MANCHESTER 1824

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tide™

together in dementia everyday

Alzheimer's disease and dementia drugs

Simplifying drug explanations and providing tools to find out more

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Contents

Important Disclaimer

The information in these slides is not intended as medical advice. Always refer back to your doctor for your own personal circumstances.

Statistics and definitions

In the whole of the UK, the number of people with dementia is estimated at 944,000.

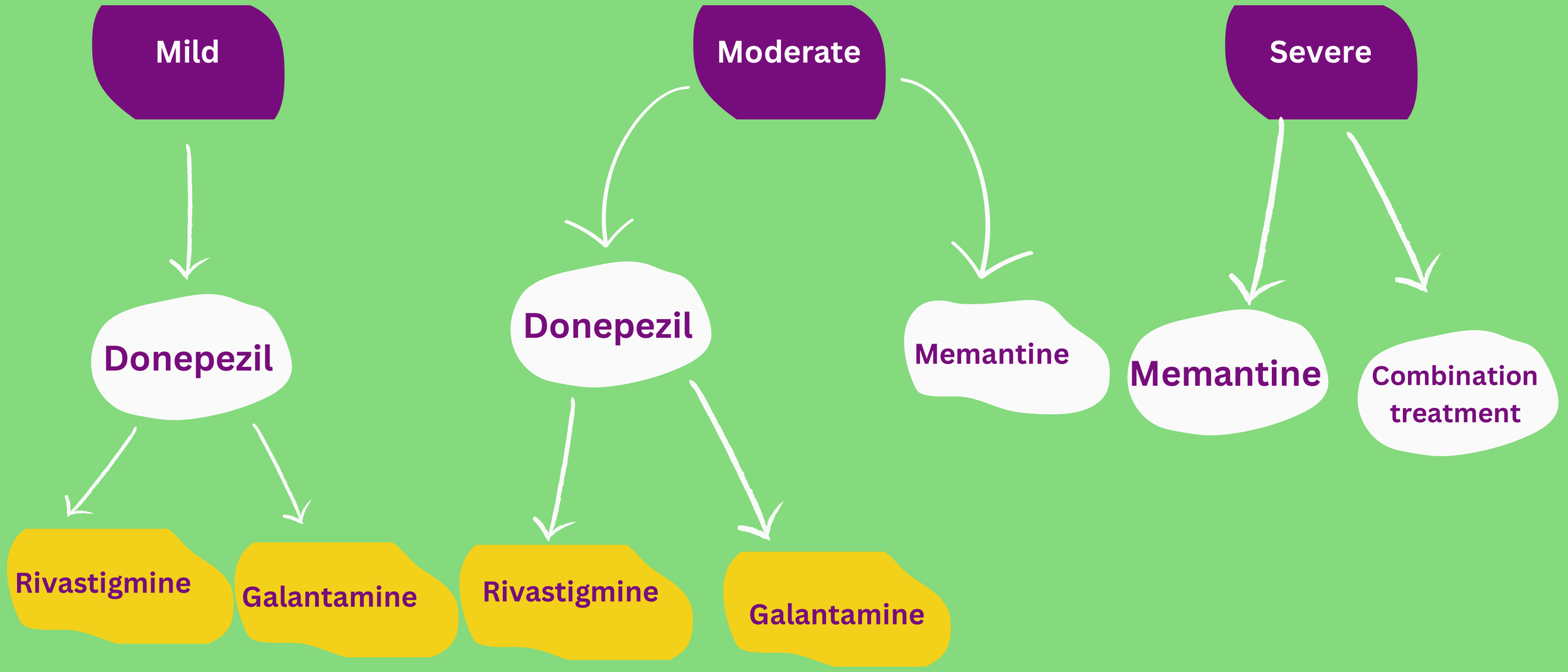
~1 in 3 people will care for a person with dementia at one point in their life. In England there are approximately 540,000 carers for dementia.

Dementia refers to a group of particular symptoms. These symptoms can have several causes, which relate to the areas of the brain affected.

Alzheimer’s Disease is one of the most common causes of dementia (60-70% of cases).

