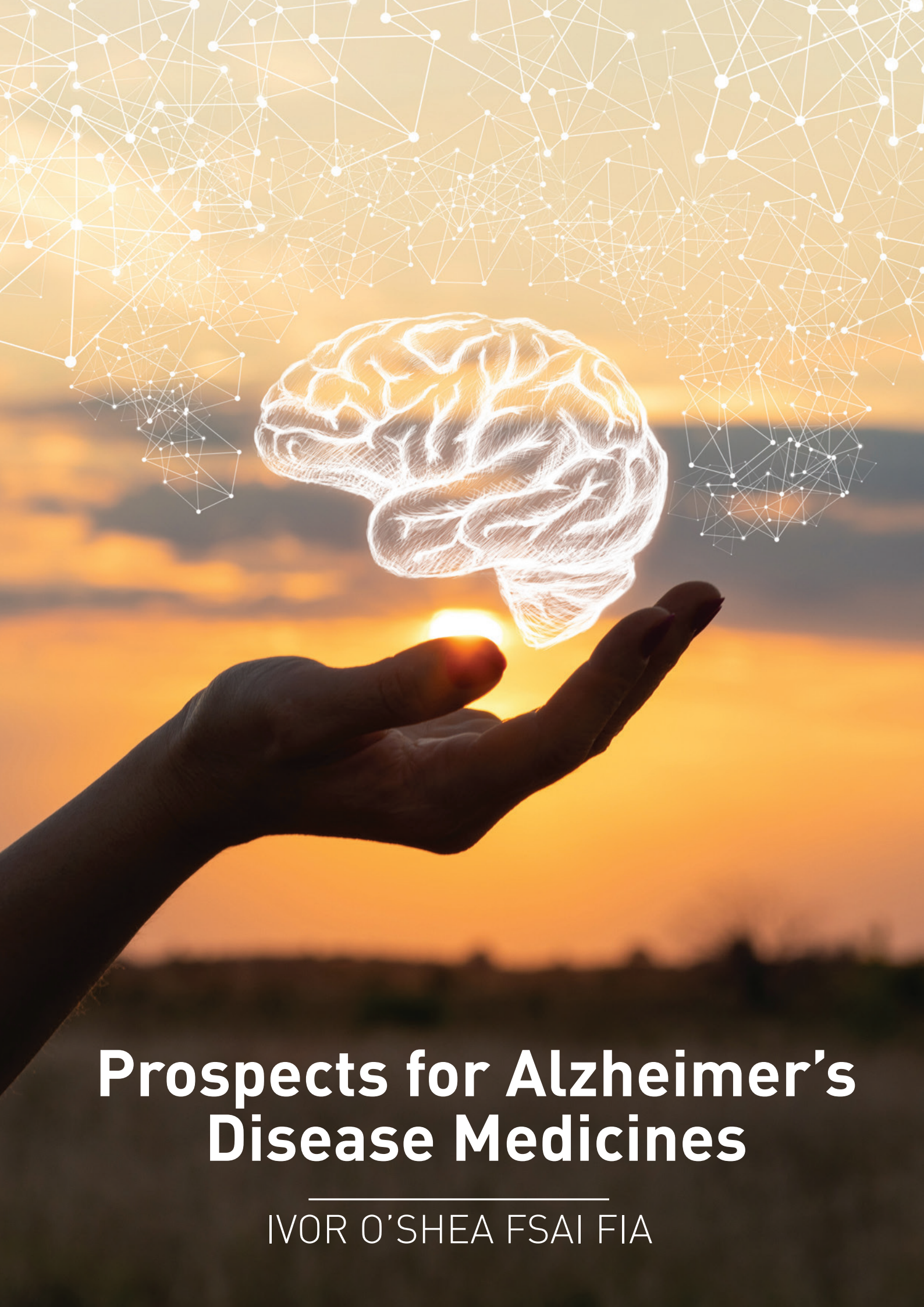

Prospects for Alzheimer's Disease Medicines

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Introduction

Since I first started investing in biotech companies in 2008, I have always been fascinated by Alzheimer's Disease (AD).

It is one of the leading causes of death in all developed countries. As things stand, deaths are set to escalate over the coming decades as populations age in most developed and middle-income countries. In addition, unlike other major causes of death, e.g. cancer and many heart-related illnesses, AD patients increasingly struggle with the activities of daily life as the illness gradually advances. This in turn requires high levels of care that strain both caregivers and national health systems.

AD is, at the time of writing, the only major cause of death without any fully approved medicines that can treat the underlying illness. However, two important breakthroughs have recently been made in developing medicines to treat AD. Although neither medicine will radically transform the status quo, they should make a meaningful improvement to patients' quality of life.

This paper sets out to provide some answers to key questions arising from the above, including the following:

- What is AD?
- What medicines are currently approved to partially mitigate the symptoms of AD?
- Why has the track record up to now in developing medicines to treat AD been so poor?
- What are the two important recent breakthroughs in developing medicines to treat AD?
- What impacts could these two breakthroughs have on patients' quality of life, longevity, and healthcare system utilisation levels?
- What are the prospects of developing additional medicines capable of treating AD?
- What are the broad implications for longevity improvement assumptions from current advancements in treating AD?

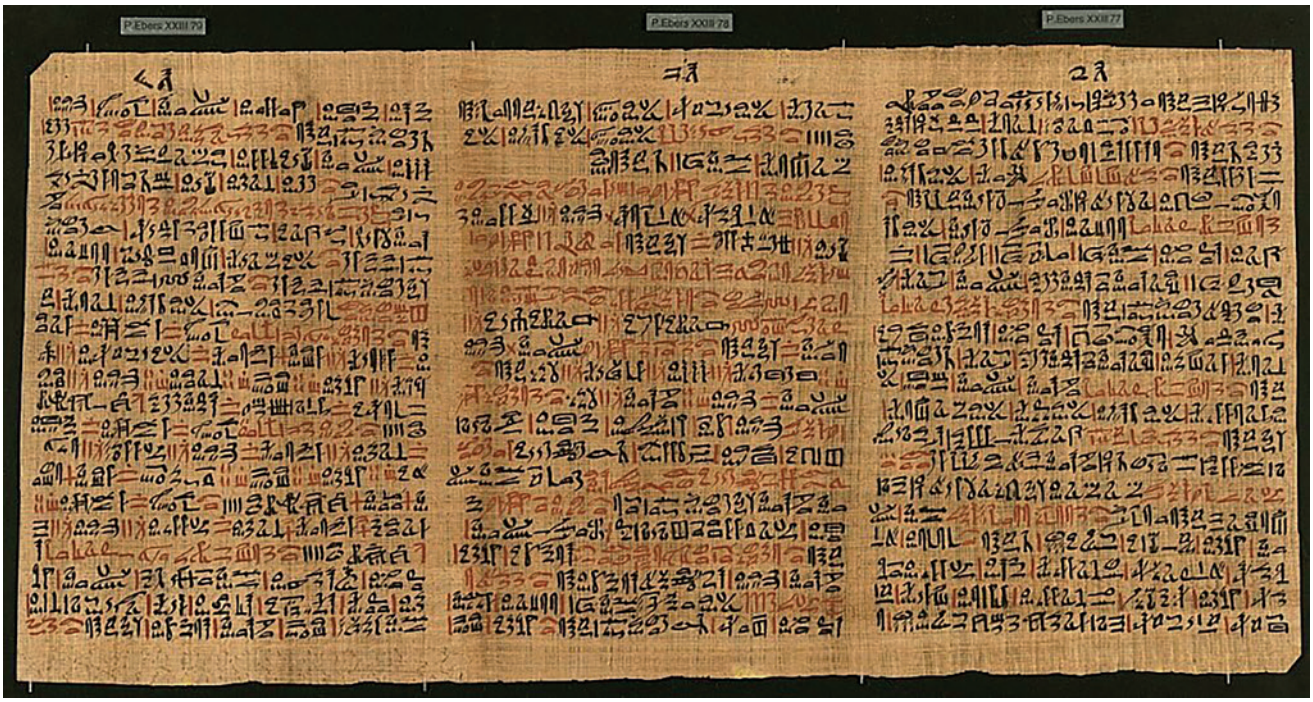
Finally, a presentation is to be made to the Society of Actuaries in Ireland on Wednesday, 22 March 2023 covering the main topics in this paper. That presentation should be regarded as a summary of this paper.

Ivor O'Shea
8 March 2023

1

Alzheimer's Disease in History

The concept of dementia has been understood since ancient times. Surviving texts from Pharaonic Egypt written c.1500 BC (which in turn were very likely compendiums of medical knowledge originating around 2500 BC-3000 BC) demonstrate people at the time understood the condition. Multiple written sources from classical Greece also recognised dementia as a medical condition. However, the ancient Egyptians and Greeks—like all other similar cultures—regarded dementia not as a disease but instead more as a sad but natural part of the aging process. That view generally prevailed up to modern times.



Ebers Papyrus, c.1500 BC

However, not everyone in history regarded dementia as a natural part of the human condition. For instance, the noted Roman statesman, lawyer, and scholar Marcus Cicero (Huppert, et al., 1994) in about 43 BC noted that while dementia was certainly correlated with old age, not all elderly people suffered from it. He believed those who remained mentally active and curious to learn could stave off dementia.

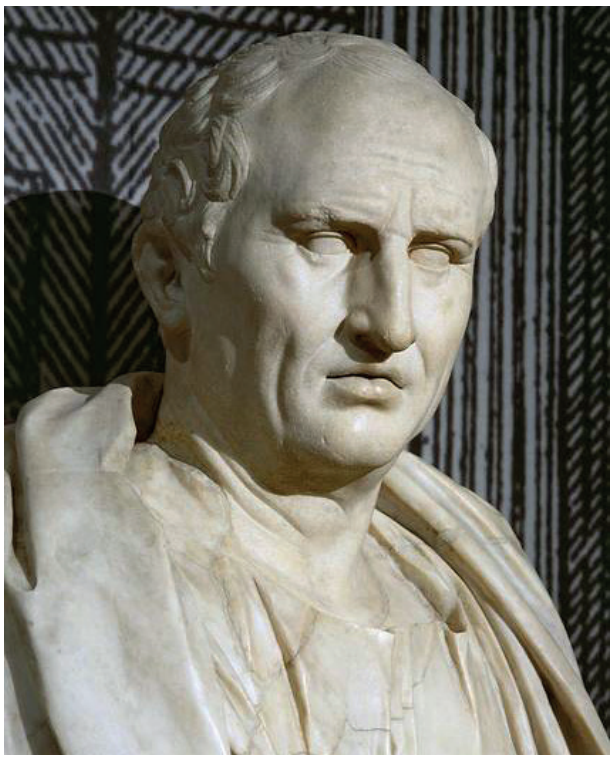
Views only began to change in the 19th century when dementia gradually became a recognised non-psychiatric condition that deserved distinct medical care. However, the prevailing view was of the disease as a vascular condition caused either by narrowing of the arteries supplying blood to the brain or mini-strokes occurring in the brain.

