JULY 2024

90 SLOANE STREET

Patient Bulletin

ALZHEIMER'S: MAJOR MEDICAL BREAKTHROUGHS

DR MICHAEL SANDBERG

MHRA licences imminent

The need to start treatment at the earliest stage: even prior to symptom development

Alzheimer's affects so many of us. In 2021 an estimated 50 million people in the world had dementia, mostly Alzheimer's. It can wreck personal independence and quality of life, creating enormous strain and sadness for the whole family with the diminution of personality of their loved one, as well as the terrifying costs of care.

This article will give you and your family the background knowledge of recent breakthroughs. It is necessary to have a high level of understanding about the new treatments and investigations for this historically tragic disease to make the best decisions. For some of you, it may be one of the most important articles you ever read.

"Making a real change in any disease is not just about achieving the scientific breakthrough, it is also seeing patients taking it up and at the right stage."

THE REVOLUTION IS DRIVEN BY TWO BREAKTHROUGHS:

1. NEW TESTS

PREDICTING DIAGNOSIS 10-15 YEARS
BEFORE A PERSON IS AFFECTED

2. NEW TREATMENTS

FINALLY - DRUGS THAT ACT ON THE ALZHEIMER'S PROCESS -
STOPPING BRAIN CELLS DYING: THE KEY TO OVERCOMING THIS DISEASE

MAKING A REAL CHANGE IN ANY DISEASE IS NOT JUST ABOUT ACHIEVING THE SCIENTIFIC BREAKTHROUGH, IT IS ALSO SEEING PATIENTS TAKING IT UP AND AT THE RIGHT STAGE. IN THIS CONDITION, TREATMENT NEEDS TO BE EARLY SO ONE NEEDS TO BE THINKING AHEAD PROACTIVELY

In 2014 my mother and our family were so lucky that she was able to be involved in an early trial of the anti-tau medicine HMTM. Ten years later this anti-tau medicine has turned out to have extremely impressive results. She made it into the trial on the very last day, transforming her final 6 years for her and our family. In horse racing terms we "saw the gap" and went for it. It required a lot of trust and determination on her part. She had to come off an opiate and suffer pain to make it, but her mental ability was her top priority, and she was of Scottish determination. Such will be the demand for these new medicines that we are going to need the same focused philosophy, future trials potentially being open sometimes for a few weeks, only, before closing, due to immense demand across the world and only a predetermined number of places.

Our luck came through a remarkable friend - Dr Emer MacSweeney - who bravely set up Re:Cognition Health and kindly offered my mother the last place in the world for a trial. Recent discussions with Emer have been the driver of this article and provide us with the early opportunity, through her clinical centres, to gain access to the new sophisticated diagnostic biomarker tests and international trial drugs for new generation treatments designed to slow and ideally halt progression of Alzheimer's disease and its ultimately devastating symptoms. Emer has enthusiastically led this field from the start.

THE PATHOLOGY

In the presence of amyloid, tau protein starts to spread throughout the brain and the tau explosion kills your brain cells. Amyloid can be present for a decade before the spread of tau. Early detection of the amyloid load is what we are looking for. In summary, the pathology includes extracellular amyloid plaques and intra neuronal neurofibrillary tangles and loss of neurons and synapses. Misfolding and aggregation of tau proteins and the subsequent formation of tau tangles disrupt neuronal function.

