, syncope and insomnia. Postmarketing studies indicate that up to 35% of patients cease cholinesterase inhibitors because of adverse events.3 Relative contraindications include cardiac conduction delays, bradyarrhythmias, active peptic ulcer disease and obstructive urinary disease. Memantine, an N-methyl-D-aspartate receptor antagonist, is approved for moderate to severe Alzheimer disease. It provides a small benefit to

cognition, behaviour and the ability to perform activities of daily living; there is no evidence for benefit in mild disease.4 A reduction in agitation was identified in some but not all trials.5 Cost–benefit studies for cholinesterase inhibitors and memantine have failed to identify economic benefit, nor is there evidence that cholinesterase inhibitors delay transition to residential care.6,7 Therefore, although these drugs remain the mainstay of pharmacological management for Alzheimer disease, they fail to provide substantial symptomatic benefit and do not modify disease progression.

New and emerging therapies

Research into new therapies for Alzheimer disease has largely been dominated by the amyloid cascade hypothesis, whereby abnormal processing of the amyloid precursor protein results in pathological aggregation of the amyloid-beta protein into amyloid plaques and hyperphosphorylation of the protein tau to form neurofibrillary tangles in the brain. Biomarker measures have been integral to patient selection and efficacy monitoring in Alzheimer disease clinical trials. Amyloid, tau and other biomarkers of neurodegeneration are measured through cerebrospinal fluid, magnetic resonance imaging (MRI) and positron emission tomography (PET) biomarker studies. Plasma biomarkers remain in development.

Anti-amyloid monoclonal antibodies

The amyloid hypothesis has driven the development of monoclonal antibodies targeting specific epitopes of the amyloid-beta protein, with close to 30 monoclonal antibodies having been tested. The vast majority of monoclonal antibodies effectively remove amyloid, but improvements in cognitive function have been limited, and trials have identified an increased risk of amyloid-related imaging abnormalities (ARIA) (see below).8 In 2021 and 2023 respectively, the anti-amyloid monoclonal antibodies aducanumab and lecanemab received FDA approval for the treatment of mild cognitive impairment and mild Alzheimer disease. Aducanumab was recently discontinued by its manufacturer for commercial reasons. Donanemab is currently under consideration for approval by the FDA.

Aducanumab and lecanemab

Aducanumab was approved by the FDA on the basis of reduction in brain amyloid in 76-week clinical trials (EMERGE and ENGAGE).9 The primary outcome, an 18-point integrated scale of cognition and function, the Clinical Dementia Rating-Sum of Boxes (CDR-SOB), failed to identify any improvement at low dose, while at high dose there was a statistically significant difference. The 76-week lecanemab trial (CLARITY AD) found a statistically significant reduction in the CDR-SOB, with reduced brain amyloid burden.10 Of note, neither aducanumab or lecanemab achieved the minimal clinically important difference (MCID) in cognitive or functional endpoints. The MCID refers to the smallest change in cognitive or functional endpoints that constitutes a clinically meaningful treatment effect. The MCID for the CDR-SOB endpoint is a reduction of 0.98 points in people with mild cognitive impairment and 1.63 points in people with Alzheimer disease.11 In the high-dose aducanumab group the mean reduction in CDR-SOB was 0.39 (95% confidence interval [CI] 0.09 to 0.69) while lecanemab achieved a mean reduction of 0.45 (95% CI 0.23 to 0.67).9,10 That is, although the differences were statistically significant, they did not achieve a level that is viewed as clinically meaningful. While a degree of controversy surrounds the defining of clinically meaningful endpoints, particularly from the perspective of patients and carers, alternative approaches remain unvalidated.

Donanemab

In a 76-week phase 3 clinical trial of donanemab (TRAILBLAZER-ALZ 2), there was a significant difference in the primary outcome measure, the integrated Alzheimer's disease rating scale (iADRS), which is a 144-point scale incorporating cognition and function.12 Significant reduction in brain amyloid was demonstrated. However, the change in the iADRS of 2.92 (95% CI 1.51 to 4.33) did not achieve the MCID of 5 points for mild cognitive impairment and 9 for Alzheimer disease. In contrast to aducanumab and lecanemab, where therapy continued unless contraindicated, donanemab was switched to placebo when levels of brain PET amyloid reduced below a designated threshold, with the mean time for this being 47 weeks. Therefore, for the 3 monoclonal antibodies at the forefront of approval, brain amyloid was effectively removed but measures of cognitive and functional improvement did not achieve MCIDs.