Current drugs available to patients

Flowchart guidance for prescription of Alzheimer's Disease drugs

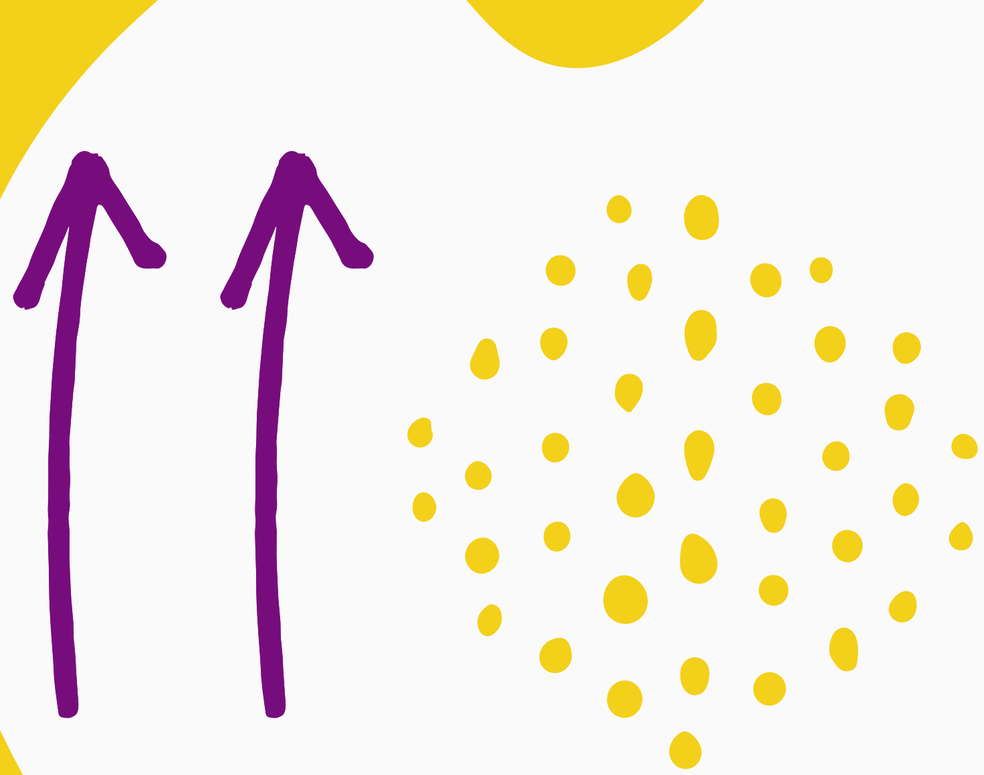


Flowchart guidance for prescription of Alzheimer's Disease drugs notes

This is a visualization of a likely NHS care pathway that a GP will follow in order to decide which medication to prescribe. It will first depend upon what stage of Alzheimer's Disease the patient is diagnosed with. Another consideration will be what medication they have tried before and how well it worked for the patient, for example, what benefits did they see and what side effects did they have? If the patient is already taking other medications for other conditions this might mean the medications may not work well together. Other medications may also influence what form the Alzheimer's Disease medication will be best taken in (tablet, liquid or patch) which will make certain drugs better suited than others. Some Alzheimer's Disease medications do not work well if mixed with alcohol so they may not be suitable for a patient that drinks alcohol.

Acetylcholinesterase inhibitors (AChEI)

- Donepezil
- Rivastigmine
- Galantamine



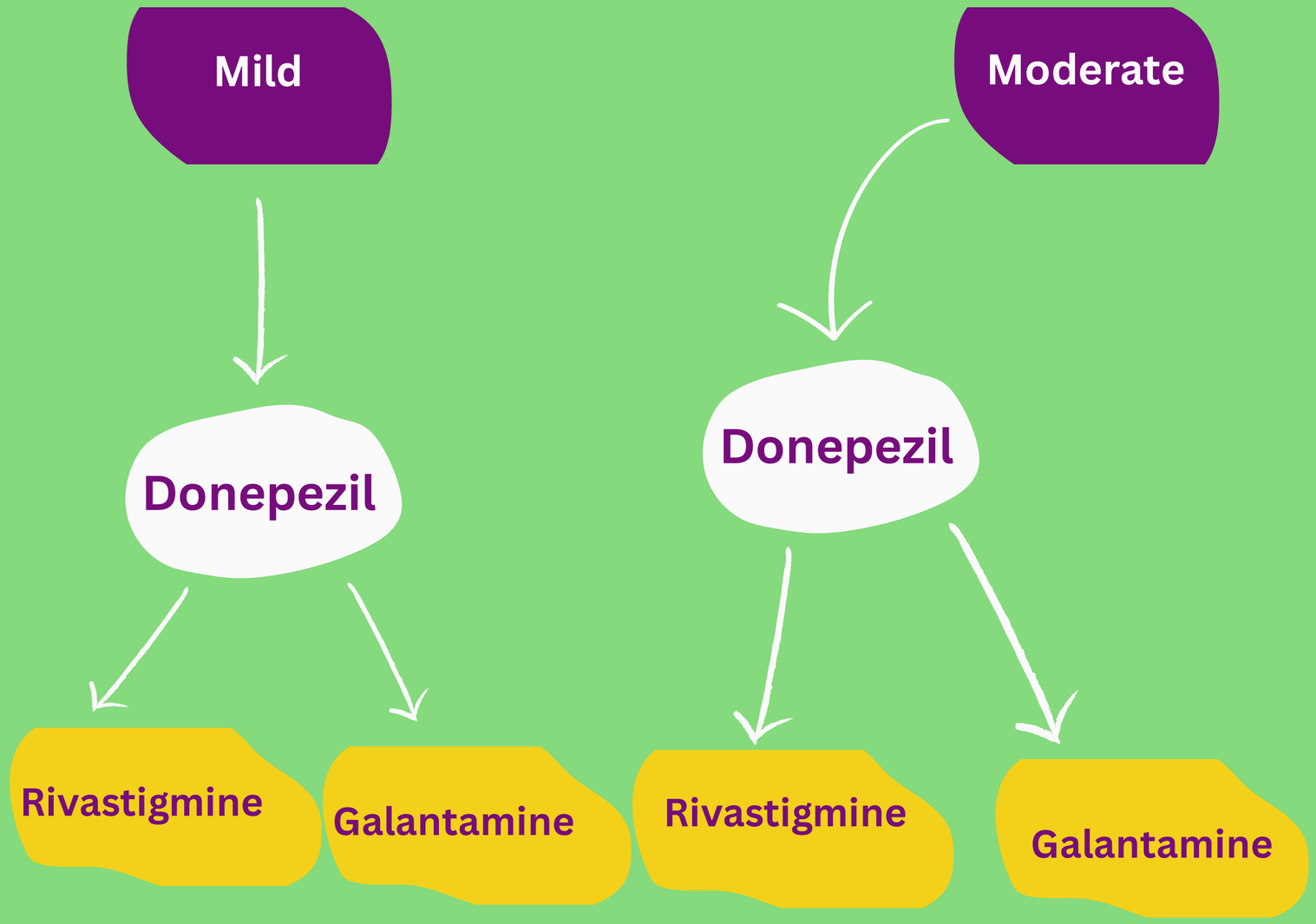
These drugs increase acetylcholine, a chemical messenger in the brain which is linked to memory formation and learning, by blocking the protein which usually removes it.