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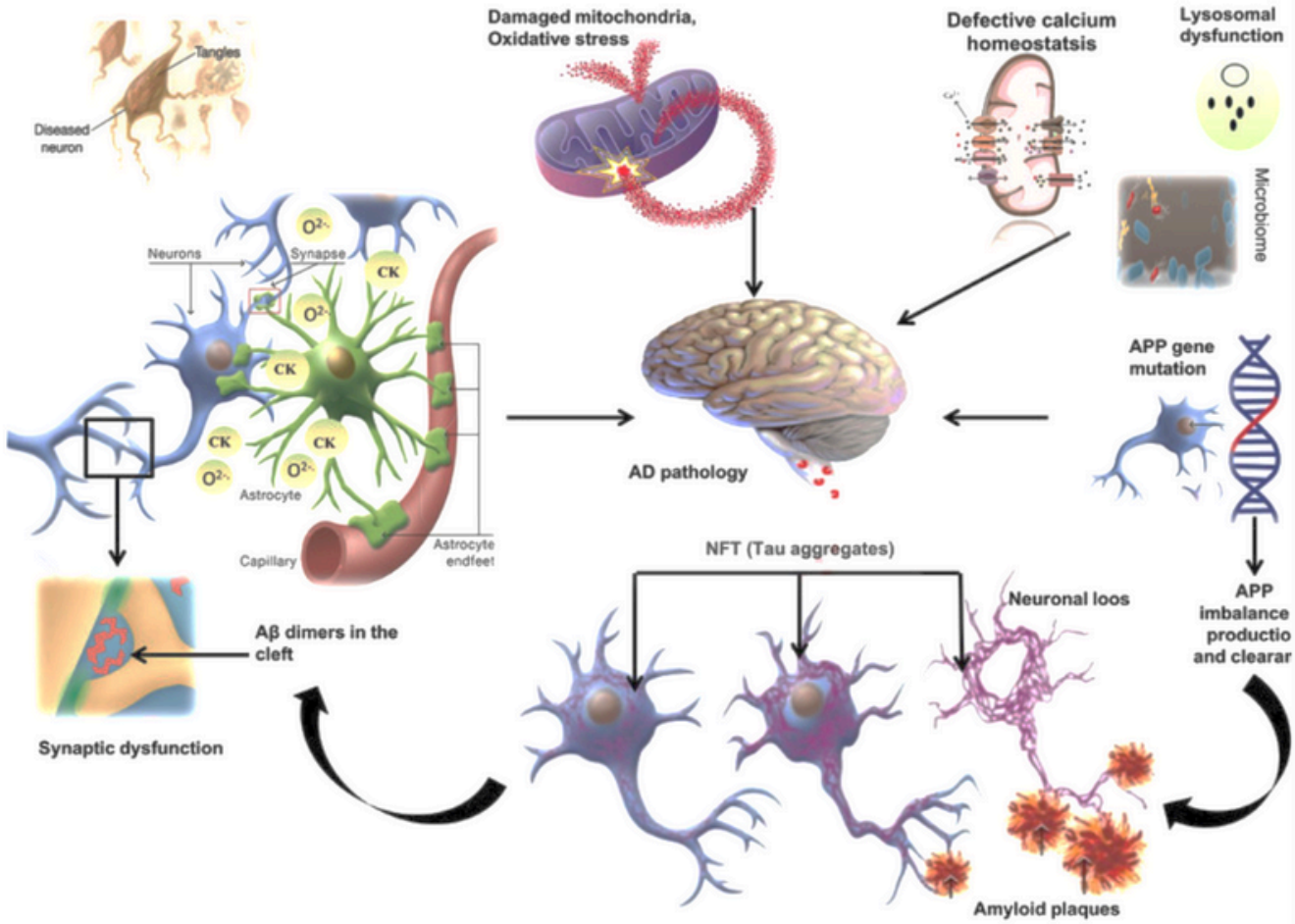

Schematic representation of the pathology of Alzheimer's disease depicting the multifactorial perplexed feature AD disease. The figure depicts the role of amyloid-β (Aβ) in the formation of extracellular amyloid aggregates which in turn will results in the formation of Tau aggregates and neurofibrillary tangles (NFTs) which contribute the neuronal loss, synaptic dysfunction, and diseased neurons characteristic of AD. In addition, the periplaque activation of astrocytes, resulting in the release of various cytokines (CK), and microglia, leading to the generation of superoxide radicals (O 2-). The contribution of damaged mitochondria due to aging plays a role i the accumulation of free radicles which leads to change in the energetic efficiency of neuron. The loss of Ca 2+ homeostasis explained by the excitotoxic activity is a core contributing cause in AD pathogenesis. Changes in the gut microbiome composition may also contribute to AD pathology. [Parts of the figure were reproduced with permission from references [17, 27, 32]].

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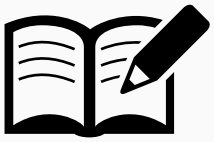
LIFESTYLE HABITS THAT *CONSIDERABLY* REDUCE THE RISK OF ALZHEIMER'S *AND ITS PROGRESSION*

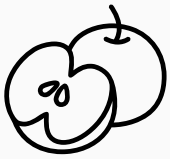
EXERCISE

The most important protective action modulating epigenetic expression



ACTIVITY

Keep mentally and socially active



DIET

Mediterranean, low sugar, increased olive oil and nuts are all recommended. *

**There is a neuronal additional element:*
saturated cream and dairy are helpful in prevention.
Greek yoghurts are good for your brain,
but they may have negative cardiovascular effects

SLEEP

7-8 HOURS

LIMIT ALCOHOL AND STOP SMOKING

CURRENT AVAILABLE TREATMENT FOR ALZHEIMER'S

These do nothing to slow the disease process which is caused by loss of brain cells (neurons).