Amyloid-related imaging abnormalities (ARIA)

ARIA are detected on MRI, necessitating regular monitoring scans. There are two subtypes of ARIA, which often co-occur: ARIA-E (vasogenic oedema) and ARIA-H (microhaemorrhage). ARIA occurred in 42 to 44% of patients who received high-dose aducanumab, compared with 9% who received placebo.9 In the lecanemab trial, ARIA occurred in 21.5% of treated patients versus 9.5% with placebo.10 ARIA occurred in 36.8% of donanemab-treated patients versus 14.9% in the placebo arm.12 The majority of ARIA are asymptomatic or mild with symptoms including headache, delirium and gait disturbance. Continuation or temporary suspension of the monoclonal antibody, with MRI monitoring, is recommended in mild or asymptomatic cases. However, severe ARIA are life-threatening, necessitating withdrawal of the monoclonal antibody and commencement of immunosuppressive therapy. Risk of ARIA is associated with increased age, higher monoclonal antibody dose, and apolipoprotein E ε4 homozygosity (the strongest genetic risk factor for sporadic Alzheimer disease).8

Will treating earlier with anti-amyloid monoclonal antibodies be more effective?

The TRAILBLAZER-ALZ 2 donanemab trial stratified patients according to biomarker tau load, and identified that those with low or medium tau levels had a better response, suggesting that treating earlier was more efficacious. Trials are in development for lecanemab and donanemab in participants with positive Alzheimer biomarkers and intact cognition. In 2 recently published papers looking at preclinical Alzheimer disease and mild cognitive impairment, solanezumab attenuated accumulation of amyloid in a 240-week trial but had no impact on cognition,13 while gantenerumab effectively reduced amyloid but did not impact cognitive decline over 116 weeks.14 Therefore, although amyloid removal was effective in prodromal disease, there was no impact on cognition. An alternative, more optimistic view is that there may be a delayed benefit of amyloid removal in prodromal disease but, in the absence of supporting data, benefits are not confirmed.

Other unanswered questions about amyloid removal

Where amyloid removal is confirmed, there is a concurrent reduction in brain volume and an increase in ventricular size, termed pseudoatrophy.15 While postulated to reflect amyloid removal, the relevance and long-term effects of reduction in brain size are unknown.16

The potential impact of ARIA on natural progression of Alzheimer disease is unknown, with one study demonstrating that microbleeds, though often asymptomatic, resulted in faster decline.17 Further unanswered questions include the rate and impact of amyloid re-accumulation and changes in symptom trajectory beyond the duration of trials.

Post-trial data with 3-year follow-up is anticipated and will assist in identifying whether there is a delayed benefit of amyloid removal.

Challenges with anti-amyloid monoclonal antibodies

There will be challenges in delivering anti-amyloid monoclonal antibodies. Studies suggest that less than 10% of patients with confirmed mild cognitive impairment or Alzheimer disease will be eligible for ARTICLE monoclonal antibody therapy,18 with the youngest and least comorbid likely to be most appropriate. Those where MRI is contraindicated will be excluded, as will those with significant comorbidities, other immune conditions, a history of seizures or stroke, and bleeding disorders or use of anticoagulants given the risk of ARIA-H. In those who pass initial medical screening, MRI scans to ensure that ARIA are not present and PET scans to confirm biomarker based eligibility will be required. The complexity of screening, staffing and infrastructure required to enable monoclonal antibody therapy has significant capacity implications with a concurrent need for counselling and care of those ineligible.

There is lower response to monoclonal antibody therapies in the setting of apolipoprotein E ε4 homozygosity,8 and increased risk of ARIA. Therefore, apolipoprotein E genotyping will be required to risk stratify and predict response in people assessed as eligible for treatment and without contraindications.

Lecanemab and donanemab are administered by intravenous infusion, at 2- and 4-weekly intervals respectively. This creates substantial patient and carer burden. Infrastructure requirements are significant, including skilled infusion services and ongoing access to MRI and amyloid and tau PET imaging to monitor response and adverse effects. In the event of symptoms suggestive of ARIA, additional MRI scans beyond recommended monitoring scans will be required.

Multidisciplinary teams of expert clinicians, nurses, radiologists and nuclear medicine physicians will be needed to assess, prescribe, administer and manage monoclonal antibodies, restricting their use to tertiary facilities thereby exacerbating existing inequities of socioeconomic status, cultural background and rural urban divide.

