JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

LITERATURE REVIEW Open Access

Treatment of Memory Disorders – II. Pharmacotherapy

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Received date: February 28, 2024, **Accepted date:** March 04, 2024, **Published date:** March 11, 2024.

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Abstract

There are presently no disease-modifying medications for memory loss. Cholinesterase inhibitors, NMDA glutamate regulators, and their combination can only stop memory loss symptoms for a short time. They can help manage these symptoms and perhaps modify the progression of their condition, but they cannot stop or reverse that progression.

Additional research will help scientists understand the effectiveness of amyloid-clearing therapies to produce novel drug therapies. The therapy will depend on the cause of memory loss. Various drugs have been suggested in recent years. For the treatment of Alzheimer's disease (Donepezil, Galantamine, Rivastigmine, Tacrine, and Leqembi) all acting on the cholinergic system, which may reduce symptoms for up to eighteen months for mild or moderate dementia, but do not forestall the ultimate decline to full dementia. In this article, I present and discuss these several medications, the role of melatonin in memory formation, changes in medication management, and participation in clinical trials

Abbreviations

AAP: (FDA) Accelerated Approval Program; AD: Alzheimer's disease; ADD: AD dementia; ADEAR: Alzheimer's and related Dementias Education and Referral; ARIA: Amyloid-related imaging abnormalities; BBB: Blood - brain barrier; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease; CRO: Contract research organization; CT: Clinical trials; CTP: Clinical trial protocol; DHHS: (U.S.) Department of Health and Human Services; FDA: (U.S.) Food & Drug Administration; MATCH-D: Medications Appropriateness Tool for Co-Morbid Health – Dementia; MCI: Mild cognitive impairment; MDS: Mild dementia stage; NIA: (U.S.) National Institute on Aging; NCCIH: (U.S.) National Center for Complementary & Integrative Health; NMDA: N-Methryl-D Aspartate; NSAID: Non-steroidal anti-inflammatory drugs; PD: Parkinson's

disease; PDD: PD dementia; PET: Positron emission tomography; PUD: Peptic ulcer disease; RCT: Randomized clinical trials; SSD: Sick sinus syndrome; SSRI: Selective serotonin re-uptake inhibitors; TBI: Traumatic brain injury; VD: Vascular disease; VDD: VD dementia.

Keywords

Alzheimer's disease dementia; memory disorders; mild cognitive impairment; mild dementia stage; Parkinson's disease dementia; pharmacotherapy; vascular disease dementia.

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It is typical for people to have mild memory lapses over time; these may be age-related and should not cause concern. However, people with memory loss experience greater than expected levels of forgetfulness, and may have difficulty with both short- and long-term memory recall. When memory loss occurs more frequently and affects a person's daily activities, a doctor should be consulted to discuss symptoms and effects of memory loss. Without medication, symptoms of memory loss can become severe.

There are presently no disease-modifying medications for memory loss. Cholinesterase inhibitors, N-Methyl-D-aspartic Acid (NMDA) glutamate regulators, and their combination can only stop memory loss symptoms for a short time. They can help manage such symptoms and hopefully modify the progression of their condition. However, they cannot stop or reverse that progression. Additional research will help scientists understand the effectiveness of amyloid-clearing therapies to produce novel drug therapies.

The treatment will depend on the cause of memory loss. Various drugs have been suggested in recent years. For the treatment of Alzheimer's disease (AD), five drugs are currently FDA-approved, all acting on the cholinergic system: Donepezil, Galantamine, Rivastigmine, Tacrine, and Leqembi (this last medication approved only in July 2023). Although these medications are not a cure, AD symptoms may be reduced for up to eighteen months for mild or moderate dementia but do not forestall the ultimate decline to full AD.

This article outlines the various medications for memory loss, their indications, and potential side effects as well as their management.

Can medication help slow memory loss?

How memories are formed has been a puzzle that has perplexed researchers for over a century, and there are still many questions that remain about the biological mechanisms that underpin them. Perhaps because of this gap in understanding, there are no pharmacological interventions that can be taken to improve memory. No drug treatment can effectively cure memory loss. The (U.S.) National Institute on Aging (NIA) states that *"people should avoid any treatment that promises to restore brain function and improve memory"*. It further notes that these medications are typically unsafe and can cause negative drug interactions with other medications.