Presently **anti-cholinesterase inhibitors** simply increase the amount of acetyl choline (the messenger between cells) thus improving the connectivity of the cells you still have. For many, these treatments do make a difference over a couple of years, but they will not affect whether you will develop Alzheimer's or make a really major long-term difference. **Donepezil** and **Galantamine** are the main examples. They help memory and concentration, and the majority of people taking them stay stable for longer, by simply increasing the efficiency of the dying brain cells. Side effects: nausea, diarrhoea, nightmares and slowed heart rate.
With moderate stage dementia **Memantine** is added. This is an **NMDA blocker** which helps to maintain day to day function.

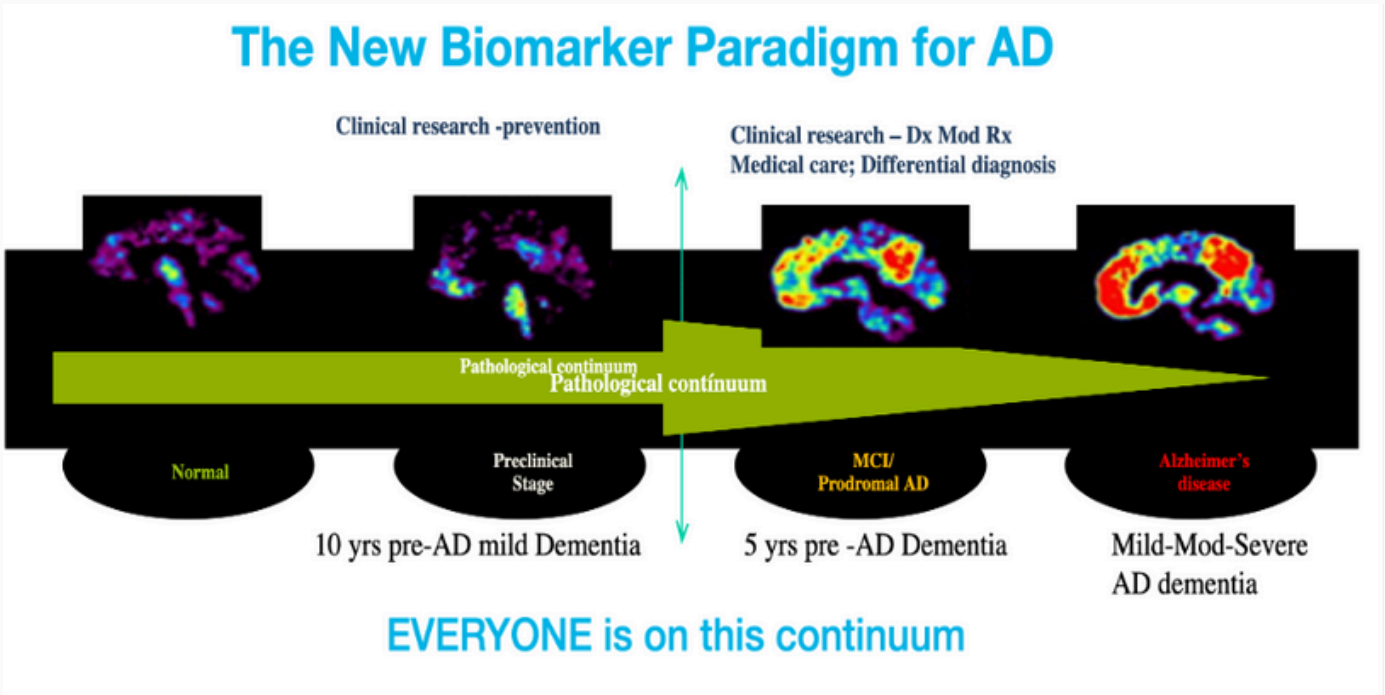
Side effects: dizziness, headaches, constipation and shortness of breath.