Acetylcholinesterase inhibitors (AChEI) notes

This category of drugs are used for mild to moderate stages of Alzheimer’s Disease. They are used to treat the symptoms of Alzheimer's Disease (and other forms of dementia). They do this by increasing levels of acetylcholine, a type of chemical messenger in the brain, which helps with learning and memory formation. They do this by blocking the protein which usually removes the acetylcholine which allows the levels to increase back to a normal functioning level.

Pronunciation: Don-eh-peh-zil,
Ra-va-stig-meen,
Gal-ant-a-meen.

Flowchart guidance for prescription of Alzheimer’s Disease drugs



Flowchart guidance for prescription of Alzheimer’s Disease drugs notes

This shows the Acetylcholinesterase Inhibitors on the likely NHS care pathway used to determine which drug should be prescribed. A patient will normally start off with Donepezil and then, if that doesn’t work, they will try Rivastigmine or Galantamine.

Donepezil

In NHS care pathway for **mild / moderate Alzheimer's disease**. Used to treat **symptoms of dementia** associated with Alzheimer's disease.

Names

- Aricept
- Aricept Evess

Forms

- Tablets
- Melt in the mouth (orodispersible)
- Liquid (oral solution)

Used for

- Alzheimer's disease
- Parkinson's disease
- Dementia with Lewy bodies (unlicensed).
- mixed dementia

Donepezil notes

Medications will have a molecule/drug name as well as a brand name. The brand name will be what you see on the packaging whereas the drug name will be what you see when you research dementia drugs online. Donepezil comes in three different forms, tablet, melt in the mouth and liquid. The tablet will most likely be what is prescribed first as this is the cheapest but if this isn't suitable for the patient, they may try other forms or another drug entirely. Although Donepezil is licensed as an Alzheimer's Disease medication it can be used for different forms of dementia that have similar symptoms linked to acetylcholine.

Rivastigmine

In NHS care pathway for **mild / moderate Alzheimer’s disease**. Used to treat **symptoms of dementia** associated with Alzheimer's disease.

Names

- Alzest
- Exelon
- Kerstipon
- Nimvastid
- Prometax
- Almuriva

Forms

- Capsules
- Liquid
- Skin patches

Used for

- Alzheimer's disease
- Parkinson's disease
- Lewy body dementia (unlicencesd)

Rivastigmine notes

Rivastigmine is special as it can come in skin patch form which means it can be used by anyone that cannot tolerate medication taken via the mouth. These are more expensive than the capsule or liquid form and so would not be offered unless there is a special need for them.

Galantamine

In NHS care pathway for **mild to moderately severe Alzheimer's disease**. Used to treat **symptoms of dementia** associated with Alzheimer's disease.

Names

- Reminyl
- Razadyne
- Razadyne ER123
- Gatalin
- Galysa
- Acumor
- Elmino
- Gazylan
- Lotprosin
- Luventa