The story then jumps forward to 1901 in Frankfurt, Germany. Dr. Alois Alzheimer was working in the city asylum as a psychiatrist and neurologist. He came across a newly admitted female patient, Auguste Deter. Auguste had started exhibiting clear signs of dementia in the 1890s and, by the end of the decade, increasingly severe agitation symptoms were manifesting. She was admitted to the asylum when her condition escalated to being unmanageable by her family. Dr. Alzheimer took a sustained interest in her unusual case. In particular, he was struck by her combination of severe symptoms and relatively young age, just 51 when admitted. As Auguste struggled to answer Dr. Alzheimer's questions (partially transcribed and translated in Appendix A) that measured her ongoing cognitive decline, she would frequently respond with, "I have lost myself."

Auguste succumbed to her illness in 1906—6 weeks short of her 56th birthday. After her death, Dr. Alzheimer ordered an autopsy be carried out on Auguste's brain. There were three striking findings:

- The brain had suffered considerable shrinkage (or atrophy), in particular the cortex (the thin, outer grey layer that is involved in memory, language, judgment, and thought in general).
- Microscopic examination of brain tissue revealed unusual deposits outside nerve cells (today referred to as "amyloid plaques").
- The microscopic examination also revealed additional unusual deposits inside nerve cells (today often referred to as "tau tangles").

Dr. Alzheimer reasoned such a distinct pathology meant this was a newly discovered disease. However,



Bust of Marcus Tullius Cicero

his findings on the case were largely ignored after publication. There the matter may have rested except for an unusual twist of fate. Dr. Alzheimer's mentor was Emil Kraepelin, an important figure in the history of psychiatry. Kraepelin had been publishing a highly influential and regularly updated manual on psychiatry. He included Dr. Alzheimer's case in the manual as representing a distinct disease and on which Kraepelin bestowed the title "Alzheimer's Disease". This single inclusion effectively regularised AD as a new and distinct disease across the world. However, this was a double-edged development. Kraepelin had divided dementia into two distinct categories: senile dementia (which covers the vast number of cases and is still a term in use today) and pre-senile dementia (for the much rarer cases occurring at younger ages). Kraepelin bracketed AD under the pre-senile dementia category. As a result, AD would languish as a rare medical oddity for the next half century, with the vascular theory of dementia remaining the established medical orthodoxy.

This orthodoxy started to come under attack in the late 1960s. For instance, two UK psychiatrists, Tomlinson and Roth, (Roth, et al., 1967) persuasively argued that the presence of the amyloid plaques observed by Dr. Alzheimer in 1906 were very tightly correlated with dementia progression. Matters came to a head in

Dr. Alois Alzheimer

Dr. Robert Katzman

1976 when the U.S. neurologist Robert Katzman in a landmark journal editorial (Katzman, 1976) forcefully shone the spotlight on AD. His main themes were:

- The still partially prevailing orthodoxy of pre-senile and senile dementia was objectively wrong.
- AD was in fact the dominant form of dementia, not vascular dementia.
- By his calculations, AD was then either the fourth or fifth largest killer of U.S. citizens.
- The medical profession needed to radically transform the priority and resources it gave to researching and treating AD.

At that point, the modern understanding and context of AD came into being.

Today—as an example—according to the UK's classification methodology, AD and dementia are, excluding the temporary pandemic impact, the combined leading cause of death in England and Wales (ONS, 2022). Despite this, there are no effective medical treatments available for this complicated, slow-developing, but inevitably fatal disease. As seen above, humanity has observed and recorded the broad outlines of AD for perhaps as long as fifty centuries.

Views only began to change in the 19th century when dementia gradually became a recognised non-psychiatric condition that deserved distinct medical care.

However, only in the last half century has the true shape of the disease come into sharp focus. There is no other precedent for such a major cause of death to be misunderstood for so long. This paper seeks to analyse and assess the prospects for new medicines to overcome this historical error and provide effective treatment for AD patients.

2

What is Alzheimer's Disease?

AD is the most common form of dementia in the modern world. No precise estimate exists, but it is thought to make up to 60%-80% of all dementia cases. It is characterised by a gradual but persistent erosion of the patient's cognitive abilities—in particular, remembering, thinking and reasoning—and behavioural abilities until it interferes with and, eventually, severely compromises the patient's daily activities of life.

The root biological causes of AD are not currently understood although Section 3 will explore background factors correlated with developing the disease. What is known is four key changes can be observed in patients' brains:

Key Change	Description
Amyloid Plaques	Amyloid is a naturally occurring protein in the brain that is benign. However, in AD, the amyloid protein undergoes a series of intermediate transformations, while in a soluble state, and then begins to clump together, eventually forming plaques. Importantly, these plaques exist outside the brain's neurons. This process is correlated with the progression of the disease, and there is evidence its intermediate corrupted forms are harmful to the brain. This point will be discussed in more detail later in this paper. As noted earlier, these amyloid plaques were present in Dr. Alzheimer's original autopsy and are a hallmark of the disease.
Tau Tangles	Tau is another naturally occurring protein in the brain that is also benign. However, in AD, the tau protein also undergoes alterations and begins to clump together—this time inside the brain's neurons—and form tangles. Again, there is evidence its corrupted form is harmful to the brain. Interestingly, there is some evidence the formation of tau tangles is more closely correlated with cognitive decline than amyloid plaques. As noted earlier, these tau tangles were present in Dr. Alzheimer's original autopsy and are another hallmark of the disease.
Neuronal Death	As the disease progresses, previously healthy neurons begin to cease functioning, start to lose their connections with other neurons, and eventually begin to die. Since neurons are at the heart of the brain's functioning, their loss automatically leads to cognitive decline and other observed disorders.
Brain Atrophy	As neurons die, the brain begins to atrophy in response. This atrophy can be readily seen in brain scans of patients at more advanced stages of the disease. Once again, brain atrophy was present in Dr. Alzheimer's original autopsy.

Interestingly, these key changes always begin in the same parts of the brain for AD patients, specifically, the entorhinal cortex and the hippocampus. These parts of the brain play key roles in memory and learning. This explains why the loss of memory is a hallmark of the disease. Importantly, loss of memory is not a key early symptom of most other forms of dementia, and the fairly common assumption linking loss of memory with dementia in general is not accurate.

AD is typically divided into a number of discrete stages:

AD Stage	Description
Pre-Clinical Stage	As the name suggests, at this stage, patients exhibit no symptoms that they themselves or those around them can observe. However, modern brain scans will detect amyloid plaques forming in these patients' brains; in fact, it was the development of these modern brain scans that revealed the extent of this pre-clinical stage. It is now generally accepted this pre-clinical stage can be present for up to 20 years, or even longer, before the first symptoms become apparent.
Prodromal Stage	During this stage, patients first begin to exhibit symptoms of the disease such as memory lapses or misjudging the amount of time needed for a task. However, a patient can still hold a cognitively demanding job during this stage. In addition, the symptoms observed at this stage can also occur under a number of different medical conditions. Accordingly, doctors—based on reviews of symptoms and their personal judgements—may suspect AD is present but will often stop short of making a formal diagnosis. This stage of the disease is also often referred to as "mild cognitive impairment."
Mild Alzheimer's Stage	This is where symptoms become clearcut to family members and where most AD diagnoses are made. Symptoms include struggling to learn new information, difficulties with problem-solving (e.g., planning a holiday or making financial decisions), changes in personality, struggling to find the right words or express thoughts, and getting lost or misplacing belongings. However, patients can still manage most daily activities without appreciable help or oversight.
Moderate Alzheimer's Stage	This is where symptoms intensify and start to become relatively serious. This includes widespread confusion (e.g., mistaking strangers for family members), substantive memory loss (e.g., their address or their phone number), and potentially significant personality changes. Patients will now need support with many daily activities and require ongoing oversight.
Severe Alzheimer's Stage	The disease is now very advanced. Cognitive ability is now severely degraded, and patients lose the ability to communicate and start to lose control over muscle function (including walking, swallowing, and bladder/bowel control). Patients require near total support for daily activities and are usually bedridden.

For potentially fatal diseases like many heart-related illnesses and cancer, the direct cause of death is usually directly linked to the underlying disease. That is not the case with AD. Although highly degraded by the severe stage, patients' brains do not fully cease to function. The most common direct cause of death with AD is pneumonia. This frequently arises from the loss of control of swallowing leading to food particles lodging in the lungs. This is exacerbated by elderly people's weakened immune systems and their increasing frailty undermining the use of potent antibiotics. Severe-stage patients are also at significantly elevated risk of falls. This issue has considerably complicated calculating the true death rate for AD and has significantly contributed to its underreporting for so long.

Age is by far the single most predictive factor for AD with cases starting to generally occur from the mid-60s onwards. Ironically, the case studied by Dr. Alzheimer would today be referred to as Early-Onset Alzheimer's disease (accounting for about 5%-6% of all Alzheimer's cases). Estimating AD prevalence by age is not

straightforward (e.g., should the prodromal stage count or not?). However, one prominent U.S. study (Rajan, et al., 2019) derived the following estimates of AD yearly diagnosis by age band:

Age Band	Yearly AD Diagnosis Rate
65-74	0.4%
75-84	3.2%
85+	7.6%

Many also believe that sex is another predictor of the disease since AD appears to be notably more prevalent in women. For instance, about two-thirds of current U.S. patients with AD are women, and the lifetime risk of developing AD for women in the United States is nearly double that of men. However, as noted above, disease incidence rates rise steeply from age 65 onwards. Accordingly, when analyses that take account of women's longer lifespans are carried out, the apparent elevated risk for women significantly dissipates.

The duration of the illness from diagnosis to eventual death fluctuates from case to case. Assuming diagnosis at the start of the mild stage, it might take about 8-10 years for an AD-related death to occur at the severe stage (but cases taking up to 20 years are possible). However, a massive complicating factor is the impact of "background" mortality—e.g., a patient diagnosed at age 65 may well die 10 years later from AD, but a patient diagnosed at age 90 would most likely die of other causes before even reaching the severe stage. As context on this issue, the following table presents sample yearly mortality rates from the most recent Irish population mortality table (CSO, 2020):

Age	Male Yearly Mortality Rate	Female Yearly Mortality Rate
65	1.1%	0.7%
75	3.3%	2.1%
85	10.6%	7.8%
95	25.9%	24.1%

This interaction of the lifespan of an AD patient and the patient's age at diagnosis is very important when considering the net impact on longevity of any new AD medicine, so this topic will be explored later in this paper.