New treatments prevent the death of precious brain cells caused by the accumulation of toxic levels of amyloid and tau protein.

The earlier the new drugs are given, the more effective their outcome. Indeed clinical trials are taking place, currently at Re:Cognition Health Centres, designed to not only slow progression of MCI (mild cognitive impairment) and more advanced symptoms of Alzheimer's disease, but also to prevent or delay the onset of memory loss in asymptomatic, high risk, individuals, with biomarker detection of elevated amyloid and tau protein.
This rapidly developing new proactive world is similar to the genetic testing that we do at 90 Sloane Street. If you have potholes ahead in your lifepath and have that knowledge, you can do something about them.

We predict that those who do our genetic testing will have a reduction of cancer death of between a fifth and a seventh.

The same philosophy of asymptomatic testing will also be the key for Alzheimer's.



Slide courtesy of Recognition Health

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CURRENT AVAILABLE TREATMENT FOR ALZHEIMER'S

Diagnosing the risk of Alzheimer's: the new tests warn that you are building up amyloid and tau.

Until recently we have been using **structural MRI and functional brain imaging**. Looking for atrophy (shrinkage) of specific areas of the brain - the hippocampus, ventromedial, prefrontal and lateral temporal cortex - on MRI is considered suspicious evidence of neurodegeneration. However, by the time there is significant evidence of visible brain loss on MRI, the disease is already well under way. Unlike most other cells in the brain, brain cells cannot regenerate, so once lost they are lost for ever. This is why today it's critical to act as early as possible.

Amyloid PET Scans: a type of functional neuroimaging that detects the amount of amyloid deposition in the brain, the fundamental diagnostic test in Alzheimer's.

This diagram – an amyloid PET (positron emission tomography) CT - shows the increasing levels of amyloid developing over time.

**PET TAU IMAGING IS ALSO AVAILABLE IN THE UK,
BUT CAN BE ACCESSED ONLY BY CLINICAL TRIALS.**

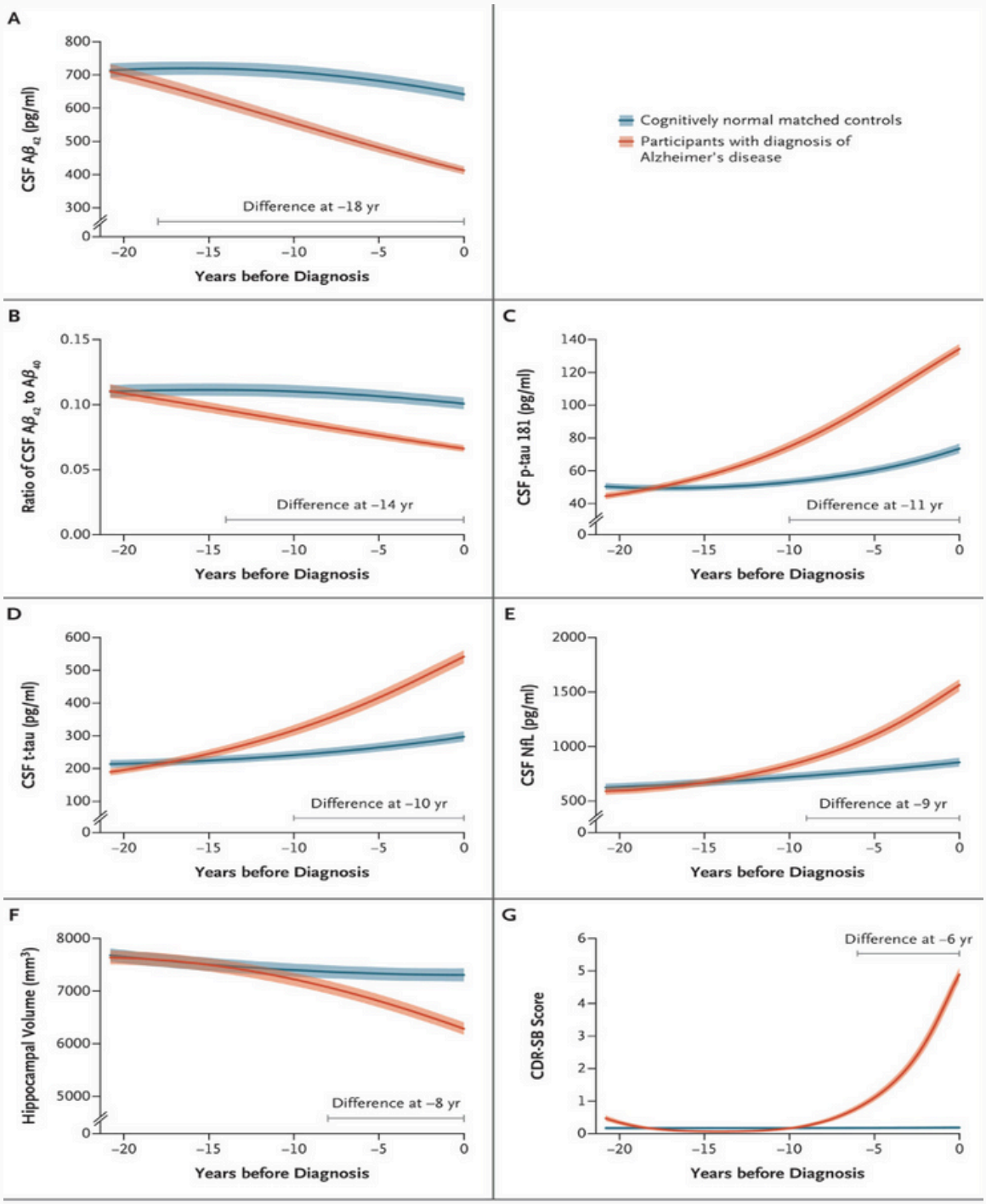
The new liquid test-predictive biomarkers - different from scanning.