Forms

- Tablet
- Slow-release capsule
- Liquid

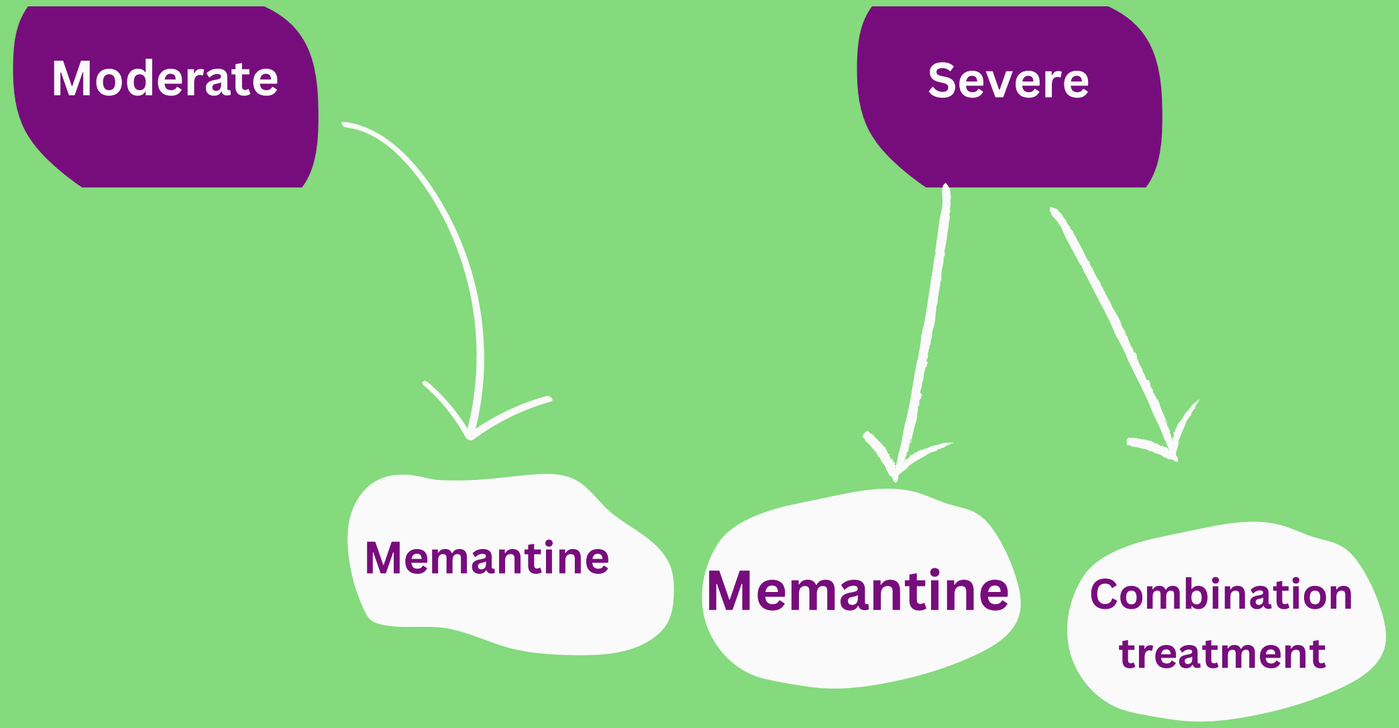
Used for

- Alzheimer's disease
- Parkinson's disease
- Lewy body dementia (unlicencesd)

Galantamine notes

Galantamine can be used for a slightly more sever stage of Alzheimer’s Disease than Rivastigmine. Additionally, Galantamine can come in a slow-release capsule form which can make certain side effects more manageable or the drug work with other medications that the other acetylcholinesterase inhibitors cannot.

Flowchart guidance for prescription of Alzheimer’s Disease drugs



Glutamate Blockers

- Memantine

Overactivity with no blocked receptors

Normal activity with blocked receptors

This drug prevents the overactivity of glutamate by blocking glutamate receptors which can cause issues in brain signaling, helping to reinstate normal function and prevent future damage

Glutamate blocker notes

Memantine can be prescribed for either moderate or severe Alzheimer's Disease. It can also be used in combination treatment with Acetylcholinesterase Inhibitors from the previous slides.

Memantine is a glutamate blocker medication. Glutamate is another chemical messenger, like acetylcholine. However, in Alzheimer's Disease and other forms of dementia there is an overactivity of glutamate, as opposed to the underactivity of acetylcholine. Therefore, memantine works to block the action of glutamate. It does this by binding to and blocking some of the receptors that glutamate normally binds to, therefore limiting their action in the brain. A receptor acts as a sensor in the body so when certain substances, such as chemical messengers bind to them it can cause a change in the body. By blocking the glutamate receptors this drug helps to reduce some of the symptoms of dementia and prevent further future damage.

Memantine

In NHS care pathway for **severe Alzheimer’s disease** *or,* if AChEIs cannot be tolerated, prescribed for **moderate Alzheimer’s disease**. Used to treat **symptoms of dementia** associated with Alzheimer's disease and can be used alongside AChEIs.

Names

- Alzhok
- Ebixa
- Marixino
- Nemtadine
- Valios

Forms

- Tablets
- Soluble tablets
- Melt-in-the-mouth (orodispersible)
- Liquid

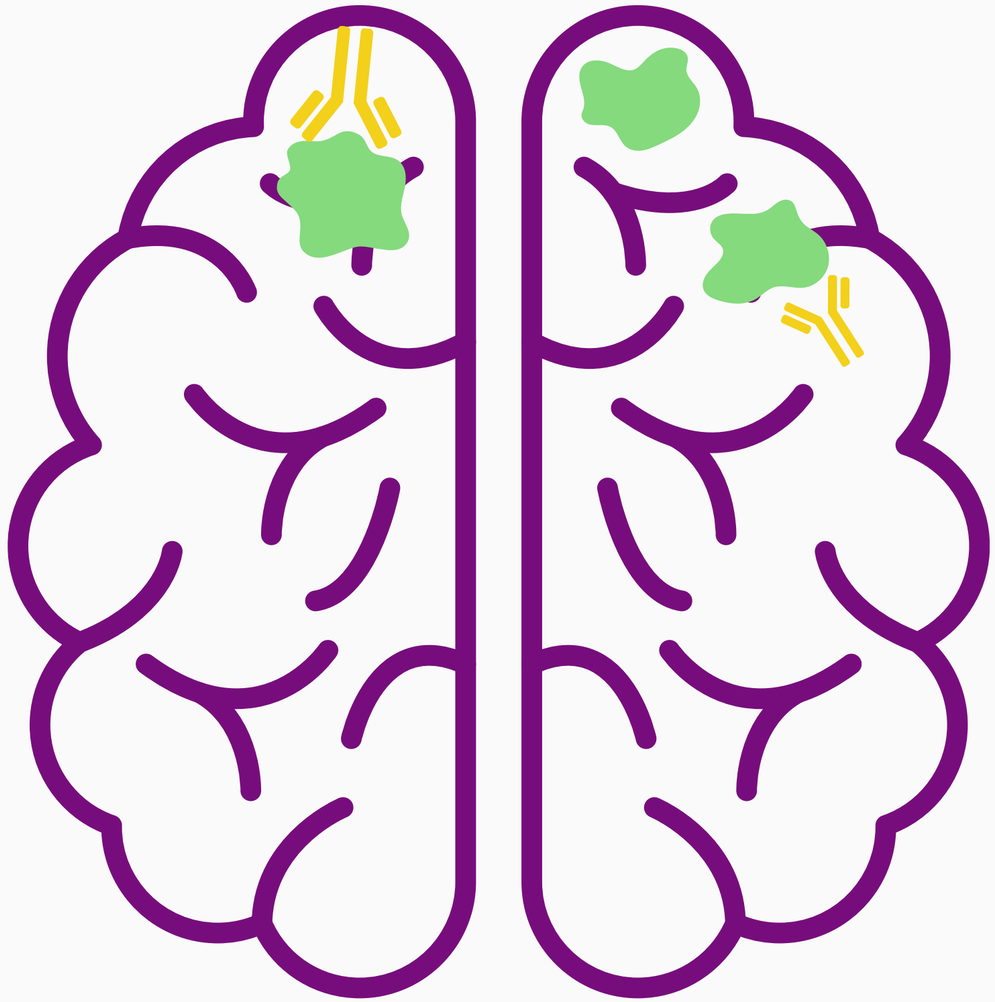
Used for

- Alzheimer's disease
- Parkinson's disease
- Lewy body dementia (unlicencesd)