However, certain medications can help individuals ease the symptoms and manage the condition's progression. Health experts recommend that those with memory loss follow doctor-approved prescriptions only.

Types of medication for memory loss

Few medications are available to help manage memory loss. The severity of a person's memory loss and the underlying cause will indicate the most suitable drug therapy. Table 1 summarizes memory loss medications, including drug information and side effects. For most people with memory loss, a doctor will recommend one of the types of drugs therein listed.

Generic/brand name	Drug type	Drug indication	Side effects
Aducanumab/ Aduhelm*	o Monoclonal antibody => Biologic drug comprising living cells. It destroys plaques of toxic beta-amyloid protein	o First-line treatment for early stage AD or ADD => May be prescribed for MCI => Withdrawn from market	o Delirium o Edema o Falls o Hypersensitivity o Immunogenicity
Donepezil/ Aricept	o Cholinesterase inhibitor	o ADD =>Can be prescribed off-label for: o PDD o LBD o VDD o TBI	o Anorexia o Diarrhea o Edema o Fatigue o Hyper/hypotension o Insomnia o Muscle cramps o Nausea o Vomiting
Donepezil+Memantine/ Namzaric	o Cholinesterase inhibitor + Glutamate regulator	o Moderate-to-severe memory loss due to AD	o Anorexia o Breathing difficulty o Diarrhea o Seizure o Slow heartbeat o Urinary hesitancy
Galantamine/ Razadyne	o Cholinesterase inhibitor	o ADD	o Atrioventricular blockage o Gastrointestinal bleeding o Headache o Low appetite o Sinus bradychardia o Skin reactions o Slow heart rate o Stomach ulcer o Weight loss o Other common side effects
Lecanumab/ Leqembi	o Monoclonal antibody	o ADD	
Rivastigmine/ Exelon	o Cholinesterase inhibitor	o ADD o PDD	o General irritability o Increased risk of death from long-term use o Involuntary movements o Muscular contractions o Sleep disturbances o Tremors
Memantine/ Namenda	o Glutamate regulator and NMDA receptor antagonist	o Moderate-to-severe memory loss due to AD	o Confusion o Constipation o Dizziness o Headache o High stomach acid level

Table 1: Memory loss medications, including drug information and side effects

Key: AD: Alzheimer's disease; ADD: AD dementia; MCI: Mild cognitive impairment; PD: Parkinson's disease; PDD: PD dementia; TBI: Traumatic brain injury; VD: Vascular disease; VDD: VD dementia.

(*** Note:** Some hail human monoclonal antibodies that clear beta-amyloid deposits from the brain as the first disease-modifying treatments for the condition. However, they are not without controversy such as the one concerning the FDA-approved Aducanumab despite a lack of evidence for its efficacy and concerns about adverse effects.)

- **Cholinesterase inhibitors:** These medications can manage various conditions affecting memory, including AD and PD. They work by blocking the enzyme cholinesterase from breaking down acetylcholine, which is a chemical messenger that plays a vital role in memory and learning. Increasing the levels of acetylcholine in the brain can help maintain memory and delay worsening symptoms. They are the first choice treatment for memory loss. The treating physician may also prescribe the single-dose drug combination (cholinesterase inhibitor + glutamate regulator) to treat moderate-to-severe memory loss.

- **Glutamate regulators:** Glutamate regulators control the amount of glutamate in the central nervous system (CNS) to an optimal level. Glutamate is the most common neurotransmitter in the brain. It can excite nerve cells to their death through a process known as 'excitotoxicity'. Excitotoxic cell death can cause neurodegenerative conditions that affect memory. One example of a glutamate regulator is Memantine (Namenda), an NMDA (N-Methryl-D Aspartate) receptor antagonist that stops calcium from invading the neurons and causing nerve injury. Due to their minimal side effects, glutamate regulators may be prescribed either alone or alongside a cholinesterase inhibitor.