One final issue is about one-fifth of AD patients also have an additional form of dementia. This is most typically the aforementioned vascular dementia but can also be a rarer form of dementia called Lewy Body Dementia. Such cases are referred to as "mixed dementia" and tend to become more common from age 75 onwards. This creates an additional hurdle for developing medicines to treat the totality of these patients' dementia.

3

Alzheimer's: Falling Incidence Rates?

Although this paper is focussed on the prospects for new medicines to treat AD, it is relevant to discuss a parallel phenomenon in which the incidence of the disease appears to have undergone a structural decline in recent decades and why this might be so.

This is clearly shown in a recent study (Wolters, et al., 2020) that measured a declining incidence of AD between 1988 and 2015 at 13% per decade. The study was based on aggregating seven cohort studies in the United States and Europe covering just under 50,000 individuals (aged 65+) over this period. The study did note a difference between the sexes: Women showed an 8% rate of decline per decade while men showed a 24% rate of decline per decade. It was beyond the scope of the study to attempt to attribute the potential underlying causes of this sustained structural decline. However, the study did note improvements in educational achievement and in the management of medical issues such as blood pressure, cholesterol, and inflammation. A key limitation of this study is it only focused on two specific parts of the world, so it may not be relevant to other countries with varying levels of economic development or ethnic backgrounds.

Another influential recently updated study (Livingston, et al., 2020) seeks to deal with the attribution of the potential underlying causes of dementia (i.e., not just AD). The updated study identified 12 potentially modifiable risk factors that were mathematically correlated with dementia incidence. The qualifier of "modifiable" risk factors is critical, i.e., it automatically excludes issues such as age and genetic makeup. It noted modifying these 12 risk factors might prevent or delay up to 40% of dementia cases. The updated study also set out potential ways these risk factors modified dementia incidence levels, e.g., it has been demonstrated that hearing loss leads to follow-on atrophy and shrinkage in the same parts of the brain where AD first starts to manifest.

The table below sets out the potential modifiers and the updated study's estimates of the associated increase in the relative risk of dementia:

Modifiable Risk Factor	Estimate of Increased Relative Risk of Dementia
Hearing Loss	90%
Depression	90%
Traumatic Brain Injury	80%
Education	60%
Smoking	60%
High Blood Pressure	60%
Obesity	60%
Social Isolation	60%
Diabetes	50%
Physical Inactivity	40%
Alcohol Abuse	20%
Air Pollution	10%

Since the majority of AD incidence is concentrated in people in their 80s and 90s, assessing the impact of these risk factors on falling incidence rates in recent decades means taking account of relevant trends from the early part of the 20th century onwards. Over this extended time frame, there have been significant improvements in developed countries across several of

these risk factors. The table below highlights some of these improvements:

Modifiable Risk Factor	Significant Improvements
Hearing Loss	• Development and widespread use of hearing aids to restore hearing ability • Health and safety practices to reduce industrial- and military -induced loss of hearing
Depression	• Development and widespread use of medicines that provide moderate to good treatments for many patients
Education	• Mandatory non-fee paying secondary-level education • Rising levels of subsidised third-level education
Smoking	• Significant and sustained reductions in smoking levels • Health and safety practices to minimise passive smoking
High Blood Pressure	• Development and widespread use of medicines that provide effective treatments for most patients
Diabetes	• Development and growing use of a series of effective medicines that increasingly allow patients to effectively control their condition
Air Pollution	• Legislation that significantly reduced air pollution in urban areas (e.g., banning coal fires) • Mandating new technologies to mitigate remaining sources of air pollution

The sheer breadth of these improvements does provide plausible—but not categoric—rationales for the observed declines in dementia incidence rates in recent decades.

A key question then arises as to whether such observed declines in incidence rates will continue into future decades. It could be argued there are reasonable grounds for optimism here. As stated above, the concentration of AD cases for people in their 80s and 90s means improvements that have occurred several decades ago have yet to fully manifest themselves in incidence rates. As an example, consider the risk factor of education in the specific context of the Republic of Ireland:

- Non-fee paying secondary school education was mandated in the Republic of Ireland beginning in 1967. Before that, only 36% of children aged 16 were in school. Less than a decade later, participation in secondary school levels had doubled. The people in the cohort who just missed out on this key policy change are currently about 70 years old. Therefore, it will be more than two decades from now before this 1967 policy change is fully reflected in Irish AD incidence rates.
- The Republic of Ireland began a sustained campaign in the 1970s to expand third-level education. As examples, what eventually would become the University of Limerick accepted its first students in 1972 and what would become Dublin City University accepted its first students in 1980. Analyses of the 2016 Census reveal the impact of this multi-decade strategy: Less than 20% of people then aged 70 and older had completed some form of third-level education but roughly 60% of people then aged 25-40 had the same achievement. As a result, it will plausibly take more than another half a century from now before this multi-generational trend is fully reflected in Irish AD incidence rates.

However, while the above discussion on potential falling incidence rates is heartening, for most developed countries with aging populations, all projections still show a material rise in the absolute number of AD cases over the coming decades. The rest of this paper concerns itself with the quest to develop effective medicines to treat this projected rising number of AD patients.

4

Approved Alzheimer's Disease Medicines

Several medicines have been approved for temporarily treating some of the main symptoms of AD. It is worth examining their development in some detail to understand both their benefit and the inherent difficulties involved in developing successful medicines for this complicated disease.

After the true importance of AD became apparent in the 1970s, scientific effort into finding effective treatments began in earnest. However, the underlying cause of the disease was not understood. The initial leading theory was the so-called "cholinergic hypothesis." This theory was based on the then known fact that acetylcholine is a key chemical messenger, or neurotransmitter, in the brain, and its functions were clearly understood by scientists. Its presence is essential for such cognitive functions as learning, memory, and attention. Scientists also knew that acetlycholine was produced through the activity of an enzyme, choline acetyltransferase (ChAT). Critically, ChAT is produced in the brain's neurons. As AD progresses, it gradually destroys more and more neurons. Scientists understood this in turn lowered the levels of ChAT in the brain, which ultimately meant less acetylcholine was produced. This led directly to AD's signature symptom of a gradual but sustained decline of cognitive abilities in the areas of learning, memory, and attention. This "cholinergic hypothesis" held that normalising the levels of acetylcholine and/or ChAT was essential to preventing cognitive decline and thus halting AD in its tracks.

Scientists were also acting in the wake of a recent major breakthrough in the treatment of Parkinson's disease. An increasing deficit of the neurotransmitter dopamine is chiefly responsible for the signature movement and coordination symptoms that are a hallmark of Parkinson's disease. Beginning with its worldwide approval in 1975, the medicine Sinemet indirectly supplies the brain with significant levels of dopamine. This medication transformed the management of the movement and coordination symptoms of Parkinson's disease. Scientists were hopeful a similar strategy could be applied to AD.

However, scientists came up against a proverbial brick wall. Despite many efforts, it proved impossible to find an effective method to transport acetlycholine or ChAT across what is called the blood-brain barrier. As explanation, the brain is encased in an almost unique semi-permeable cell barrier that protects it against infection. A side effect of this "blood-brain barrier" is that most medicines have difficulty penetrating it to access the brain. To appreciate the practical difficulties this causes, consider the only other human organ to have a similar cell barrier, the eye (which is an evolutionary outgrowth of the brain). Anyone who has had pain or infection in the eye will appreciate treatment generally requires the use of eye drops because standard pain relief or antibiotic swallowable tablets will not have any effect. There is no equivalent practical bypass method to administer medicines to the brain.

In 1983, the Japanese pharmaceutical company Eisai began work on a trial medicine that would later be named donepezil. The Eisai scientists had focussed on a different brain enzyme, acetylcholinesterase, whose function is to break down acetylcholine and thus keep its concentration in the brain at an appropriate equilibrium. The scientists' goal was to develop a medicine that would inhibit acetylcholinesterase. They theorised that in AD patients, this would have the net impact of restoring acetylcholine to a more normal concentration level. They also needed the medicine to be able to pass through the blood-brain barrier and not

cause significant side effects to the brain's functioning. This was a challenging set of criteria, but the Japanese scientists succeeded when they synthesised donepezil.

Thirteen years later in 1996—an example of the long development cycle for experimental medicines—donepezil would be approved in the United States under the brand name Aricept. Aricept became a clear commercial success, and in its last year of patent-protected sales before generics entered the market, garnered worldwide sales of $5.4 billion (stated in December 2022 dollars).

However, it was observed that although patients did show a clear initial cognitive gain, this progress gradually faded over time (generally lasting between 5 and 18 months, depending on the individual patient). The problem is Aricept does not affect or slow down the disease's progression. Over time, more and more neurons are destroyed, so less and less acetylcholine is created. Even if acetylcholinesterase were completely inhibited by Aricept, over time acetylcholine levels inevitably fade away again and cognitive decline resumes. It had been hoped this temporary boost of acetylcholine and associated cognitive function would lead to at least some longevity benefit, but, very disappointedly, this has never been demonstrated in placebo-controlled clinical trials. In turn, this meant that although the cholinergic hypothesis was useful in developing a medicine that temporarily alleviated cognitive symptoms, it was ultimately an incorrect explanation for the disease's underlying root cause(s).

Two other medicines, Exelon and Razadyne, using the same approach as Aricept were approved to treat AD cognitive symptoms. However, Aricept was the clear market leader in this medicine category as its efficacy was perceived to be somewhat superior.

One other medicine, memantine (brand name Namenda), was approved to treat AD cognitive symptoms using another approach. Some scientists had noted another brain neurotransmitter, glutamate, is significantly elevated in AD patients, and this was known to cause harm to the brain. Memantine was designed to dampen particular brain receptors (NMDA) with which glutamate interacts and thus have the effect of cancelling out the excessive glutamate levels. The medicine was originally developed and launched in Germany in 1989 by the pharma company Merz and was then launched much later in the United States in 2003. Memantine was also a clear commercial success with worldwide peak sales of $2.6 billion (in December 2022 dollars) in 2012. However, similar to Aricept, memantine's effects are not permanent, and cognitive decline gradually reasserts itself. Memantine was not demonstrated to improve longevity in clinical trials, so once again, the theory behind memantine's development was ultimately demonstrated to be an incorrect explanation for the disease's underlying root cause(s).