Drugs that are in the process of being approved

Amyloid Beta (Aβ) / Anti-Amyloid drugs

- Aducenemab
- Donenamab
- Lacenumab



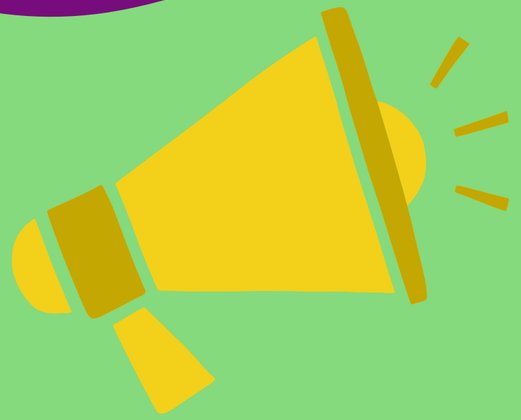
These drugs aim to reduce levels of amyloid beta in the brain, by preventing initial buildup or increasing removal. They target the protein and either destroy it themselves or help other immune cells identify it to destroy it. None of these are currently available in the UK.

Amyloid Beta (Aβ) / Anti-Amyloid drugs

The following section is on Amyloid Beta drugs, these can also be referred to as anti-amyloid drugs. This category of drugs are not yet available in the UK but are the new direction the Alzheimer's Disease treatment is going in, they should be available in the next few years.

In Alzheimer's Disease research has found that there is a build up of a protein called amyloid beta which can clump together into what we call 'plaques'. These plaques can interfere with brain signaling and cause areas in the brain to not work properly or die, resulting in the symptoms of dementia. The anti-amyloid drugs aim to reduce the levels of amyloid by either preventing its buildup or increasing its removal. They do this by targeting the amyloid in the same way that our body's natural immune system targets harmful substances, by binding to them and destroying the substance by themselves or helping other immune cells to find it and have them destroy it instead.

Top tip when reading news or research articles..



Look out for ‘-mab’ in drug names!

- When drug companies name their new drugs they often follow certain patterns. If you see ‘-mab’ at the end of a drug name this means the drug is probably a Monoclonal Anti-Body that will target amyloid.
- A monoclonal antibody is a protein usually used in our immune system which can bind to harmful substances in order to destroy or help block negative effects.
- Scientists can design these to target specific harmful substances such as amyloid beta in the case of Alzheimer’s disease

Early diagnosis

Results show the current anti-amyloid drugs have a greater impact on daily life the earlier they are given. This requires **early diagnosis** of amyloid plaques using **PET scans** and **lumbar punctures** (spinal taps).

Early diagnosis notes

It is worth noting that the current anti-amyloid drugs have a greater impact on daily life for patients with Alzheimer’s Disease in the early stages, this requires earlier diagnosis. Both the PET scan and spinal tap can be distressing and so are not part of routine procedures and would have to be requested specifically for the investigation of an Alzheimer’s Disease diagnosis.

Aducenemab

This is advertised as the first monoclonal antibody to treat not only the symptoms of Alzheimer's disease but also slow its progress. It was the first Alzheimer's Disease drug approval since 2003 (only in America by the Food and Drug Agency (FDA) not the UK).

However, due to a lack of impactful results and significant side effects **approval was rejected by the European and UK health agencies** (EMA and MHRA). Biogen have since announced that they are discontuining the development and sale of aducenemab (brand name Aduhelm)

Reported to "slow the rate of cognitive decline"

BUT this was not found to be of 'clinically important difference' for patients. This means the decline was not enough to have a real impactful difference in every day symptoms.

Aducenemab notes

Despite this drug not being approved in the UK and the company discontinuing its development it has been very important in the advancement of Alzheimer's Disease treatment as the first drug to slow the progression of the disease as well as treat symptoms. It was the first drug to have had approval (in America) since 2003. Unfortunately, the benefits were not great enough to have a positive impact on patients and it had some significant side effects such as brain bleeds and brain swelling.

Donanemab

The UK regulatory board (MHRA) have a new system for drug approval called the International Recognition Procedure which means they will follow suit from other regulatory authorities but still retain the right to make their own decision.
If approval decisions are positive, the very earliest donanemab **might be available from the NHS is 2025.**

Slows cognitive decline by 35%

Donanemab would be given as an infusion **once a month**

Donanemab notes

MHRA- Medicines and Healthcare products Regulatory Agency.
Donanemab has been shown to slow cognitive decline by 35%. This means that when they were testing the drug they had a group of participants taking the drug and a group of participants not taking the drug. The participants would not know which group they were in as they would be given a placebo/dummy drug instead which takes out any chance that any positive effects are due to a happy hopeful attitude rather than the drug itself. Both groups will do an assessment that evaluates their cognitive ability before and after the study. The patients that were taking the donanemab drug were shown to have declined 35% less than the patients that were not taking the drug which means it slowed the rate of cognitive decline. This drug would be given as an infusion once a month meaning you would have to go somewhere that a healthcare professional can administer it.

Lecanumab

Monoclonal antibody aimed for people with mild Alzheimer's in the early stages. This means it will also require PET scans and spinal taps in order to be prescribed.