- **Combined cholinesterase inhibitor and glutamate regulator drug:** Combining the two classes of drugs is more effective than using only one medication. While it is superior to single drug therapy, it can complicate treatment plans for patients and their caregivers.

Currently, there are no specifically approved drugs for improving memory formation. While some prescription medications are used to improve memory in conditions like AD, they are not recommended for general memory enhancement in healthy adults.

Pathology	Drugs	Precautions	Side effects
Memory problems (Monitored over an 8-week course)	Provide no cure: o Cholinesterase inhibitors*: Donepezil (Aricept®), Rivastigmine (Exelon®), Galantamine (Razadyne®) o Glutamate regulators: - Memantine (Namenda®): o Used in combination with anti-cholinesterase - N-Methyl D-Aspartate (NMDA) receptor blockers o Folate or Vitamin B-12 o Statins o Blood pressure medications	o Symptoms may worsen if the treatment is stopped or after treatment o Periodic evaluation of the treatment is required o May cause increase in cardiovascular-related events	o Aggression o Diarrhea o Dizziness o Difficulty sleeping with very vivid dreams (when taken at bedtime) o Fainting spells in people with heart problem(s) o Gastro-intestinal upset o Hallucinations o Muscle cramping o Nausea o Slow heart rate o Vomiting o Weight loss o No benefit o No clear link with dementia o No improved outcomes
Behavioral symptoms	o Environment change, physical exercise, avoiding triggers that cause sadness, socializing with others, engaging in pleasant activities		o Agitation o Anxiety o Irritability

	o Antipsychotics:		o Not usually recommended due to little benefits, side effects, increased risk of death
Depression	o Behavioral therapy and/or medications o Selective serotonin re-uptake inhibitors (SSRI): - Citalopram** (Celexa®) - Escitalopram (Lexapro®) - Fluoxetine (Prozac®) - Paroxetine (Paxil®) - Sertraline** (Zoloft®)		
Anxiety & Aggression	o Medications		Can be caused by several factors: o Confusion o Depression o Disorientation o Frightening o Hallucinations o Medical conditions (such as difficulty urinating or severe constipation) o Misunderstanding o Paranoid delusions o Sleep: disorders, Reduced altered sleep/wake cycles o Other causes of physical pain or discomfort
Sleep problems	o Medications or/and behavior changes o Benzodiazepines (Diazepam) and non-benzodiazepine hypnotics To be avoided: o Melatonin, Ramelteon, Trazodone		o Increased cognitive impairment o Falls: Increased o Worsened confusion o Little evidence to improve sleep in dementia patients
Pain	o Medications		o Ambulation decrease o Appetite impaired o Cognitive impairment exacerbated o Falls o Functional implications profound o Functional psychosocial implications o Mood depression o Quality of life implications o Sleep disturbances
Eating difficulties	o Assisted feeding, gastrostomy, feeding tube		o Pressure ulcers worsening o Fluid overload o Diarrhea o Abdominal pain o Complications local o Aspiration risk

Table 2: Psychopharmacotherapy for Alzheimer-type and other dementias

Key: NMDA: N-Methyl D-Aspartate; SSRI: Selective serotonin re-uptake inhibitors.

(Notes: * Precautions: Donepezil should be used with caution in people with: (a) cardiac problems: heart disease, cardiac conduction disturbances, chronic obstructive pulmonary disease (COPD), severe cardiac arrhythmias; (b) asthma; (c) sick sinus syndrome (SSD); (d) peptic ulcer disease (PUD) or taking non-steroidal anti-inflammatory drugs (NSAID); and (e) in case of predisposition to seizures.

** Sertraline and Citalopram do not reduce symptoms of agitation compared to placebo and do not affect outcomes.)

Changes in medication management

Dementia is a life‐limiting disease with an average survival time of less than 5 years from diagnosis. Co‐morbidities and polypharmacy are common, though evidence is scarce for medication safety, tolerability, and efficacy. Compared to their peers (i.e., cognitively intact people of a comparable age), people with dementia have many co‐morbidities, take a mean of five or more medications daily, and are more likely to use certain medication classes (antihypertensives, laxatives, diuretics, antidepressants, and antipsychotics). This medication use may reflect risk factors for dementia and common co‐morbidities such as cardio- and reno-vascular disease.