5

Recent Key Alzheimer's Disease Trials

Clinical trials, designed to prove medicines are both effective and safe, are divided into three classifications referred to as Phases I, II, and III. Phase III are the final clinical trials carried out in the developmental process. They are the largest trials and are pivotal in demonstrating a specific dose of the medicine, taken according to a particular schedule, will pass specific statistical endpoints (prescribed by regulators) designed to conclusively demonstrate the medicine's effectiveness and safety. These trials are also expensive; in the case of AD Phase III trials, each one will likely cost hundreds of millions of dollars. The following table shows my own compilation of Phase III trials for potential AD-modifying medicines run by pharmaceutical companies that have reported their outcomes since 2010:

Medicine Name	Alzheimer's Hypothesis	Medicine Mechanism	Year Trial Launched	Year of Trial Results	Number of Trials	Alzheimer's Stage(s)
Dimebon	Unclear	H1	2008	2010	5	Mild, Moderate, & Severe
Semagacestat	Amyloid	Gamma Secratase	2008	2011	2	Mild & Moderate
Solanezumab	Amyloid	Amyloid	2009	2012	2	Mild & Moderate
Bapineuzumab	Amyloid	Amyloid	2007	2012	4	Mild & Moderate
HMTM	Tau	Tau	2013	2016	2	Mild & Moderate
Solanezumab	Amyloid	Amyloid	2013	2017	1	Mild
Verubecestat	Amyloid	BACE	2013	2018	2	Prodromal, Mild, & Moderate
Azeliragon	Amyloid & Inflammation	RAGE	2015	2018	1	Mild
Albutein 20%	Amyloid & Inflammation	Albumin	2012	2018	1	Mild & Moderate
Atabecestat	Amyloid	BACE	2015	2018	1	Prodromal
Lanabecestat	Amyloid	BACE	2014	2018	2	Prodromal & Mild

Table continues overleaf

Medicine Name	Alzheimer's Hypothesis	Medicine Mechanism	Year Trial Launched	Year of Trial Results	Number of Trials	Alzheimer's Stage(s)
Crenezumab	Amyloid	Amyloid	2016	2019	2	Prodromal & Mild
CNP520	Amyloid	BACE	2017	2019	1	Prodromal
Elenbecestat	Amyloid	BACE	2016	2019	2	Prodromal & Mild
Aduhelm	Amyloid (Soluble)	Amyloid (Soluble)	2015	2019	2	Prodromal & Mild
Troriluzole	Glutamate	Glutamate	2018	2021	1	Mild & Moderate
ALZT-OP1	Amyloid & Inflammation	Amyloid & Inflammation	2015	2021	1	Prodromal & Mild
CNP520 & CAD106	Amyloid	BACE & Amyloid	2015	2021	1	Prodromal
COR388	Periodontitis	Gingipains	2019	2021	1	Mild & Moderate
HMTM	Tau	Tau	2018	2022	1	Prodromal & Mild
Gantenerumab	Amyloid (Soluble)	Amyloid (Soluble)	2017	2022	2	Prodromal & Mild
Anavex 2-73	Neuroprotective	Sigma-1	2018	2022	1	Prodromal & Mild

The "Alzheimer's Hypothesis" column in this table refers to the assumed hypothesis for the underlying root cause of AD that the experimental medicine in question is designed to treat. The amyloid hypothesis has clearly been the most popularly tested hypothesis since 2010. The amyloid hypothesis holds that the amyloid plaques discussed in previous sections are the root cause of AD. Hence, a medicine that could remove or otherwise neutralise these amyloid plaques in patients' brains should hold the key to treating the disease. The amyloid (soluble) hypothesis is, as the name suggests, a modified form of the original amyloid hypothesis and instead argues it is not the final amyloid plaques that are the problem; instead, it is the intermediate corrupted forms (soluble in nature) of the original amyloid protein that are the root cause of the disease.

The "Medicine Mechanism" column refers to the tactical biological approach the experimental medicine uses in the context of the chosen Alzheimer's hypothesis. As illustrated, several distinct medicine mechanisms have been used in relation to the amyloid hypothesis.

This table highlights several other important points:

- All 38 of the Phase III trials officially failed. The complicated story of the two Aduhelm trials is discussed later in this section.
- Of the 20 medicines tested, 13 were expected to work based on the assumption the amyloid hypothesis was correct. Aduhelm and Gantenerumab were somewhat different as they operated using the modified amyloid (soluble) hypothesis. It is unheard of in other disease areas for a particular disease hypothesis to be tested repeatedly in key trials and repeatedly fail in those trials, yet the hypothesis remained credible for many years.
- There has been a trend for trials to gradually focus on earlier disease stages. As an example, only the Dimebon trial that reported in 2010 catered to the severe stage. Also, from 2018 onwards, the early prodromal stage starts to make a regular appearance. The example of HMTM is instructive: Its first trial failed in 2016 and focussed on the mild and moderate stages. Post hoc statistical analyses showed positive trends in some data subsets, and this encouraged another Phase III trial to be run. However, this time around, the focus moved to the earlier prodromal and mild stages.
- The table focuses only on trials run by commercial pharmaceutical companies. Some other AD trials are operated by universities, public sector organisations, and charities. However, the track record of clinical trials, run by such non-profit organisations, in finding successful new medicines is poor. It should be noted that non-profit clinical trials do have some success in expanding the uses of existing medicines that have become generic, e.g., Oxford University's trial that rapidly demonstrated the generic steroid dexamethasone was effective for hospitalised Covid-19 patients was a notable recent example.

The amyloid (soluble) hypothesis is, as the name suggests, a modified form of the original amyloid hypothesis and instead argues it is not the final amyloid plaques that are the problem

Aduhelm

Aduhelm is a novel medicine for AD that relies on the modified amyloid (soluble) hypothesis, and two parallel Phase III trials were started in 2015 to prove its efficacy and safety. The trials' statistical design had built in a "futility" test. This was an intermediate check on the trial patients to see whether the medicine was having some beneficial impact; if not, both trials would be stopped. The purpose was two-fold: to save the pharmaceutical companies substantial money from continuing to run expensive clinical trials that had very little chance of success and to stop AD patients taking an experimental medicine that was unlikely to benefit them but did have side effects. In March 2019, the futility test result was announced: Combined available interim data up to 26 December 2018 from both trials had failed to show a positive efficacy trend, and both trials were to be halted. The pharmaceutical companies funding the trials, Biogen and Eisai, did say they would gather more data from the trials and present a complete picture at a later point.

> When scientists analysed the full clinical trial data, it turned out one of the two trials actually was successful in demonstrating efficacy at the higher of two tested drug dose levels.

However, in October 2019, came a stunning reversal: When scientists analysed the full clinical trial data, it turned out one of the two trials actually was successful in demonstrating efficacy at the higher of two tested drug dose levels. It was also announced the U.S. regulator had been made aware of these new results and welcomed an application for Aduhelm to be approved at the higher dose level. The following table sets out summary efficacy results for both trials:

Trial	Enrolled Patients	Lower Drug Dose (vs. Placebo)	Lower Drug Dose *P* Value	Higher Drug Dose (vs. Placebo)	Higher Drug Dose *P* Value
1st	1,647	12% Benefit	22.5%	-2% Benefit	83.3%
2nd	1,678	15% Benefit	9.0%	22% Benefit	1.2%

"*P Value*" refers to the probability the difference in benefit between the patients taking the active medicine versus those taking the placebo is due to chance. The global regulatory standard is for the *p* value to be less than 5% for the trial medicine to be deemed superior to placebo.

The above table highlights the 22% relative cognitive benefit observed in the second trial for the higher drug dose (assessed after 78 weeks of taking the medicine and using a cognitive testing methodology called CDR-SB) versus the placebo had a *p* value of only 1.2%, an impressive outcome. However, that is where the good news stopped. The first trial showed the higher drug dose left patients relatively 2% worse off from a cognitive benefit perspective. Neither trial showed the lower drug dose met the regulatory standard.

This development caused consternation amongst doctors, academics, health insurers, and pharmaceutical industry observers. Some of the concerns were:

- Declaring a clinical trial to be futile is, from a statistical perspective, an irreversible action. The 1.2% *p* value discussed above can only be regarded as a post hoc calculation, which does not meet the regulatory standard for approval. To put it another way, you cannot have your cake and eat it too.
- From a regulatory perspective, potential new medicines like Aduhelm require two separate successful trials to meet the 5% *p* value efficacy threshold. In the first trial, patients were apparently marginally worse off from taking the higher drug dose.
- Over half of the patients taking the higher drug dose suffered from a serious side effect called ARIA (explained later in Section 9). Letting patients take a new medicine with weak evidence for efficacy but with a prevalent serious side effect seemed a questionable risk/benefit decision.
- Because so many trials had been run testing variations of the amyloid hypothesis, it was only a matter of time before a rogue "false positive" trial emerged that met the 5% *p* value regulatory threshold.

It was argued the first trial had several difficulties during its operation, so these may have obscured the underlying efficacy of the medicine. This argument may indeed have had some merit, but a clinical trial is fundamentally an exercise focussed on outcomes. The general consensus amongst observers was these combined efficacy results were intriguing but a third Phase III trial was required to settle the matter.

Despite all this, the U.S. regulator accepted the application to approve Aduhelm and started its detailed review processes. As is frequently the case for potential new medicines with questionable efficacy and/or safety, the U.S. regulator assembled a pre-existing panel of neurological disease experts to assess the application. Reflecting widespread concerns, the panel voted 8 to 1 against approval (with 2 abstentions). Such a decisive panel rejection nearly always means a U.S. regulatory approval application ends up being rejected. Despite all this, Aduhelm was approved by U.S. regulators on 7 June 2021. Three panel members resigned from their role in protest against the approval, an unprecedented reaction.

Despite being the first medicine approved to treat the underlying disease, Aduhelm was a disastrous commercial flop for multiple reasons:

- Most doctors had weak confidence in the clinical trial efficacy data and were unnerved by the expert panel rejection.
- Doctors were also concerned by the serious ARIA side effect. This was exacerbated by reports of several patients who took the medicine and subsequently died and where ARIA was apparently a contributory factor.
- The price was set in the United States at a very high level of $56,000 per annum. This heavily alienated

insurers and the federal Medicare system, which—again unprecedently in the U.S. context—refused to cover Aduhelm. The Medicare rejection was critical because that programme covers most Americans over age 65—precisely the target age group for AD. The price would later be nearly halved to $28,200 per annum, but the damage had then been done.