The company that created Lecanumab has submitted an application for approval in the UK and Europe. It has been granted accelerated approval in America.

You may also see this referred to as Leqembi.

Slows cognitive decline by 27%

Lacenumab would be given as an infusion **once every 2 weeks**

Understanding Minimum Clinically Important Difference

Although there might be a difference seen clinically on these different scales and assessments, this difference might not be great enough to see a real life improvement for the patient.

Different cognitive tests used in trials

We compare how much Lecanumab and Donanemab slow the cognitive decline of patients, but it is important to remember that the way they measure cognitive decline is different. Lecanumab used four different types of assessment to measure cognitive decline and Donanemab used two other assessments.

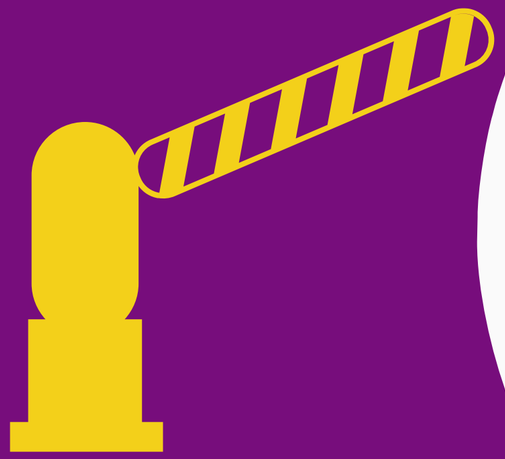
Minimum Clinically Important Difference notes

For example, in the case of Donanemab this study used a 144 point scale to assess cognitive ability of the participants. It was shown that an average of a 5 point change was needed in order to see effects that were noticeable to patients and their loved ones in real life. However, only an average of 3 point change was seen in trial results suggesting that despite there is a slow in cognitive decline seen ‘on paper’ or in the results that these are not impactful enough to make a real change to people's lives.

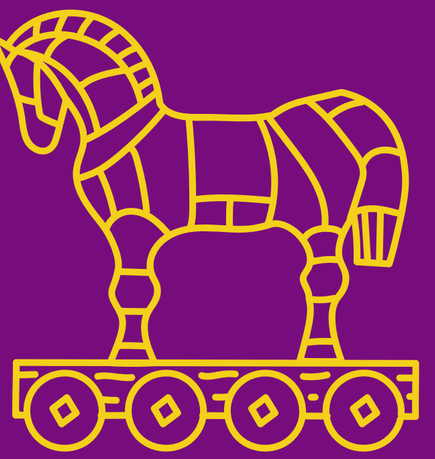
Additionally, Donanemab and Lecanumab are often compared as they are both monoclonal antibody drugs set to be released soon. It is important to consider that even though they both present their results as a percentage of cognitive decline the way that they measure this is different. Therefore, it is a little bit like comparing apples and oranges.

Future therapies

Despite the promising developments with the latest anti-amyloid drugs, the limited results seen by patients are thought to be due to the blood brain barrier.
The blood brain barrier protects the brain environment by controlling the passage of substances between the blood and the brain. The new drugs are too big to pass this barrier easily and so they cannot reach their target which hinders their results.



Future therapies aim to overcome this by using ‘trojan horse’ technologies. These will use pre-existing transporters in the brain to help the drug across the barrier. This would ‘sneak in’ the drug so it has better access to its target, hopefully improving its effect.



Future therapies notes

As previously mentioned, some of the future drugs have questions around their impact on everyday life. The limited results of these drugs are thought to be due to the blood brain barrier. This barrier protects the brain environment by controlling the passage of substances between the blood and the brain. Currently these drugs are too big to pass this barrier easily and must by find the thinnest points in the barrier. Due to this, it is thought that not much of the drug makes it into the brain environment. This means that the drug is not in the best location to target the amyloid protein most effectively. There is current research being done that hopes to overcome this issue by using transporters that already exist in the blood brain barrier. By using the pre-existing transporters, they could essentially sneak in the anti-amyloid drugs, allowing them better access and improving their effect.

Dementia in the media

Blood tests for dementia

News has circulated that there are new blood tests that can detect dementia 15 years before diagnosis. This appears hugely promising as it is a great alternative to a spinal tap. However, its use to the general public may not be as significant as it seems. 15 years advance warning does not give much more relevant information than the other current known risk factors, such as age, smoking and/or previous head injuries.

BBC panorama

This episode, ‘Alzheimer’s: A Turning Point?’, focuses on new anti-amyloid drugs and what their release could mean for patients and the NHS.

Clinical trials simplified

Pre- clinical testing

This stage can involve building protocol (plan), computer simulations to predict likely outcomes and the first stages of testing. This testing can be *in vitro* which means ‘in glass’ which would be cells in a lab or *in vivo* which means ‘in the living’ which would be in living animals.

Pre-clinical testing can take **12-15 years** from concept to clinical testing (in humans)

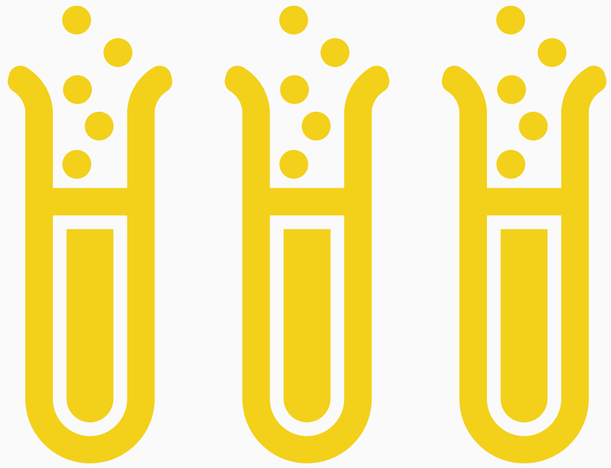
Pre- clinical testing notes

When building the protocol (plan) for the study, the scientists must decide what exactly they want to study and how they want to do this. Computer simulations can predict what results should be seen at what stage. This is helpful so the researchers can know If they are on track so they can decide whether or not to make changes to/move forward/stop the study. Testing in cells can show straight away how the drug interacts with these cells and whether it will be safe and useful in the body. Testing in animals further shows how the drug may work and if it is safe or beneficial to move to the next stage of testing.