Age‐related pharmacokinetic changes occur in all older people, and an altered blood‐brain barrier (BBB) permeability in people with dementia renders them more sensitive to neurological and cognitive effects of medications than their peers. These pharmacokinetic changes are additional to drug‐disease interactions that occur in dementia. The safety profile and efficacy of many medications in people with dementia are undetermined due to their active exclusion from 85% of published clinical trials. Furthermore, the tendency for people with dementia to under‐report disease‐related symptoms means that it is likely they also under‐report side‐effects.

Research in people with dementia focuses on treatments that prevent or delay dementia onset and/or progression and manage dementia-specific neuropsychiatric or behavioral symptoms. Evidence for the efficacy of these medications is conflicting and the harms of some, such as antipsychotics and benzodiazepines, make them potentially inappropriate in this population.

Despite the frequency of co-morbidities and medication use among people with dementia, appropriate medication management in this life-limiting condition is infrequently studied and poorly understood. For example, studies of antihypertensives, hypoglycemics, statins, and anti-inflammatories mainly assess their ability to delay dementia onset. After dementia onset, medication appropriateness to manage co-morbidities is complicated by a relative absence of evidence.

Preventive treatments may require a treatment time to benefit that exceeds life expectancy, or may target treatment goals that are not relevant to the individual or their families. This is combined with a shifting focus on the priorities of healthcare in this patient cohort and the balance between the benefits and harms of medicines.

Medication management is subsequently complicated for people with dementia so that careful consideration should be given to initiation and continuation of all medications. Medication management decisions for people with dementia are often based on data collected in younger adults or peers, which may not be generalizable or relevant to this population. The existing explicit prescribing criteria developed for older people do not account for the additional complexities of

dementia or its life-limiting nature.

Specific guidance for people with dementia would assist clinicians with decision-making in this population.

For people living with dementia, medication management remains a complex task as it is unclear what constitutes optimal medication management in this population due to the shifting focus of health priorities and the balance between the benefits and harms of medications. A study was conducted by a large panel of mltidisciplinary experts in geriatric therapeutics (including pharmacists, doctors, nurse practitioners, a patient advocate, and a psychologist) to define the appropriate medication management of co-morbidities. It developed the Medications Appropriateness Tool for Co-Morbid Health – Dementia (MATCH-D), including criteria that can help identify ways in which a diagnosis of dementia changes medication management for other health conditions. More information on MATCH-D is provided in Sidebar 1. Sidebar 2 provides some information on the FDA accelerated drug approval process, specifically for the latest drug Leqembi.

Participation in clinical trials

Clinical trials (CTs) are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison.

They generate data on dosage, safety, and efficacy and look at new ways to prevent, detect, or treat diseases. Treatments might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. They can also look at other aspects of care such as improving the quality of life for people with chronic illnesses. Their overriding goal is to determine if a new test or treatment works and is safe.

People with memory problems may be able to take part in clinical trials. Healthy people with no memory problems and no family history of such conditions may also be able to participate. Joining a clinical trial or other research study is also a way to help fight such issues. Sidebar 3 provides the main particulars of clinical trials. Out of the 1908 clinical trials listed on clinicaltrials.gov website as of the date of this writing (25 September 2023), the first 100 trials dealing with memory included:

- Ten trials on memory functions and physiological processes, some of which involved the following drugs: Bacopa, Cincalcet, Luteolin, Resveratrol, and Salbutamol.
- Two trials on memory processes.
- Nine trials on memory lapse/ consolidation (the transformation of recent experiences into stable, long-term memories)/ reactivation.
- Twenty trials on memory delays, deficits, impairments, and disorders.
- Three trials on memory and mental health.
- Fifty-two trials on various types of memory: Autobiographical (1), declarative (1), emotional (2), episodic (7), intrusive (sensory memories of a traumatic event(s) that spring to mind involuntarily, and can evoke strong emotions and disrupt functioning in daily life. They are debilitating and triggered by certain clinical symptoms such as PTSD, anxiety, depression, and insomnia - 13), motor (motor skills require motor memories without which behavior is only reflexes and stereotypes – 2), prospective (1), spatial (1), subjective (3), verbal and visual (1), working (deficits are a transdiagnostic feature of adolescent psychopathology that substantially contribute to poor clinical and functional outcomes – 13), memory aids and tools (6) and virtual reality helmet (1).