These detect the build-up of amyloid and tau protein, predicting the onset of Alzheimer's 15 -20 years before diagnosis. Many of them measure different levels in the cerebrospinal fluid (CSF). This is obtained by a lumbar puncture.

Jia's recent Chinese study spanning 20 years, recently published in the New England Journal, validated the sequence of changes in biomarkers in sporadic Alzheimer's disease. The trial ran from 2000-2020. Median follow-up being 19.9 years.

1. **CSF alpha-beta42 levels** - (cerebro spinal fluid- taken at a lumbar puncture), raised 18 years before onset.
2. **CSF ratio of a-beta42 to alpha-beta40** - abnormal 14 years before Alzheimer's disease developed.
3. **CSF Phosphorylated Tau** - The level increases 11 years before onset in participants in whom Alzheimer's disease developed.
4. **Level of neurofilament light chain (NfL)** - neurodegeneration increased 9 years before diagnosis.
5. **Hippocampal (an area of the brain) atrophy on MRI brain scan** - changes noted 8 years before Alzheimer's developed with cognitive decline being a few years later.

The adjacent graphs show the changes in the biomarkers over the years, predating the onset of Alzheimer's which is at zero (bottom right of each graph). Reduction in CSF alpha-beta ratios occurs first, then increased levels of CSF phosphorylated Tau, later brain atrophy on MRI brain scan and cognitive decline.



Tests detecting the build-up of amyloid and tau protein predicting onset of Alzheimer's 15 -20 years before diagnosis.

NEW BLOOD TEST MARKERS

Phosphorylated tau ptau 217 is a great marker of amyloid and an effective marker of tau phospho tau 217. We will learn more how to use these markers and how much early prediction from them works.

In the future a blood test will likely be done in the same way as we now measure cholesterol. However, within clinical trials it is essential to use these biomarkers to confirm an individual has elevated toxic levels of amyloid and/or tau protein, prior to providing the individual the opportunity to access new medications designed to bring these toxic amyloid and tau levels back into the normal range and thereby protect the brain cells form further destruction.

TREATMENTS

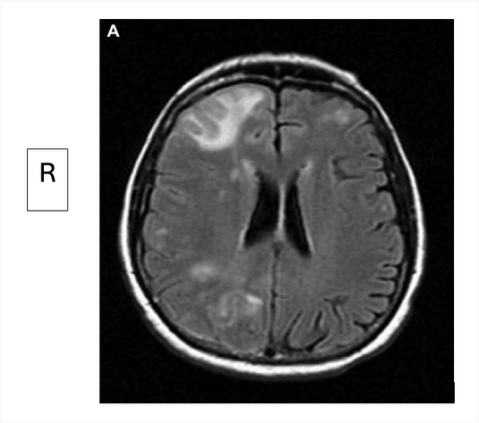
Lecanemab and Donanemab are the two new amyloid-removing monoclonal antibodies of trial-proven benefit. They both remove amyloid like a hoover and are effective, but their gains need to be balanced against the **risk of their causing bleeding in the brain: ARIA (Amyloid regulated imaging abnormality).**