Phase 1 of clinical testing

Clinical testing is **done in humans**. The main aim of this phase is to test **how safe the drug is** and to find the **best dosage**. They want to find the maximum tolerated dose that has a positive effect. They will have a small number of participants that each have different dosages that they will slowly increase whilst monitoring the effect in the body.

This early phase will usually have between **20-100 participants** and depending on the study design will last **several months to a year**



Phase 1 of clinical testing notes

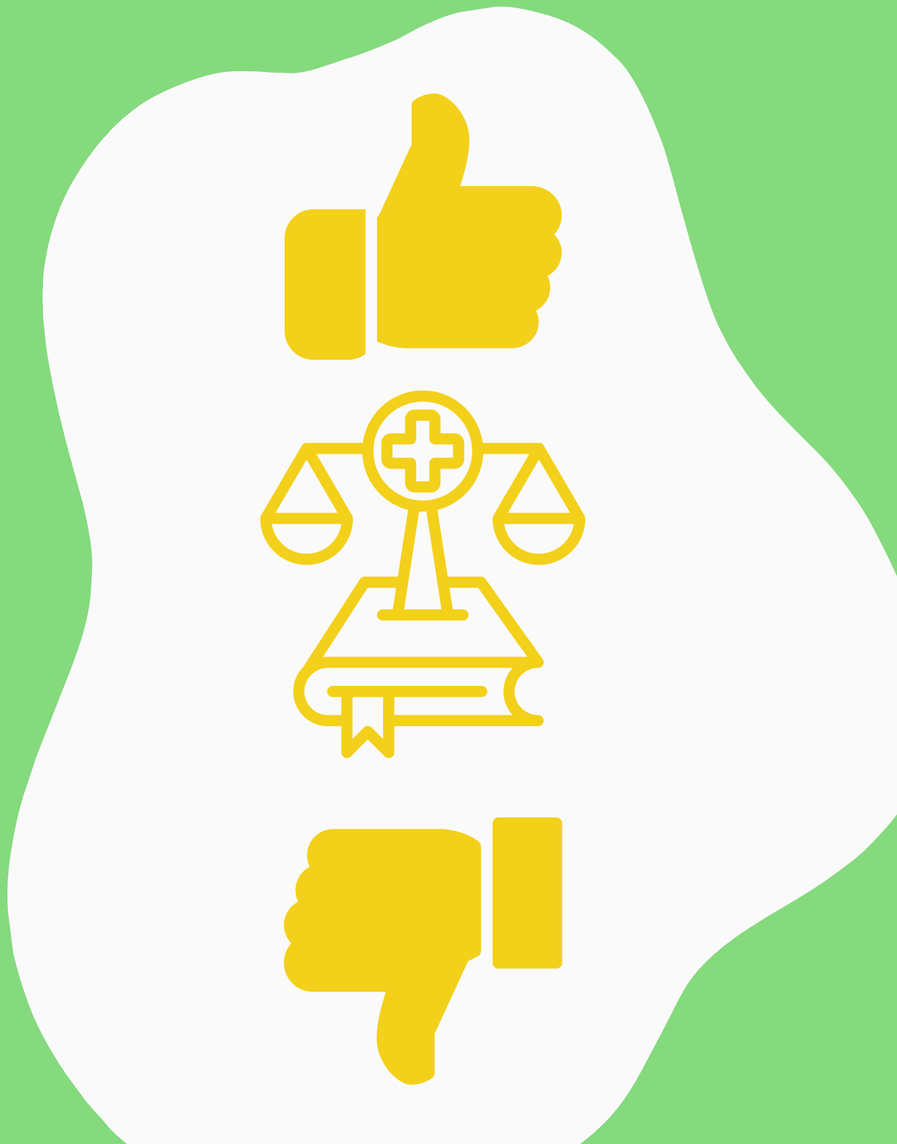
In this phase they want to establish how much of the drug to give, this is identified as the dosage that it is the safest and has the best effects. The very first patients will be given a dosage that they know is too small to have any effect in the body and they will slowly increase the dosage so they can closely monitor any changes in the body. They do this by keeping an eye on vital signs (heart rate, oxygen levels) and taking samples such as blood or urine which can tell the scientist a lot of information as to what is going on in the body.

Phase 2 of clinical testing

This next stage of human trials focuses more on the testing of the **positive and negative effects of the drug**. Now that they have an idea of the ideal dosage that they know is safe they can monitor how the drug works in a larger population of people and can watch out for any potential side effects.

Phase 2 clinical trials can involve **100-300 participants** and can last from **several months to two years**.

This stage can be skipped if phase 1 results are exceptionally promising



Phase 2 of clinical testing notes

By increasing the number of participants in this stage the scientists can find out more information about how different people with different levels and stages of disease respond to the drug. The main focus is to see if anybody reacts differently having either positive or negative responses so they can find out why and if the drug will be safe to distribute.

Phase 3 of clinical testing

Phase 3 clinical trials aim to **further test any negative effects** of the drug in a larger more diverse population of participants. By this stage they have proven that the drug is useful and works in order to continue development. The drug will continue to the next stage if it is better than others already on the market.