Conclusions and take-aways

- It is typical for people to have mild memory lapses over time; these may be age-related and should not cause concern. However, people with memory loss experience greater than expected levels of forgetfulness and may have difficulty with both short- and long-term memory recall. Without medication, symptoms of memory loss can become severe.

- Medications can help manage a person's memory loss symptoms and eventually modify the progression of their condition. However, they cannot stop or reverse the progression of the condition. For the treatment of Alzheimer's disease, five drugs are currently FDA-approved: Donepezil, Galantamine, Rivastigmine, Tacrine and, as of July 2023, Leqembi. Nonetheless, while helping ease symptoms and manage the condition's progression, medications are typically unsafe and can cause negative drug interactions with other medications.

- The severity of a person's memory loss and the underlying cause will indicate the most suitable drug therapy. The particulars of available memory loss medications, including drug information and side effects, have been provided. These include cholinesterase inhibitors, glutamate regulators, or their combination.

- The link between sleep and improved memory retention has still not been elucidated. It is thought that the brain state during sleep is optimized for memory consolidation. However, the exact mechanisms underlying this link are unclear.

- Melatonin and its derivatives may have effects on memory formation by modulating the phosphorylation levels of memory-related proteins, which are involved in receptor binding related to memory formation pathways and pathways not associated with receptor binding.

- Co‐morbidities and polypharmacy in dementia are common, though evidence is scarce for medication safety, tolerability, and efficacy. People with dementia are likely to use daily five or more medications on the average (antihypertensives, laxatives, diuretics, antidepressants, and antipsychotics), reflecting risk factors for dementia and common co‐morbidities such as cardio- and reno-vascular disease.

- Age‐related pharmacokinetic and changes in additional drug‐disease interactions occur in older people. Further, an altered blood‐brain barrier permeability in people with dementia renders them more sensitive to neurological and cognitive effects of medications.

- The safety profile and efficacy of many medications in people with dementia are undetermined due to their active exclusion from 85% of published clinical trials. Furthermore, the tendency for people with dementia to under‐report disease‐related symptoms means that it is likely they also under‐report side‐effects.

- Research in people with dementia focuses on treatments that prevent or delay dementia onset and/or progression and manage dementia‐specific neuropsychiatric or behavioral symptoms. Evidence for the efficacy of these medications is conflicting.

- Despite the frequency of co‐morbidities and medication use among people with dementia,

appropriate medication management in this life - limiting condition is infrequently studied and poorly understood.

- Preventive treatments may require a treatment time to benefit that exceeds life expectancy, or may target treatment goals that are not relevant to the individual or their families.

- Medication management is complicated for people with dementia so that careful consideration should be given to initiation and continuation of all medications. Medication management decisions for people with dementia are often based on data collected in younger adults or peers, which may not be generalizable or relevant to this population.

- For people living with dementia, medication management is a complex task as it is unclear what constitutes optimal medication management for them due to the shifting focus of health priorities and the balance between the benefits and harms of medications.

- The Medications Appropriateness Tool for Co-Morbid Health – Dementia (MATCH-D) criteria can help identify ways that a diagnosis of dementia changes medication management for other health conditions.

- Clinical trials are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Their overriding goal is to determine if a new test or treatment works and is safe.

- People with memory problems may be able to take part in clinical trials. Healthy people with no memory problems and no family history of such conditions may also be able to participate. Joining a clinical trial or other research study is also a way to help fight such issues.