Aduhelm sales never exceeded $3 million per quarter in its first year of launch despite initial expectations of peak yearly sales as high as $10 billion. The pharmaceutical company selling Aduhelm in the United States was Biogen. On 3 May 2022, less than a year after its launch, Biogen withdrew Aduhelm from sale in the United States. Factors likely linked to this decision included:

- Biogen's stock price had halved since the launch date as the market priced in the Aduhelm launch failure.
- Biogen implied stopping the failed launch would save them about $500 million a year in costs.
- Biogen's then CEO announced his resignation the same day as the withdrawal announcement.

At the time of writing, no national regulator outside of the United States has approved Aduhelm to treat AD.

This lengthy description of Aduhelm's remarkable U.S. regulatory approval and subsequent complete commercial failure illustrates some very important points:

- Just because a new medicine may treat AD does not mean it will automatically be rapidly taken up by patients.
- Any issue of mediocre efficacy, challenging side effects, or high medicine costs can severely diminish the number of patients who will take a new medicine for AD.
- Despite its approval by U.S. regulators, the totality of the circumstances surrounding Aduhelm means it cannot reasonably be accepted as the first medicine demonstrated to treat the underlying causes of AD.

Aduhelm sales never exceeded $3 million per quarter in its first year of launch despite initial expectations of peak yearly sales as high as $10 billion.

6

Alzheimer's Disease Medicine Development Issues

The dismal failure of so many disease-modifying trials since 2010 highlights that AD is an inherently difficult target for medicine development. To illustrate some of the underlying reasons for this difficulty, this section compares various facets of medicine development issues for AD-modifying medicines to the recent highly successful effort to develop Covid-19 vaccines.

Facet	Disease Understanding
Alzheimer's	As mentioned already, the underlying causes of AD are not yet properly understood. Clearly, this severely compromises picking a suitable medicine candidate to treat the disease.
Covid-19	The novel SARS-Cov-2 coronavirus was very quickly identified as the root cause of the pandemic that first publicly emerged in November 2019.

Facet	Accessing the Disease
Alzheimer's	For any medicine to treat AD, it will very likely need to access and penetrate the human brain. However, as previously discussed in Section 4, the blood-brain barrier represents a highly formidable obstacle to readily administer medicines to that organ.
Covid-19	The SARS-Cov-2 virus is readily accessible by the immune system during its life cycle inside the human body. This makes it a very suitable infectious disease for vaccine development. Not all viruses are like this; in particular, the HIV virus can lie dormant for decades inside immune system T-cells, thus frustrating the ability of a vaccine-trained immune system to eradicate it.

Facet	Representative Animal Model
Alzheimer's	No animal has been found that also suffers from AD (or something resembling it). Genetically modified mice have been created that mimic some of the features of AD, but, in practice, these mice have proven a poor predictive model for the disease in human beings. This lack of a representative animal disease model creates two major problems: (1) It eliminates a practical way to reverse-engineer the underlying causes of the disease; and (2) it removes a quick, accurate, and economical way to test whether a potential new medicine is effective and safe.
Covid-19	Many different animals can be infected by SARS-Cov-2. This allowed scientists to quickly and accurately understand how the virus infects a living creature and how the infection process thereafter proceeds. This also allowed scientists to see whether vaccine candidates could effectively stimulate and train animals' immune systems. As an example, Pfizer and BioNTech demonstrated their vaccine candidate offered safe protection to infected rhesus macaques, and this result accelerated its green-lighting for human clinical trials.

Facet	Viable Tissue Sample
Alzheimer's	For obvious reasons, one cannot extract a portion of a living AD patient's brain. Like animal models, a lack of access to living tissue samples creates real problems: (1) It eliminates a practical way to reverse-engineer the underlying causes of the disease; and (2) it removes a quick, accurate, and economical way to test whether a potential new medicine is effective and safe.
Covid-19	It is practical and safe to remove usable samples of many tissue types from living Covid-19 patients, including blood, saliva, mucus, and lung fluid. Indeed, if you have ever completed a Covid-19 antigen test, you have done so through the removal of a usable sample of your nasal mucus tissue.

Facet	Duration of Clinical Trials
Alzheimer's	It requires substantial periods of elapsed time to monitor patients' cognitive ability and observe whether candidate medicines are meaningfully slowing the rate of cognitive decline. In practice, most AD clinical trials follow patients for 18 months while they take the candidate medicine. This adds considerable financial cost and required time for such clinical trials. More broadly, the cumulative impact of such lengthy clinical trials means it has taken over 2 decades to discredit the original amyloid hypothesis.
Covid-19	Covid-19 vaccine trials are run until a statistically viable number of trial participants are cumulatively infected. During a global pandemic, this does not take long. It took Pfizer just 4 months to enrol over 43,000 vaccine trial patients, observe 170 confirmed cases of Covid-19, cleanse the raw trial data from 150 global clinical sites, and carefully perform the required statistical analyses.

Facet	Recruiting Patients
Alzheimer's	Recruiting large numbers of AD patients for clinical trials is surprisingly difficult. Firstly, they can only be from the stage(s) of the disease under investigation. Secondly, clinical trials prudently only enrol patients up to ages 85-90, so this excludes many AD patients. Thirdly, clinical trials also prudently exclude patients with significant co-morbidities, again excluding many AD patients. Fourthly, only a small number of clinical trial sites in the world have the infrastructure, expertise, and experience to correctly identify, enrol and accurately monitor the progress of AD patients.
Covid-19	The eligibility of Covid-19 vaccine trial participants is very broad, essentially any reasonably healthy adult up to ages 80-85. In addition, most clinical trial sites in the world can cope with the moderate requirements of running a vaccine trial.

7

Advances in Alzheimer's Disease Research

While the list of failed AD trials since 2010 is long and dispiriting, it is important to recognise there have been some important advances in the search for an effective medicine over this time.

Improved Diagnosis (2012 onwards)

AD diagnoses were traditionally performed using questionnaires and similar tests probing areas such as memory, problem solving, and language use. However, these various tests could be significantly distorted if the patient were suffering from a separate psychiatric condition. Besides the direct problems caused by such misdiagnoses, these tests also had significant knock-on problems for AD clinical trials, i.e., a significant number of diagnosed patients being recruited to clinical trials did not in fact have AD. As an example of this issue, Eli Lilly executives estimated around 25% of enrolled patients in their two Phase III clinical trials of Solanezumab (that reported failed results in 2012) did not in fact have the disease.

Aware of this issue, Eli Lilly also in 2012 gained approval for the injected diagnostic agent Amyvid. Injected Amyvid accurately highlights the hallmark amyloid plaque when a PET brain scan of an AD patient is undertaken. In practice, this substantially mitigated the issue of misdiagnosed AD patients being enrolled into AD trials. Two further amyloid plaque injectable diagnostic agents, Vizamyl and Neuraceq, gained approval in 2013 and 2014, respectively.

Finally, in 2020, the diagnostic imaging agent Tauvid was approved. Unlike the other injected agents, Tauvid accurately highlights the hallmark tau tangles when a PET brain scan of an AD patient is undertaken.

Trial Success Bar Lowered (2018 onwards)

Regulators have traditionally required potential disease-modifying AD medicines to pass dual statistical tests in their clinical trials, i.e., such medicines were required to statistically demonstrate efficacy in both cognitive ability and functional ability (e.g., activities of daily living). However, in 2018, the U.S. regulator relaxed this standard for the earliest pre-clinical and prodromal stages. From that point on, clinical trials for these two disease stages were simply required to demonstrate efficacy on cognitive ability alone. The regulator also signalled some more flexibility in how trials for later stages of the disease could be designed. Since the United States is the world's dominant commercial market for patented medicines, the U.S. regulator's revised views on AD clinical trial design implicitly rewrote the standard for the rest of the world.

It is perhaps noteworthy that AD-modifying Phase III trials started after this regulatory change in 2018 have begun to include patients in the pre-clinical stage of the disease.

Original "Amyloid Hypothesis" Discredited (2015 onwards)

The failure of the Bapineuzumab medicine Phase III trial in 2012 was a heavy blow to the original amyloid hypothesis. It had been co-financed by industry leaders Pfizer and Johnson & Johnson. In addition, Bapineuzumab had originally been developed by the Irish pharmaceutical company Elan, and their neurological disease research scientists were well

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the modified amyloid (soluble) hypothesis that focuses on an intermediate soluble state of amyloid has become the most promising avenue of research.

regarded in the industry. Its clear failure raised real doubts as to whether the original amyloid hypothesis could be correct.

Against that backdrop, the failure of the similar Solanezumab potential medicine in two earlier trials in 2012 was much more ambiguous. Although the trials collectively failed, post hoc statistical analyses that showed apparently convincing efficacy in the earlier mild stage of the disease looked promising. Eli Lilly's decision to fund a third clinical trial focussing only on mild stage patients and utilising amyloid plaque imaging agents to ensure only genuine AD patients were admitted temporarily bolstered confidence in the hypothesis. However, the resulting trial outcome was a clear failure when announced in 2015. At that point, it was generally accepted the original amyloid hypothesis was incorrect.

Since then, as mentioned already, the modified amyloid (soluble) hypothesis that focuses on an intermediate soluble state of amyloid has become the most promising avenue of research. As discussed later in Section 9, it seems there is now established validity to this hypothesis even though it is still far from a complete explanation for how the disease occurs. In addition, the weakening hold of the original amyloid hypothesis has created the space for separate hypotheses (particularly regarding inflammation) to be tested in major clinical trials.

Blood Diagnosis (2023 onwards)

This section has already highlighted the advancements made in AD diagnosis in recent years. However, these advances have multiple limitations: They require very expensive testing equipment, the imaging agents themselves are not inexpensive, the tests are invasive to the patients, and they require skilled medical personnel to operate and interpret the tests.

The Swiss pharmaceutical company Roche is also a leading supplier of laboratory testing equipment. In December 2022, Roche received U.S. regulatory approval for a panel of AD diagnostic tests that require only a blood draw from the patient. Two rounds of testing are required, but the final results appear to have a high level of credibility: Claimed "sensitivity" is greater than 90% (i.e., the probability of a positive test result, assuming the patient truly does have AD) and claimed "specificity" is also greater than 90% (i.e., the probability of a negative test result, assuming the patient truly does not have AD).

Diagnosis by blood sample is potentially a significant step forward in terms of reducing cost, minimising patient invasiveness, and deskilling the test operation. Such methods should also make AD diagnosis a more economically viable prospect for middle-income countries, many of which also have aging populations.

However, at the time of writing, it remains to be seen what the commercial take-up level of these new blood tests will be and whether their claimed sensitivity and specificity outcomes stand up in real-world use.

8

Dementias Can Be Successfully Treated

Finding an effective medicine for a progressive dementia disease like AD is a highly difficult undertaking. However, the lack of success here to date is not grounds for despair. The purpose of this section is to discuss a dementia disease where highly successful medicines have been developed, specifically syphilis.