If the medication is of special interest this phase can be accelerated.

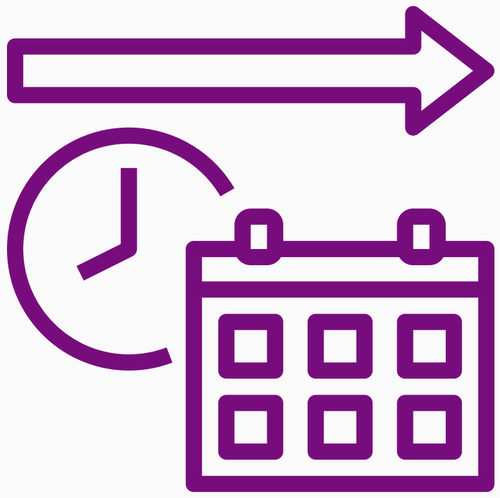
This phase can have **300-3000 participants**. It can take as long as **1-4 years** but if accelerated can be **shortened to 3-9months.**

Phase 3 of clinical testing notes

In order for a drug to progress to phase 3 it must be a strong candidate to be made available to be submitted for approval. Within phase 3 they need to build their argument as to why this drug is good and will be better than others. This can be as ‘first in class’ wherein it could be the first drug to target a specific area in a specific way so there are no other medications to rival it. Alternatively, it could be ‘best in class’ this means it will be better than the other drugs due to a special feature, this could be its better results, better cost, its convenience, its lack of side effects or many other reasons. Once compared to other current medications and assurance that there aren’t any significant negative effects, the drug will be submitted for approval.

Phase 4 of clinical testing/ follow up

Phase 4 testing happens after the drug is licensed, the aim is to study the long term effects of the drug to check that it stays safe and doesn't lose its positive effects. They may also test for if the drug works on other diseases with similar mechanisms.



This phase will include **several thousand participants**. The length of this stage varies but often can go on for **many years** with follow up checks at intervals.

Phase 4 of clinical testing/ follow up notes

Phase 4 happens after the drug has been approved and licensed for release. In this stage they monitor for any long-term effects. As mentioned in slides 9-14 some of the current Alzheimer’s Disease drugs can also be used for other forms of dementia, this is because they share the same symptoms.

Glossary

Placebo- A treatment that feels real but has no therapeutic result. This pretend drug is used as a comparison to the real treatment and eliminates the chance that positive results are due to people believing they're getting better.

Progression- In the context of dementia and Alzheimer's Disease, progression relates to the worsening of physical and psychological symptoms.

Cognitive decline- In the context of dementia and Alzheimer's Disease, this relates to the worsening of memory and thinking skills of patients.

Blood Brain Barrier- A biological barrier in the brain that maintains an optimum environment.

Soluble/insoluble- A soluble medication dissolves in liquid easily whereas an insoluble one does not.

Aggregate- A cluster in the brain, often made up of antibodies or proteins such as amyloid when they clump together

Plaque- a clump of harmful amyloid. When these plaques build up they contribute to the decline of memory and thinking.

Primary endpoint- The main goal of the clinical trial e.g See if the drug is safe for early stage or if it works better than other drugs for a later stage

Secondary endpoint- Something to collect information on during a trial that might not be the main focus e.g other effects on the body

Baseline- The starting measurement used as a reference point to compare against in a clinical trial.

Tablet- A form of medication that is solid, it is often small and round, swallowed whole.

Capsule- A form of medication where the active ingredients are within a shell (hard or soft), swallowed whole.

Glossary

FDA- Food and Drug Agency in America that approves or rejects new drugs.
NICE- National Institute for Health and Care Excellence, publishes guidelines for drugs in England.
EMA- European Medicines Agency approves or rejects new drugs for Europe (the UK almost always follows suit).
MHRA- Medicines and Healthcare products Regulatory Agency, which approves or rejects new drugs in the UK.
PET Scan- Positron Emission Tomography which shows not only images of the body but how well parts of the body are functioning.
MCID- Minimum Clinical Important Difference, the minimum change seen clinically which is also noticeable for patients.
Amyloid- A protein that occurs naturally in the brain but can be harmful if there is an irregular buildup.
Immunotherapies- Drugs which utilise the body's immune system response to fight disease.
Monoclonal antibody- Part of the body's immune system that can bind to specific harmful substances to help get rid of them.
Glutamate- A chemical messenger in the brain linked to learning and memory as well as other roles.
ARIA- Amyloid-related Imaging Abnormalities, changes in brain images seen as a result of anti-amyloid drugs which show either swelling or bleeds in the brain.

Links

- NHS care pathway, **slide 6** Dementia-Care-Pathway-guidance-for-prescribing-acetylcholinesterase-inhibitors-and-memantine.pdf (tewv.nhs.uk)
- Radio 4 more or less episode on minimum clinically important difference, **slide 22** ‘Vaccine claims, Alzheimer's treatment and Tim's Parkrun times’ https://www.bbc.co.uk/programmes/m001r1mq
- Article on minimum clinically important difference, **slide 22** https://alz-journals.onlinelibrary.wiley.com/doi/pdf/10.1002/trc2.12411
- Roche future therapy results, **slide 23** https://firstwordpharma.com/story/5836350
- BBC Panorama, **slide 24** https://www.bbc.co.uk/iplayer/episode/m001wb1t/panorama-alzheimers-a-turning-point
- Blood tests for dementia, **slide 24** https://www.theguardian.com/society/2024/feb/12/early-blood-test-to-predict-dementia-is-step-closer-as-biological-markers-identified