While the development of subcutaneously administered monoclonal antibodies and plasma-based biomarkers may alleviate some of these inequities, workforce and infrastructure needs will remain.

Economic studies have predicted significant strain on the health dollar in the setting of unfavourable cost-effectiveness of amyloid monoclonal antibody therapies.19,20 The economic question will need to be asked as to how essential services to facilitate safe community living can be afforded for the vast majority who will be ineligible for monoclonal antibodies or for those who continue to decline cognitively and functionally despite receiving a monoclonal antibody.

Future directions

Current scientific consensus is that amyloid-based strategies are unlikely to be sufficient for managing Alzheimer disease, and multiple pathogenic pathways will need to be addressed. The location and volume of tau correlates with clinical phenotype and severity;21 however, trials of monoclonal antibodies targeting tau have been discontinued because of lack of efficacy, or they are in their early stages.22 Other processes such as inflammation, vascular disease and metabolic pathways are recognised as key in pathogenesis. Tyrosine kinase inhibitors targeting inflammatory cells have shown mixed results and have been limited by the absence of biomarker measures.23 Trials of metformin,

semaglutide, insulin and empagliflozin are in progress, targeting insulin signalling, insulin resistance, and metabolic and inflammatory pathways.24

One of the major challenges is the epidemiology of dementia. In Australia, 43% of people with dementia are aged over 85 years.1 Pathological series confirm a high prevalence of mixed dementia pathology in this age group, with Alzheimer disease being only one of many pathologies present.25 With advancing age, the correlation between biomarkers, clinical phenotype and pathology attenuates making both interpretation and monitoring of biomarkers more challenging.26 Frailty increases with age, and the burden of neuropathology required for dementia to develop is less in the setting of frailty.27 Comorbidities correlate with age and predict biomarker positivity,28 with poorly controlled comorbidities predicting faster cognitive decline.29 Therefore, in the age group where the burden of dementia is greatest, single-disease therapies are unlikely to result in a 'cure', and focusing on comorbidities and frailty may be equally or more efficacious.

Is prevention the answer?

The Lancet Commission 2020 report identified 12 life course risk factors for dementia, with modification of these socioeconomic, lifestyle and environmental risk factors calculated as having the potential to prevent or delay up to 40% of dementias.30 However, the data are from observational studies and provide limited evidence that risk factor modification will produce the calculated reduction in dementia. Despite this, implementation of preventative strategies is supported, as they will enhance population health and not induce harm.

Conclusion

While trials of anti-amyloid monoclonal antibodies have generated much excitement regarding a potential cure for Alzheimer disease, the removal of amyloid has not translated to clinically meaningful cognitive or functional benefits. Trials of Alzheimer disease therapies targeting multiple pathogenic pathways are in progress, acknowledging that multimodal therapies may be required. Until disease modifying therapies are effective and broadly available, multidisciplinary care remains the mainstay of dementia management, including carer and patient education, post-diagnostic care, optimisation of comorbidities, and implementation of services.

Conflicts of interest: Non Declared

References

1. Australian Institute of Health and Welfare. Dementia in Australia Summary report 2022. AIHW catalogue number DEM 6. 2023. https://www.aihw.gov.au/reports/dementia/dementia-in-australia-summary-report-2022/overview [cited 2024 Apr 16]
2. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev2006;2006:CD005593. https://doi.org/10.1002/14651858.CD005593
3. Campbell NL, Perkins AJ, Gao S, Skaar TC, Li L, Hendrie HC, et al. Adherence and Tolerability of Alzheimer's Disease Medications: A Pragmatic Randomized Trial. J Am Geriatr Soc 2017;65:1497-504. https://doi.org/10.1111/jgs.14827
4. McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, et al. Memantine for dementia. Cochrane Database Syst Rev 2019;3:CD003154. https://doi.org/10.1002/14651858.CD003154.pub6
5. Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PLoS One