Syphilis was first recorded in Europe in 1494-1495. It is generally thought, but not categorically proven, to be an uncommon example of a communicable disease that originated in the Americas before being introduced into the rest of the world. It is mainly transmitted by sexual activity although maternal transmission is also possible. Initial acute symptoms are very wide ranging (including rashes, lesions, fever, sore throat, headache, and weight loss) and typically last for several weeks. The disease will then often go into apparent remission for up to 15 years. At that stage, 15%-40% of cases will advance to a more dangerous phase, which manifests in three ways: widespread growth of non-cancerous but often disfiguring tumours, neurosyphilis, and cardiac issues. It is neurosyphilis that is relevant to this section. This is where the disease advances into the central nervous system and can result in dementia, psychosis, depression, and difficulties walking. Allied to other symptoms, this leads to significantly elevated mortality.

Due to its links with sexual activity, syphilis was a taboo subject in many societies, so the incidence of the disease is not clear. However, it was certainly common, e.g., a study (Szreter & Siena, 2021) estimated more than one fifth of people aged 15-34 in late 18th century London were being treated for syphilis.

As regards initial medical treatment of syphilis, mercury was a pre-existing treatment in Europe for various skin diseases. By the early 16th century, mercury ointment applied to syphilis sores and lesions was materially alleviating patients' symptoms. However, doctors noted that higher and higher doses of mercury were gradually required to achieve the same results, but rising doses of mercury, a highly toxic metal, inevitably led to increasingly severe side effects that patients eventually were unable to endure. As a result, capping the mercury dosing level meant the disease reasserted itself and progressed to its more advanced stages.

Four centuries later in 1905, two German scientists, Fritz Schaudinn and Erich Hoffmann, made a critical breakthrough; they identified infection by the bacteria Treponema pallidum as the root cause of syphilis. The reason for mercury's moderate success as a treatment then became clear: Although not an antibiotic, mercury does have strong antimicrobial properties. Four years later in 1909, a combined team of German and Japanese scientists made a further critical breakthrough. They theorised that arsenic-based compounds could prove more effective than mercury. In what was likely the first example of modern medicine development workflow, they systematically experimented on multiple variations of arsenic compounds until they eventually found one with an excellent ability to kill the Treponema pallidum bacteria. This arsenic compound became known as Salvarsan and quickly proved it could cure many patients of the disease, and, although side effects were significant, it was much more tolerable than mercury. Rapidly launched in 1910, it quickly became the world's best-selling medicine of its time.

Ivor O'Shea

However, Salvarsan was not a complete treatment because it was difficult to administer, it had significant side effects, and, critically for our interest, it could not treat advanced cases where neurosyphilis had emerged. The story then progresses into the early 1940s, when UK scientists successfully isolated the world's first antibiotic, penicillin and began to establish its clinical possibilities. The U.S. and UK governments then funded the emergency mass production of the complicated penicillin molecule for use in World War II. As an aside, two of the companies contracted for leading roles in this emergency production were antecedents of two modern pharmaceutical companies, Pfizer and AstraZeneca.

In 1943, a clinical trial demonstrated penicillin could reliably cure syphilis, with mild side effects, and was also effective, critically, for advanced forms of the disease such as neurosyphilis. Thanks to the wartime boost to its production, penicillin became commonly available in the mid- to late-1940s. At that point, syphilis was effectively removed as one of the most common forms of dementia and thus solidifying AD's position as the dominant form of the condition.

Finally, it is worth noting that is not quite the end of the story. In the decades since the 1940s, modified forms of penicillin have been developed that are easier to administer. Alternative antibiotics and chemotherapies have also been discovered to effectively treat the minority of patients who are allergic to penicillin.

There are a number of general points in relation to dementia diseases that arise from this summarised history of medicine development for syphilis:

- Firstly, despite dementia diseases being severe, long-term, and progressive illnesses, it is possible to develop highly effective medicines.
- Once the root cause of the dementia disease in question is fully understood, the task of developing an effective medicine becomes exponentially more manageable.
- The example of mercury treatment highlights it is still possible to develop a medicine without an understanding of the illness's root cause(s), but this runs the real risk of only offering moderate and, in the long term, inadequate benefit to patients.
- The example of Salvarsan highlights the first effective medicine developed for a dementia disease may indeed represent a major step forward, but it may not provide comprehensive treatment for all patient sub-groups.
- It may be several decades before the ultimate medicine is developed that essentially represents a clear-cut cure for the disease.

Four centuries later in 1905, two German scientists, Fritz Schaudinn and Erich Hoffmann, made a critical breakthrough; they identified infection by the bacteria Treponema pallidum as the root cause of syphilis.

9 First Breakthrough

Leqembi is an experimental AD medicine similar to the previously discussed Aduhelm, in that it was based on the modified amyloid (soluble) hypothesis. Its history is interesting. It arose from research into a rare mutation that afflicted a single multi-generational family in Sweden and left them very vulnerable to Early-Onset Alzheimer's disease. Testing family members with this rare form of AD revealed a very unexpected finding: Signs of the hallmark amyloid plaques were not found; instead, the intermediate corrupted (and soluble) forms of the original amyloid protein were present in unusually high concentrations. The research, carried out in the 1990s and early 2000s, suggested the original (and then very dominant) amyloid hypothesis might be incorrect; instead, the research's findings seemed to support the previously described modified amyloid (soluble) hypothesis.

A Swedish pharmaceutical company was then founded to carry forward this initial research. They developed the medicine that is now called Leqembi. To finance the drug's development, the company partnered with what ended up being the same two pharmaceutical companies behind Aduhelm, Eisai from Japan and Biogen from the United States. An exploratory clinical trial (referred to as a Phase IIb trial) tested several dosing levels and two time-points of 12 and 18 months for AD patients at the prodromal and mild stages. For the highest drug dose tested and for the longer 18-month timepoint, the trial showed Leqembi was effective in slowing decline on two standard measures of cognitive ability versus patients taking the placebo.

These very promising results needed to be confirmed by a Phase III trial. Importantly, regulators agreed the initial Phase IIb trial could count as one of the two clinical trials required to demonstrate efficacy for Leqembi's commercial approval. Eisai and Biogen decided to run two parallel Phase III clinical trials using the same successful highest dose level from the Phase IIb trial: the first catering to prodromal and mild-stage patients and the other, perhaps more speculatively, to pre-clinical-stage patients (discussed in Section 12).

On 27 September 2022, the results of the first Phase III trial catering to prodromal and mild stage patients were revealed. It was the first unambiguously positive Phase III clinical trial for an experimental medicine to treat the underlying cognitive decline caused by AD. Summary efficacy and safety results on a like-for-like basis for this Phase III trial and the earlier Phase IIb trial are shown below:

Trial	Enrolled Patients	Efficacy (vs. Placebo)	Efficacy *P* Value	ARIA %
Phase III	1,795	27% Benefit	0.005%	29.9%
Phase IIb (Highest Dose)	408	26% Benefit	12.5% (post hoc)	16.7%

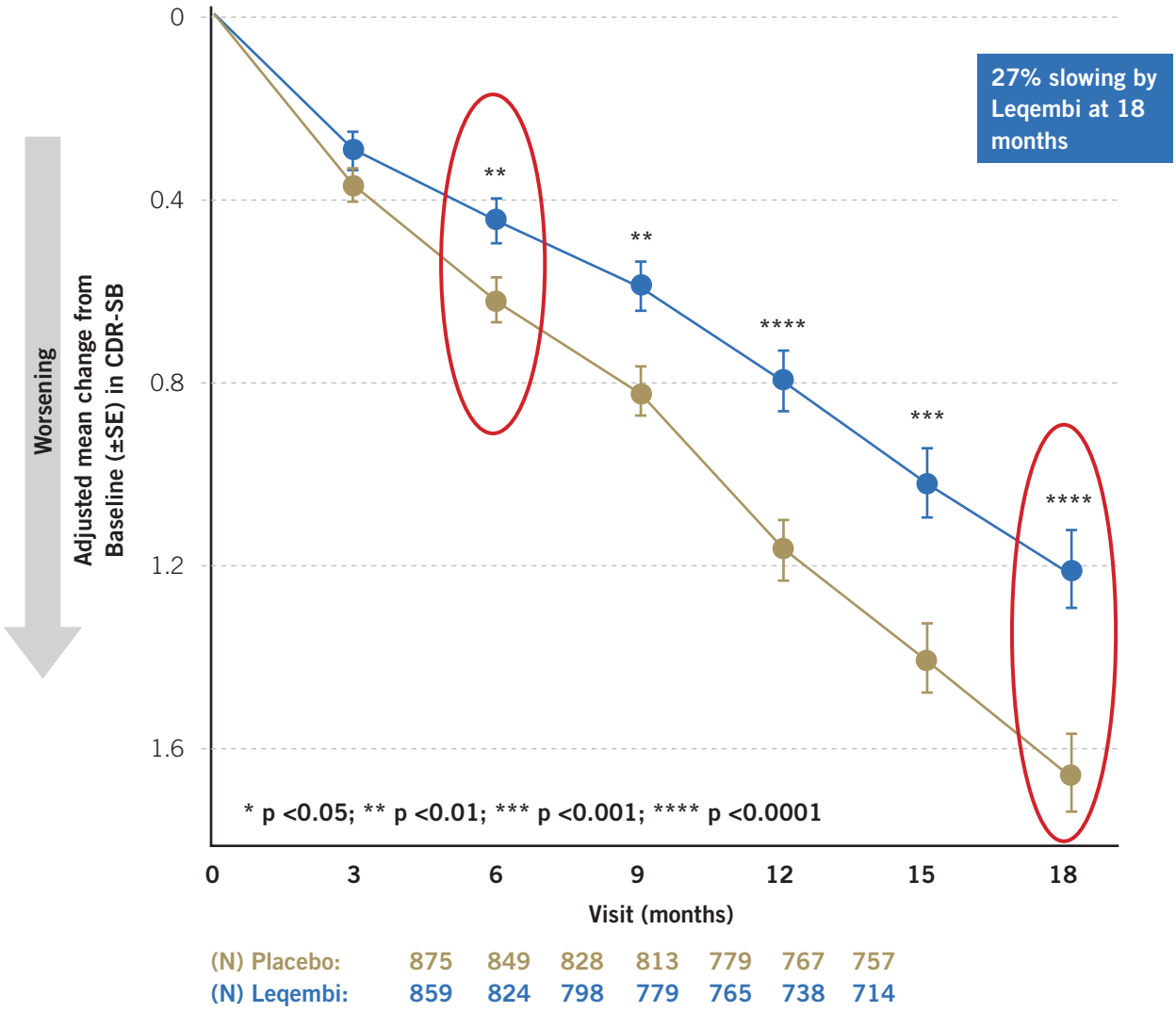
Several important points arise here:

- The very similar efficacy results between the two trials are very comforting. Such consistency of outcome is what one should see in a medicine that is genuinely effective. The sharp contrast with the two deeply discordant Phase III trials for Aduhelm is striking and helps put into context the reservations felt about that medicine.
- The highly significant *p* value of 0.005% in the Phase III trial reflects the large number of enrolled patients and the associated high statistical powering. The

quoted 12.5% *p* value for the smaller Phase IIb trial reflects its much weaker statistical powering. For reference, both efficacy measures are based on a measure of cognitive ability called CDR-SB. The Phase IIb trial also applied two other measures of cognitive ability called ADCOMS and ADAS-Cog14. These alternative approaches had nominal *p* values of 3.4% and 1.7%, respectively, both less than the regulatory minimum *p* value of 5.0%.