ARIA AND BRAIN BLEEDS WITH AMYLOID REMOVAL

The amyloid-removing medications can disturb the walls of the tiny micro-blood vessels surrounding nerves, as they remove the amyloid protein from the brain. This in turn can result in some leakiness of fluid ARIA E (edoema), or both blood ARIA H (micro haemorrhages), from these tiny blood vessels. ARIA E and ARIA H can be seen on MRI scans. Removing amyloid has been described as analogous to *"hoovering a very dusty carpet."*

ARIA can occur in Alzheimer's disease naturally, and with the anti-amyloid MAB drugs about 35% of patients may develop ARIA, but only 3.5% of people on these drugs notice any related symptom episodes; for example dizziness, headaches and feeling less alert.

The known side effect of ARIA has not prevented FDA approval for either **Lecanemab** or **Donanema**b to enter the market in the USA.



Example of ARIA E on MRI
during monoclonal antibody treatment, affecting the right side of the brain, showing as the white areas which are hardly seen on the left side
Frontiers Neurosci Jan 24

APOE4

APOE4 is a gene which comes as two pairs of alleles. If you have one pair of the alleles with the APOE4 gene change, as with 18 % of the population, you will have a 3-fold increased risk of Alzheimer's. If you have both of the gene pair with the change, then your lifetime risk of Alzheimer's is 8-12-fold, compared to an individual who does not have an APOE4 gene change.

Individuals who have both pair of alleles with the APOE4 gene change have a tendency to high levels of amyloid protein in the brain. With fast removal there is a greater risk of bleeds in the brain. Therefore homozygous APOE 4 patients (with both pairs of the gene affected for APOE4) are excluded from using certain amyloid-removing drugs, needing another treatment such as an anti-tau. To carry on the carpet hoovering analogy, the greatest amount of amyloid removal will happen within the first six months of treatment, so later on the risk of ARIA diminishes. Should ARIA occur, it may not be necessary to interrupt treatment; however if symptoms and the extent of ARIA are such that interruption of treatment is required, in most instances the ARIA E resolves, and the ARIA H stabilises and treatment may then resume. This is monitored closely by experienced physicians and neuroradiologists. Donanemab is given as a monthly intravenous infusions, and stopped when the amyloid is cleared by 6,12 or sometimes 18 months as measured on serial PET amyloid scans. (Anticoagulants such as apixaban are a contraindication for anti-amyloid drugs.)

TWO NEW AMYLOID-REMOVING MONOCLONAL ANTIBODIES

LECANEMAB AND DONANEMAB

The Trials were published at the end of 2023 in the New England Journal of Medicine. In the CLARITY study Lecanemab slowed down disease progression by about 27%.

Lecanemab is given as an infusion every 2 weeks

- Entry to the trial was by positive amyloid PET scan or positive amyloid CSF test
- Incidence of ARIA E 12.6%, symptomatic in 2.8% with headache, visual disturbance and confusion
- ARIA – H was 17.3%
- Symptomatic ARIA H in 0.7% with dizziness

Donanemab: the better of two new anti-amyloids, a Lilly drug, involves treatment infusions every month, so it is easier, and its trial benefits have been greater. Donanemab reduced progression by 42% compared to the control group

HMTM HYDROMETHYLTHIONINE MESYLATE

A third drug – and anti-tau medicine - demonstrated very impressive results in the recent LUCIDITY Clinical - and is the most practical as it is given as a tablet. No increased risk of Aria. It is a second-generation tau protein aggregation inhibitor. TauRx-Lucidity study - the most impressive study so far. (Trial name TRX0237).

- Patients with mild cognitive impairment or mild dementia
- 72% reduction in disease progression in those with mild impairment
- Some patients improved over the 18 months
- HMTM is able to cross the blood brain barrier

Evidence shows that the benefit can be maintained at 24 months.

HMTM, being an oral tablet administration, is much easier than having to go to a clinic for infusions. It has a strong safety profile and no increase in ARIA, unlike the monoclonal anti-amyloid drugs.