Sidebar 1 - Medication appropriateness tool for co-morbid health conditions in dementia (MATCH-D)

The MATCH-D study aimed to elicit opinion and gain consensus on appropriate medication management of co - morbidities in people with dementia. The intended outcome was to create a consensus - based list of statements to define appropriate medication management of co - morbidities in people with dementia. For this purpose, it convened a large panel of multidisciplinary experts in geriatric therapeutics including pharmacists, doctors, nurse practitioners, a patient advocate, and a psychologist.

The participants generated a list of statements that provided guidance on appropriate treatment goals in people with dementia and important discussion points for patient - centered care. The statements gave specific consensus - based advice in the broad themes of preventive medication, symptoms management, prescribing to reduce the risk of future events, behavioral and psychological symptoms management, treatment goals, principles of medication use, medications to slow dementia progression, psychoactive and other medications, the experience of side - effects, and medication reviews in people living with dementia.

The MATCH-D study complements existing dementia guidelines by describing appropriate pharmacological management of co - morbidities as dementia progresses. One of its strong messages was the importance of a person - centered approach to pharmacological management. Such management needs to focus on

treatment goals that are relevant to the individual and their families, as older adults vary in their preferences for treatment when they consider the potential risks and benefits of medication management. Regretfully, general prescribing criteria for older adults do not specifically consider the particularities of the progressive, life‐limiting nature of dementia.

Sidebar 2 – On the FDA's accelerated approval of Leqembi

The (U.S.) Food & Drug Administration (FDA), an agency within the U.S. Department of Health and Human Services (DHHS), *"protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of… dietary supplements, …"*.

The accelerated approval program

The FDA instituted its Accelerated Approval Program (AAP) "*to allow for earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint if a drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients"*. A surrogate endpoint is a marker (such as a laboratory measurement, radiographic image, physical sign or other measure) that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The use of a surrogate endpoints can considerably shorten the time required prior to receiving FDA approval.

Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit, FDA has regulatory procedures in place that could lead to removing the drug from the market.

The Agency's use of that shortcut approach has come under increasing scrutiny from government watchdogs and congressional investigators.

On the Leqembi approval

On January 6, 2023, FDA approved the drug Leqembi via the Accelerated Approval pathway for the treatment of AD. The FDA granted this application *Fast Track, Priority Review, and Breakthrough Therapy designations* to (Japan) Eisai R&D Management Co., Ltd (Biogen is its U.S. partner).

Leqembi is the second of a new category of AD-approved medications that target the fundamental pathophysiology of the disease. This treatment option is the latest therapy to (presumably) "target and affect the underlying disease process of AD, instead of only treating the symptoms of the disease". (I have a particular reservation regarding this statement as, it is my opinion, that amyloid-beta plaques are not the cause but the consequence of au autoimmune disease that is the true causal etiology.)

Researchers initially evaluated Leqembi's efficacy in a double-blind, placebo-controlled, parallel-group, dose-finding study of 856 patients with AD. Patients' selection criteria included: (1) Mild cognitive impairment (MCI) or mild dementia stage (MDS) of disease and (2) the confirmed presence of amyloid-beta pathology. Every two weeks, subjects received an approved dose of 10 [mg/kg] of Lecanemab. Compared to controls, subjects showed a "*statistically significant reduction in brain amyloid plaque* (a marker of AD) *from baseline to Week 79*". The accelerated approval was based on the observed reduction of amyloid beta-plaque, which was quantified using positron emission tomography (PET) imaging. The results of a Phase-3 randomized, controlled clinical trial, a larger 1,800-patient study, is under review by the FDA

to confirm the drug's benefit, paving the way for full approval later this year.

Of particular note: The prescribing information for Leqembi includes a warning for amyloid-related imaging abnormalities (ARIA), which are known to occur with antibodies of this class. Usually, the drug does not have symptoms but may present the following side effects: (1) Infusion-related reactions such as a temporary swelling in areas of the brain that usually resolves over time and may be accompanied by (2) small spots of bleeding in or on the surface of the brain, though some people may have symptoms such as (3) headache, confusion, dizziness, vision changes, nausea, and seizure. Another warning for Leqembi is for a risk of infusion-related reactions, with symptoms such as flu-like symptoms, nausea, vomiting, and changes in blood pressure. Serious and life-threatening events may rarely occur.