- The ARIA percentage column refers to the percentage of patients taking Leqembi who had a side effect called ARIA. ARIA is a grouping of symptoms that include brain swelling and brain microhaemorrhages. Importantly, many patients with ARIA show no symptoms whatsoever, and it usually only reveals itself in high resolution MRI scans. However, some patients can show symptoms like headache, confusion, vomiting, nausea, tremor, and walking difficulties. These symptoms can escalate to the stage of requiring hospitalisation and, in very rare situations, can result in eventual death. ARIA appears to be at least partially caused by medicines like Leqembi removing corrupted amyloid from the brain at a biologically accelerated rate (Withington & Turner, 2022). Only 3.5% of patients in the Phase III trial actually had a symptomatic form of ARIA. However, at the time of writing, media reports have linked the deaths of three patients participating in various Leqembi clinical trials to ARIA, but this has not yet been proven in any of these cases.

Adding some more colour to these results, the following graph (extracted from a presentation of the clinical trial results) shows the cognitive performance of patients in the Phase III trial taking Leqembi versus those patients placed on the placebo:



This graph highlights some additional positive outcomes of the Leqembi Phase III trial:

- The steady but gradual divergence over time of the patients on Leqembi versus those on placebo is very encouraging. Proven medicines for most disease areas, including cancer and heart related illnesses, show this same trend of a gradual divergence over time versus the placebo as the cumulative biological impact of ongoing dosing of the medicine gradually builds up. In contrast, rogue "false positive" clinical trials often show a much more erratic pattern between those taking the experimental medicine and the placebo.
- From visual inspection, this pattern of gradual divergence does not appear to be fully mature at the final 18-month measurement period. That opens up the possibility the ultimate benefit of taking Leqembi is in fact more than the observed 27% difference seen in this clinical trial.

Overall, it is fair to say Leqembi represents a triumph for the modified amyloid (soluble) hypothesis for AD.

The U.S. regulator gave a limited commercial approval to Leqembi in January 2023. However, this limited approval solely relates to the evidence provided by the more limited earlier Phase IIb trial. At the same time, the detailed wording of this approval did not indicate U.S. regulators were particularly concerned by the ARIA side effect. U.S. regulators are expected to give a full approval—including the results of the Phase III trial discussed above—in July 2023 (albeit a panel of neurological experts will be convened beforehand to assess the full approval). Leqembi was also filed for approval with EU regulators in January 2023 and could be expected to be approved in Q4 2023 or Q1 2024.

Not All Medicines Are Created Equal

Leqembi is one of three experimental AD medicines that rely on the modified amyloid (soluble) hypothesis with available Phase IIb and Phase III clinical trial results.

It is worth expanding the table shown earlier in this section to include equivalent results from the other two experimental medicines (see below).

This table highlights that, despite all three medicines being based on the same underlying AD hypothesis and having the same precise biological mechanism of action, they gave quite distinct results:

- Leqembi had the highest level of efficacy of the three medicines. For reference, the efficacy of all three medicines was measured using the same CDR-SB cognitive measuring methodology.
- Although the ARIA occurrence rates for Gantenerumab were not fully available at the time of writing, Leqembi looks to have the lowest rate of this potentially very serious side effect. Some caution is needed here as judgement is required in assessing whether a clinical trial patient has reached the threshold for being reported as having a particular side effect, and assessment standards can vary between clinical trials.

This highlights seemingly very minor differences in the chemical and biological design of a particular medicine molecule—involving decisions made over a decade before these Phase III trial results became available—can later create profound impacts on the relative efficacy and safety performance of that medicine. Pharmaceutical medicine development is a difficult business, and, in this case, what could well be literally microscopically small margins have clearly favoured Leqembi.

In addition, unlike Leqembi and Gantenerumab, Aduhelm gave very inconsistent efficacy results across its two trials. The ability of a pharmaceutical company to execute large, multi-year clinical trials skilfully and methodically should not be taken for granted, and, if there are any operational lapses or poor judgements, this can impair the quality of the respective trials' eventual outcomes.

Medicine - Trial	Enrolled Patients	Efficacy (vs. Placebo)	Efficacy *P* Value	ARIA %
Leqembi – Phase III	1,795	27% Benefit	0.005%	29.9%
Leqembi – Phase IIb	408	26% Benefit	12.5% (post hoc)	16.7%
Aduhelm – 1st Phase III	1,647	-2% Benefit	83.3% (post hoc)	41.3%
Aduhelm – 2nd Phase III	1,678	22% Benefit	1.2% (post hoc)	41.3%
Gantenerumab – 1st Phase III	1,016	8% Benefit	9.5%	30%-40%
Gantenerumab – 2nd Phase III	982	6% Benefit	30.0%	30%-40%

10

Potential Impact of the First Breakthrough

Longevity

Modelling the progression of a disease as long-term and complicated as AD is difficult enough. Trying to assess the difference made by a novel medicine like Leqembi where, for example, no real-world longitudinal data exists on its long-term effectiveness is harder again. Fortunately, there has been relevant research done on this topic. As noted earlier, a previous Phase IIb clinical trial of Leqembi produced very similar efficacy results to those of the key Phase III clinical trial. A paper (Abbas, et al., 2022) derived results on projected longevity and health-related benefits of AD patients taking Leqembi. This paper utilised the detailed patient-level data and biometric outcomes from the Phase IIb clinical trial to populate a well-used existing AD simulation model designed to assess the impact of medical interventions on the disease's progression.

The paper showed the projected impact of Leqembi on how long patients would, on average, spend in various stages of AD (assuming they start taking Leqembi at an equivalent stage of disease development as the patients in the Phase IIb clinical trial and they survive to at least the start of the particular disease stage in question). Summary details of this projected impact are shown below:

The paper also projected that patients taking Leqembi would live on average 1.03 years longer than equivalent patients not taking Leqembi. These high-level statistics, although only projected estimates, do highlight some key points:

- For the cohort of AD patients *who do not die from other causes* during their illness, there is an impressive projected c.3.1 extra years (i.e. 2.51 years plus 0.62 years) spent in the relatively high quality-of-life prodromal and mild disease stages.
- The apparent 0.79-year reduction of time spent at the moderate disease stage should not be interpreted as Leqembi accelerating the pace of disease progression during this stage. Indeed, the chosen projection model assumes there is a residual benefit during the moderate stage from taking Leqembi. Instead, this reduction more reflects the cohort taking Leqembi is several years older than the cohort not taking Leqembi by the time they first enter the later moderate disease stage. Accordingly, their level of background mortality is appreciably higher during the moderate disease stage.
- The perhaps unexpectedly low projected 1.03-year longevity gain is relatively disappointing at first sight, particularly versus the discussed c.3.1-year benefit

Description	Time Spent in Prodromal Stage	Time Spent in Mild Stage	Time Spent in Moderate Stage
Patients Taking Leqembi	5.61 years	3.66 years	2.14 years
Patients Not Taking Leqembi	3.10 years	3.04 years	2.93 years
Difference	**+2.51 years**	**+0.62 years**	**-0.79 years**

seen in the prodromal and mild disease stages. The key point is, as previously mentioned, the c.3.1-year benefit excludes AD patients dying during their illness from other causes. Given the typically advanced ages AD is diagnosed at and the subsequent c.8-10 year progression of illness until eventual death, the relative impact of background mortality is quite profound.

However, there are grounds for viewing the projected 1.03-year longevity gain as being somewhat understated in several contexts:

- When considering the impact of Leqembi on longevity in the commercial context of life insurance portfolios or defined-benefit pension plans, the relevant weighted background mortality could well be materially lighter than population-level background mortality.
- Background mortality in the paper was chosen to be a U.S. national mortality table for 2017. U.S. mortality has become markedly heavier than nearly all other developed countries in recent decades. Accordingly, excluding the United States, the use of Leqembi should show a stronger longevity impact in developed countries.
- On a similar theme, the chosen background mortality assumption made no allowance for future mortality improvements. This is relevant in the context of the projection period covering 14 years from when patients first started taking Leqembi.

Take-up

The above analysis on the longevity impact of Leqembi needs to be viewed in the context of how many patients will actually use the medicine in practice. It is a truism in the pharmaceutical industry that getting a high take-up of a new medicine is surprisingly difficult; hence, a defining characteristic of the pharmaceutical industry is employing large sales forces with large marketing budgets to sell newly launched medicines.

To consider the take-up potential of Leqembi, it is instructive to consider the take-up of existing symptomatic AD medicines (e.g., donepezil and memantine). As an example, the NHS in England showed the take-up of existing AD medicines in 2015 for three stages:

AD Stage	England Take-up in 2015
Mild Alzheimer's	54%
Moderate Alzheimer's	72%
Severe Alzheimer's	13%

Only one out of the four then-approved AD medicines was approved for the severe stage, which explains the low take-up there. However, all four medicines were approved for the other two stages, and their take-up provides a useful starting point to consider Leqembi. A number of conflicting issues then need to be taken account of.

The first issue to consider is the prodromal stage is not represented in the England data because none of the four medicines were approved for that disease stage. However, an equivalent take-up for the prodromal stage is likely to be materially lower than that for mild Alzheimer's, mainly, as discussed previously, because AD diagnoses mainly take place at the mild stage while some are only made at the following moderate stage (likely contributing to the higher take-up seen for the moderate stage).

The second issue to consider is Leqembi will have a greater positive impact on patients' well-being than these approved medicines. That should point to a structurally higher take-up than for the four currently approved medicines.