TauRx Pharmaceuticals was founded in 2002 in Singapore and has research facilities in Aberdeen, Scotland. The drug has a dual action: inhibiting tau aggregation in the brain, and increasing hippocampal acetylcholine.

It has demonstrated a favourable safety profile across nearly 3,000 subjects in trials, being the first oral therapy against tau protein requiring minimal testing not needing the successive MRI scans of the anti-amyloid drugs as it does not cause ARIA. The phase 3 LUCIDITY trial showed sustained benefits across the spectrum of disease from early to moderate dementia stages.

Participants experienced a significant reduction in disease progression compared to real-world data and meta-analytical controls. The early disease subgroup saw a marked decrease in transition to dementia. The trial used a dose of 16mg per day against a control group over 12 months. Followed by an open-label phase where all participants received the same dosage for an additional 12 months. The control group despite switching to HMTM after 12 months showed a significant decline.

HMTM resulted in a 95% reduction in blood neurofilament light chain (NfL) concentration relative to the control group. NfL is a biomarker for neurodegeneration. Early-stage patients were maintained significantly above baselines up to 18 months reverting to baseline only after 24 months

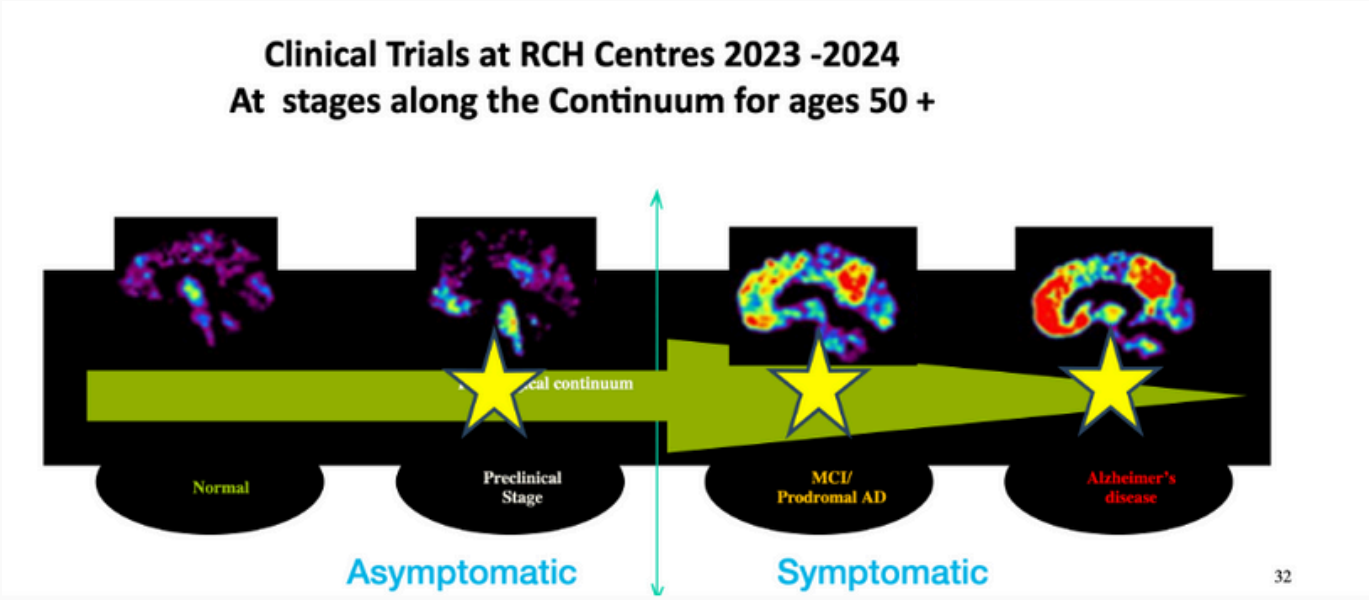
THE FUTURE

In Alzheimer's the problem is of excessive death of neurons, whereas with cancer it is about excessive cell proliferation.

Over the next ten years the new drugs just starting on their 10-year patent period will be extremely expensive. **Donanemab**, when licensed by the MHRA (the U.K. drug licensing authority) at a guess will probably cost about £60K for a year's treatment. The NHS will only be able to fund a tiny number of people compared to the vast numbers of patients who could benefit.