Criticisms of the approval

While the drug has not yet received regular approval, the following criticisms have already been levied:

On the drug itself

- The drug may only modestly slow the brain-robbing disease, albeit with potential safety risks that patients and their doctors will have to carefully weigh.
- The (apparent) delay in cognitive decline brought about by the drug likely amounts to just several months, but could (perhaps) still meaningfully improve people's lives.
- The drug is not a cure. It does not stop the disease from getting worse, but may measurably slow its progression.
- Scrutiny of the new drug, will likely mean most patients will not start receiving it for months, as insurers decide whether and how to cover it.
- The larger (1800 subjects) study tracked patients' results on an 18-point scale that measures memory, judgment, and other cognitive abilities. Doctors compile the rating from interviews with the patient and a close contact. After 18 months, patients receiving Leqembi declined more slowly — a difference of less than half a point on the scale — than patients who received a dummy infusion. The delay amounted to just over five months. There is little consensus on whether that difference translates into real benefits for patients, such as greater independence. For some neurology researchers, that is really quite a small effect and probably below the threshold of what would be called clinically significant. A meaningful improvement would require at least a difference of one full point on the 18-point scale.
- There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

On the drug's side effects and adverse events

- The medicine comes with downsides, including the need for twice-a-month infusions and possible side effects like brain swelling.
- About 13% of patients in the larger study had swelling of the brain and 17% had small brain bleeds side effects seen with earlier amyloid-targeting medications. In most cases those problems did not cause other symptoms such as dizziness and vision problems. Also, several Leqembi users died while taking the drug, including two who were on blood-thinning medications. Although the manufacturer argued that these deaths cannot be attributed to the drug,

the FDA label warns doctors to use caution if they prescribe Leqembi to patients on blood thinners.

On the approval process

- The drug has only been specifically approved for patients with Alzheimer's, mild cognitive impairment, or in mild dementia stage.
- The FDA approval came via its accelerated pathway, which allows drugs to be launched based on early results before they are confirmed to benefit patients.
- On December 2022, a congressional report found that FDA's approval of a similar Alzheimer's drug called Aducanumab/Aduhelm (also from Eisai and Biogen) was "rife with irregularities", including a number of meetings with drug company staffers that went undocumented.
- Aduhelm/Aducanumab, the similar drug previously marketed but withdrawn by the same pharmaceutical company, was marred by controversy over its effectiveness. The FDA approved that drug in 2021 against the advice of the agency's own outside experts. Doctors hesitated to prescribe the drug and insurers restricted coverage. The FDA did not consult the same expert panel before approving Leqembi.

On cost and insurance reimbursement

- The drug will cost about US $26,500 for a typical year's worth of treatment. The company pegged its value at over US $37,000 per year but said it priced it lower to reduce costs for patients and insurers. An independent group that assesses drug value recently said the drug would have to be priced below US $20,600 to be cost-effective.
- Some neurology researchers seriously doubt whether the measurable benefit of the drug is worth the hefty price tag and the side effects patients may experience.
- Insurers are likely to only cover the drug for people like those in the company study − patients with mild symptoms and confirmation of amyloid buildup. That typically requires expensive brain scans. A separate type of scan will be needed to periodically monitor for brain swelling and bleeding.
- A key question in the drug's rollout will be the coverage decision by Medicare (the U.S. federal health plan that covers 60 million seniors and other Americans). The agency severely restricted coverage of Aduhelm/Aducanumab, essentially wiping out its U.S. market and prompting Biogen to abandon marketing plans for the drug. Regarding Leqembi, coverage is not expected until after the FDA confirms the drug's benefit, likely later this year.

Sidebar 3 – A brief primer on clinical trials

Clinical trials (CTs) are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. They are part of clinical research at the heart of all medical advances. They look at new ways to prevent, detect, or treat diseases by new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. They

can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses Their goal is to determine if a new test or treatment is safe and effective.. Some CTs involve healthy subjects with no pre-existing medical conditions, others pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the CTs to follow.

Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol (CTP). This is the trial's "operating manual" to ensure that all researchers perform the trial in the same way on similar subjects, and that the data is comparable across all subjects. As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step.

CTs generate data on dosage, safety, and efficacy. They are conducted only after they have received regulatory approval (ethics committee approval and health authority), which vet the risk/benefit ratio of the trial and allow or deny it.

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger-scale comparative studies.

CTs can vary in size and cost, and can involve a single research center or multiple centers, in one or in multiple countries. The clinical study design aims to ensure the scientific validity and reproducibility of the results. Costs for clinical trials can range into the billions of dollars per approved drug. The sponsor may be a governmental organization or a pharmaceutical, biotechnology, or medical device company. Certain functions necessary to the trial, such as monitoring and laboratory work, may be managed by an outsourced partner, such as a contract research organization (CRO) or a central laboratory. Only 10% of all drugs started in human clinical trials become approved drugs.

Overall goals

There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion and both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks.

The sponsor designs the trial in coordination with a panel of expert clinical investigators who also consider what alternative or existing treatments exist to compare to the new drug and what type(s) of patients might benefit.

Categories of trials

There are three trial categories:

Drugs

They are the most common to evaluate new pharmaceutical products, biologics, diagnostic assays, psychological therapies, or other interventions.A high intake of vegetables, fruits, whole grains, beans, and legumes.

Devices

Similarly to drugs, manufacturers of medical devices may compare a new device to an established therapy, or may compare similar devices to each other. They are required for pre-market approval.

Procedures

Similarly to drugs, medical or surgical procedures may be subjected to clinical trials, They compare different surgical approaches in treatment.Limited added sugars,

sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

Types of trials

CTs are classified by the research objective(s) or purpose(s) of the investigators:

By research objectives

This will depend on the kind of study. Thus, in an:

- **Observational study:** The investigators observe the subjects and measure their outcomes. They do not actively manage the study.

- **Interventional study:** The investigators give the research subjects an experimental drug, use of a medical device, a surgical procedure, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then, the researchers assess how the subjects' health changes.

By research purposes

There are ten such types:

- **Prevention trials:** They look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.

- **Screening trials:** They test for ways to identify certain diseases or health conditions.

- **Diagnostic trials:** They are conducted to find better tests or procedures for diagnosing a particular disease or condition.

- **Treatment trials:** They test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.

- **Quality of life trials or supportive care trials:** They evaluate how to improve comfort and quality of care for people with a chronic illness.

- **Genetic trials:** They are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.

- **Epidemiological trials:** They have the goal of identifying the general causes, patterns or control(s) of diseases in large numbers of people.

- **Compassionate use trials or expanded access trials:** They provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials (RCTs). Usually in the U.S., case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

- **Fixed trials:** They consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.

- **Adaptive trials:** They use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications

- include dosage, sample size, drug undergoing trial, patient selection criteria, and "cocktail" mix.

Trial phases

CTs are conducted typically in four phases (Phases I to IV), with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect. However, for new drugs, there are five phases (Phases 0 and I to IV), each phase being treated as a separate CT.

Phase	Aim	Notes
0	o **Pharmacodynamics** (what the drug does to the body) and o **Pharmacokinetics** (what the body does to the drug) in humans	o Optional o Sub-therapeutic doses o Small number of subjects (10-15) for preliminary data o Trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected
I	o **Safety**	o Small number of subjects (20-30) o Determines safe dosage ranges o Identifies side effects
II	o **IIa. Dosing** o **IIb. Efficacy**	o IIa: Dosing requirements o IIb: Efficacy to establish therapeutic dose range
III	o **Confirmation of safety and efficacy**	o Large group of subjects (1,000-3,000) o Monitors side effects o Compares to commonly-used treatments
IV	o **Post-marketing safety**	o Delineates benefits, risks, optimal use o Ongoing during the drug's lifetime of active medical use

Reference: Wikipedia

Table 3: Phases of clinical trials

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