2012;7:e35185. https://doi.org/10.1371/journal.pone.0035185
6. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2018;6:CD001190. https://doi.org/10.1002/14651858.CD001190.pub3
7. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363:2105-15. https://doi.org/10.1016/ S0140-6736(04)16499-4
8. Lacorte E, Ancidoni A, Zaccaria V, Remoli G, Tariciotti L, Bellomo G, et al. Safety and Efficacy of Monoclonal Antibodies for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Published and Unpublished Clinical Trials. J Alzheimers Dis 2022;87:101-29. https://doi.org/10.3233/JAD-220046
9. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 2022;9:197-210. https://doi.org/ 10.14283/jpad.2022.30
10. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388:9-21. https://doi.org/10.1056/ NEJMoa2212948
11. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y) 2019;5:354-63. https://doi.org/10.1016/j.trci.2019.06.005
12. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330:512-27. https://doi.org/10.1001/jama.2023.13239
13. Sperling RA, Donohue MC, Raman R, Rafii MS, Johnson K, Masters CL, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. N Engl J Med 2023;389:1096-107. https://doi.org/10.1056/NEJMoa2305032
14. Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. N Engl J Med 2023;389:1862-76. https://doi.org/10.1056/NEJMoa2304430
15. Alves F, Kalinowski P, Ayton S. Accelerated Brain Volume Loss Caused by Anti-beta-Amyloid Drugs: A Systematic Review and Meta-analysis. Neurology 2023;100:e2114-e24. https://doi.org/10.1212/WNL.0000000000207156
16. Barkhof F, Knopman DS. Brain Shrinkage in Anti beta-Amyloid Alzheimer Trials: Neurodegeneration or Pseudoatrophy? Neurology 2023;100:941-2. https://doi.org/10.1212/WNL.0000000000207268
17. Joseph-Mathurin N, Wang G, Kantarci K, Jack CR, Jr., McDade E, Hassenstab J, et al. Longitudinal Accumulation of Cerebral Microhemorrhages in Dominantly Inherited Alzheimer Disease. Neurology 2021;96:e1632-e45.https://doi.org/10.1212/WNL.0000000000011542
18. Pittock RR, Aakre JA, Castillo AM, Ramanan VK, Kremers WK, Jack CR, Jr., et al. Eligibility for Anti-Amyloid Treatment in a Population-Based Study of Cognitive Aging. Neurology 2023;101:e1837-e49. https://doi.org/10.1212/WNL.0000000000207770

19. Arbanas JC, Damberg CL, Leng M, Harawa N, Sarkisian CA, Landon BE, et al. Estimated Annual Spending on Lecanemab and Its Ancillary Costs in the US Medicare Program. JAMA Intern Med 2023;183:885-9. https://doi.org/10.1001/jamainternmed.2023.1749
20. Ross EL, Weinberg MS, Arnold SE. Cost-effectiveness of Aducanumab and Donanemab for Early Alzheimer Disease in the US. JAMA Neurol 2022;79:478-87. https://doi.org/10.1001/jamaneurol.2022.0315
21. Gu JL, Liu F. Tau in Alzheimer's Disease: Pathological Alterations and an Attractive Therapeutic Target. Curr Med Sci 2020;40:1009-21. https://doi.org/10.1007/s11596-020-2282-1
22. Ji C, Sigurdsson EM. Current Status of Clinical Trials on Tau Immunotherapies. Drugs 2021;81:1135-52. https://doi.org/10.1007/s40265-021-01546-6 ARTICLE
23. Dubois B, Lopez-Arrieta J, Lipschitz S, Doskas T, Spiru L, Moroz S, et al. Masitinib for mild-to-moderate Alzheimer's disease: results from a randomized, placebo-controlled, phase 3, clinical trial. Alzheimers Res Ther 2023;15:39. https://doi.org/10.1186/s13195-023-01169-x
24. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. Alzheimers Dement (N Y) 2023;9:e12385. https://doi.org/ 10.1002/trc2.12385
25. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 2018;83:74-83. https://doi.org/10.1002/ana.25123
26. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924-38. https://doi.org/10.1001/jama.2015.4668
27. Wallace LMK, Theou O, Darvesh S, Bennett DA, Buchman AS, Andrew MK, et al. Neuropathologic burden and the degree of frailty in relation to global cognition and dementia. Neurology 2020;95:e3269-e79. https://doi.org/10.1212/WNL.0000000000010944
28. Mendes A, Tezenas du Montcel S, Levy M, Bertrand A, Habert MO, Bertin H, et al. Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers. Dement Geriatr Cogn Disord 2018;45:272-81. https://doi.org/ 10.1159/000489007
29. Aubert L, Pichierri S, Hommet C, Camus V, Berrut G, de Decker L. Association between comorbidity burden and rapid cognitive decline in individuals with mild to moderate Alzheimer's disease. J Am Geriatr Soc 2015;63:543-7. https://doi.org/10.1111/jgs.13314
30. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-46. https://doi.org/10.1016/ S0140-6736(20)30367-6

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