You and your families are going to need to be proactive and "see the gap" and make the choice as to whether you investigate, maybe even if you are symptom free, to see if you or your relatives are at risk.
Currently, running an Alzheimer's trial costs a minimum of a billion pounds, so no company is going to set up such a trial unless they are confident that their drug will be an improvement.

Many of you will be starting to read about **longevity**. I am hopeful that with the innate drive that such reading empowers, many of us will think more deeply about caring how we treat our bodies and individual organs. There is real potential with this motivation to make a difference against Alzheimer's. There are many overlapping themes.



ARE THERE ANY OF THESE NEW DRUGS YET COMMERCIALLY AVAILABLE OUTSIDE OF A TRIAL?

All three drugs below are under review currently, by MHRA for consideration for a licence to be available on the market.

Lecanemab has U.S. approval as well as in Japan, China and India.
Donanemab was approved in U.S. 10 days ago by the American FDA.
HTMN not yet approved in the USA.

It takes 2-3 months from MHRA approval to being available in the independent health care market. However for availability within the NHS, these medications will also need to be approved, by the National Institute of Clinical Excellence (NICE).

These new drugs are just the opening chapter in a new era of therapies.

It has taken 25 years of research to get to this position and progress over future years is going to be dramatic. If you are 40 and without a strong early family history of Alzheimer's, you should not be testing. There are risks with the current treatments and there will be better outcomes ahead, so our advice is to wait. However, if you are in your 70s or earlier, and starting to notice subtle symptoms, you should discuss the options with us.

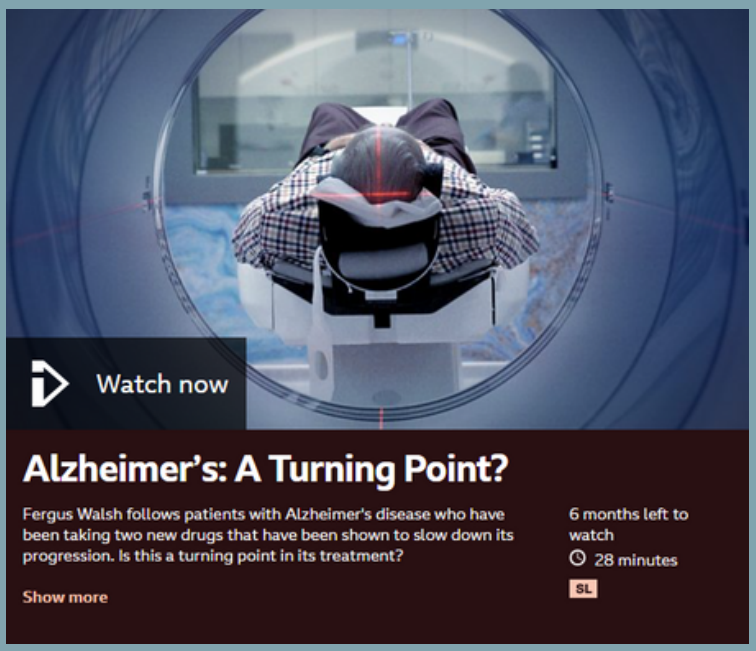
Donanemab appears to be superior in effect to Lecanemab and is also a monthly infusion, rather than two-weekly.
HMTM, as the anti-tau, is the easiest to take being a tablet, and has the most promising results of all, so far.
It is likely, as with cancer chemotherapy, that in the future multiple therapies will be used for Alzheimer's treatment simultaneously: an anti-amyloid, an anti-tau and probably an anti-inflammation drug, as a combined therapy.

Please do not underestimate the importance of testing early with Alzheimer's. All of us are affected directly or indirectly by this disease. Thank goodness we are finally moving towards a much more positive outlook as verified by the amazing pipeline of active medications presently in actively enrolling clinical trials, and in development.
With many thanks to Dr Emer MacSweeney for some of the diagrams and supporting 90 Sloane in this exciting field.

Together with our backing you, and teaming with Emer we can really make the difference. Should you wish to discuss any issues raised in this article please make an appointment at 90 in person, or for a telephone consultation if you are away. Time is really of the essence as some trials are closing imminently.

Dr Michael Sandberg
Medical Director
July 2024

DO SEE EMER'S EPISODE OF PANORAMA FEBRUARY 2024,
ALZHEIMER'S: A TURNING POINT BY FOLLOWING THIS LINK BELOW.



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