The third issue to consider is there are important counterarguments as to why Leqembi take-up could also be structurally lower than for these four current medicines:

- All 4 of the medicines in question were genericised by 2015. As a rule of thumb, such tablet format generic medicines would likely have a price point of the order of nine-tenths lower than the original patent-protected versions. In contrast, Leqembi has been priced at $26,500 a year in the United States. All national health systems have explicit and implicit methods to control take-up of expensive medicines, e.g., in this case, perhaps requiring a diagnosis of AD to be confirmed by MRI scans (which may have waiting lists to access) with invasive injected diagnostic agents or for treatment to cease if no apparent benefit is seen within, say, 12-18 months.
- None of these four medicines have side effects as serious as ARIA. Already, as previously mentioned in Section 9, media reports have linked the deaths

Overall, perhaps a 35%-50% population-level take-up for Leqembi is an appropriate range to consider in the context of AD patients in the prodromal and mild stages.

of three patients participating in various Leqembi clinical trials to this side effect. The impact of media reporting of exceptionally rare serious side effects associated with the AstraZeneca Covid-19 vaccine are a high profile recent example of what can happen in such situations.

- As noted above, these four medicines are all tablet format medicines, which are easy for patients to take at home. In contrast, Leqembi requires administration by IV infusion every 2 weeks in a medical setting. Such an onerous dosing approach is both expensive and resource-intensive for national health systems as well as off-putting to patients, especially for those living in remote areas or with mobility issues.

Given Leqembi has only received a highly conditional and limited regulatory approval in the United States, there is a considerable degree of judgement and even speculation required to assess the likely eventual take-up of Leqembi by eligible AD patients. Overall, perhaps a 35%-50% population-level take-up for Leqembi is an appropriate range to consider in the context of AD patients in the prodromal and mild stages.

However, in the commercial context of life insurance portfolios or defined-benefit pension plans, the relevant weighted take-up of Leqembi could be appreciably higher. For instance, there is good evidence that higher socioeconomic status is broadly correlated with improved medication adherence rates for patients being treated for chronic illnesses (Kvarnstrom, et al., 2021).

Longevity Impact & Timing

We must also consider when the impact of the introduction of Leqembi will be fully seen in yearly mortality data.

Leqembi is due to receive its full regulatory approval in the United States in July 2023. In Europe and other developed countries, full approval is likely to be in Q1 2024.

As mentioned above, it is surprisingly difficult getting a high take-up of new medicines. It may be thought a breakthrough medicine like Leqembi may buck this industry trend, but it must also be remembered it will be expensive, will come with a serious potential side effect, and will be difficult to administer. Many other genuine breakthrough medicines have experienced difficult and time-consuming launches (never mind the previously discussed failed Aduhelm launch).

More specifically, a pharmaceutical industry rule of thumb is it takes about 6 years of rising sales after launch before new medicines plateau at their "peak sales" level. A study of all medicine launches in the United States for 2000-2002 (Robey & David, 2017) analysed the subsequent sales levels achieved during each of the first 6 years of launch. The following table shows interquartile outcomes for each year of the analysed sample (expressed as a percentage of their ultimate "peak sales" level):

Year After Launch	Lower Quartile	Median	Third Quartile
1	5%	11%	21%
2	20%	31%	41%
3	41%	58%	67%
4	66%	76%	85%
5	85%	89%	96%
6	N/A	100%	N/A

Lastly, we need to consider how long AD patients currently live, i.e., not taking Leqembi and excluding the impact of background mortality. As per Section 2, a reasonable range to cover most AD patients would be a lifespan of 8-10 years from the start of the mild stage (which would roughly be the average point when patients would likely start taking Leqembi), excluding other causes of death during this time.

Accordingly, the following simplified table shows the various illustrative milestones in both the United States and other developed countries when the substantially complete impact of Leqembi's launch on population mortality would be felt:

Milestone	U.S. Illustrative Years	Other Developed Countries Illustrative Years
Leqembi Properly Launched	2023	2024
Leqembi Reaches "Peak Sales"	2029	2030
First Substantive Impact on Population Mortality	2031	2032
Substantially Complete Impact on Population Mortality	2039	2040

When analysed this way—and putting aside all the simplifying assumptions—it can be seen it likely will be during the 2030s when Leqembi's impact on population mortality will gradually be felt.

Healthcare Impact

An additional key finding of the Abbas, et al. paper was that taking Leqembi was projected to reduce AD patients' lifetime risk of being admitted to institutional care from 31% to 25%, a projected 19% relative reduction. Taking Leqembi was also projected to reduce the time spent in institutional care from 1.02 years to 0.89 years, a projected 13% relative reduction. Both these relative reductions arise from the aforementioned Leqembi impact on delaying by several years the need to be admitted to institutional care, which amplifies the effect of background mortality.

The combined impact of these two projected relative reductions would suggest that Leqembi could reduce a treated AD patient's projected lifetime utilisation of institutional care capacity by c.30%. This is a very important potential finding as perhaps 50%-70% of elderly people in institutional care have some form of dementia (Prince, et al., 2014). Moreover, as mentioned above, Leqembi uptake is likely to be positively correlated with socioeconomic status and institutional care utilisation is also positively correlated with socioeconomic status (Lera, et al., 2021).

As a caution on this topic, long-term longitudinal data from real-world Leqembi usage will be needed to confirm these projected benefits for institutional care utilisation levels. However, if these projected benefits are shown to be broadly accurate, it will be an important development to mitigate future strains on institutional care capacity arising from aging populations in many developed countries. Indeed, it may even be possible to argue the impact of Leqembi could be relatively more important in the context of institutional care than any beneficial impact on longevity.

Future Developments on Leqembi

One of the reasons new medicines take approximately 6 years to reach their peak sales level is additional clinical trials are carried out after the initial trial is successful. These additional trials can give doctors, patients, insurers, and national health systems more confidence in the new medicine and thus help push sales up to their eventual peak. In Leqembi's case, there are multiple important additional trials underway:

- All the participants in the key clinical trial that proved Leqembi's efficacy will be rolled into a permanent extension trial where everyone will receive Leqembi (including those on the placebo in the original trial). Effectively, this will become a longitudinal trial that will gradually reveal Leqembi's longer-term impact, including on those in the moderate and severe stages. This should help, over several years, to assess the validity of the hint from the original trial that the efficacy benefit was widening over the course of the 18 months that patients were being followed. If this hint is demonstrated to be valid, that offers the prospect of re-rating upwards Leqembi's long-term underlying efficacy.
- As noted previously, Leqembi is also being tested in a key clinical trial to assess its potential efficacy for the pre-clinical stage. Due to the extended period needed to see if trial patients progress to the prodromal stage, this trial is not expected to produce results until 2027 (as referenced in Section 12).
- Another trial is assessing whether Leqembi can be successfully dosed by subcutaneous injection (as are many vaccines and insulin medicines) instead of the current IV-infusion approach in a medical facility. This would allow either the patients themselves or caregivers to handle the injection in their own home or, if need be, in a nearby primary care practice. That would significantly lower the cost and resourcing requirements for delivering Leqembi and eliminate significant travel and time burdens for patients and their caregivers. It also would be essential should the above-mentioned pre-clinical trial be successful as patients with no symptoms are highly unlikely to agree to subjecting themselves to bi-weekly IV infusions, but they might do so if the medicine required only an insulin-like self-injection.
- Finally, another trial is assessing whether the required dosing frequency could be reduced to monthly or even quarterly after the initial bi-weekly dosing pattern for the initial 18 months of treatment is completed. Again, this would reduce the cost and burden of the current bi-weekly dosing pattern. Moreover, it offers the opportunity to appreciably reduce the side effect burden of taking Leqembi.

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Leqembi: Only an Interim Milestone?

Although the clinical success of Leqembi is highly welcome, it should not be forgotten it represents only a moderate advance in treating AD. Comparing it to the history of developing medicines to treat syphilis, Leqembi equates more to the early development level of mercury rather than Salvarsan (never mind penicillin).

Firstly, based on current evidence, Leqembi only slows down the rate of cognitive decline by just over one quarter. Salvarsan, in contrast, could fully prevent disease progression in syphilis if used relatively early in the infection cycle.

Secondly, as was the case at the time of mercury's use for syphilis, we still do not have a proper understanding of what causes AD. Leqembi's success means the modified amyloid (soluble) hypothesis now appears to have validity regarding the underlying root causes of the disease. However, there are still many basic knowledge gaps:

- There still is no clear biological explanation for why amyloid first begins to become corrupted in the brain.
- We still have no clear answer as to whether treating the other key biological hallmark of the disease—the corrupted tau protein—is relevant in treating the disease. Linked to this, there still is no clear biological explanation for why tau first begins to become corrupted in the brain.
- We have no answer yet as to whether using Leqembi in the earlier pre-clinical stage will lead to improved treatment outcomes over using it at the prodromal and mild stages.
- We do not know whether the roughly one fifth of AD patients who display the "mixed dementia" form will require parallel treatment of their other dementia-related illnesses to substantially reduce their overall rate of cognitive decline.
- Perhaps most seriously, if the amyloid (soluble) hypothesis is indeed pivotal to the biological understanding of AD, then why is a medicine like Leqembi, which we know is highly efficient at removing the soluble form of corrupted amyloid from the brain, only apparently capable of reducing the rate of cognitive decline by just over one quarter?

Thirdly, like mercury, the use of Leqembi comes with serious side effects. This is in contrast with the much milder side effects generally seen with Salvarsan and penicillin.

Accordingly, there is still a burning need for current and future clinical trials testing other potential AD medicines to be successful and further reduce the rate of patients' cognitive decline.

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Current Key Alzheimer's Disease Trials

The following table shows my own compilation of Phase III trials for potential AD-modifying medicines run by pharmaceutical companies that are under way at the time of writing:

Medicine Name	Alzheimer's Hypothesis	Medicine Mechanism	Year Trial Launched	Year of Trial Results	Number of Trials	Alzheimer's Stage
Donanemab	Amyloid (Soluble)	Amyloid (Soluble)	2020	2023	2	Mild
NE3107	Insulin & Inflammation	ERK/NFkB	2021	2023	1	Mild & Moderate
Solanezumab	Amyloid	Amyloid	2014	2023	1	Pre-Clinical
Fosgonimeton	Neuro Regeneration	HGF/MET	2020	2024	1	Mild & Moderate
ALZ-801	Amyloid (Soluble)	Amyloid (Soluble)	2021	2024	1	Mild (APOE4)
Simufilam	Neuroprotective & Inflammation	Filamin A	2021	2024	2	Mild & Moderate
Semaglutide	Insulin & Inflammation	GLP1	2021	2024	2	Mild
AR1001	Neuroprotective & Amyloid	PDE5	2022	2026	1	Mild
Masitinib	Inflammation	Mast Cells	2023	2026	1	Mild & Moderate
Leqembi	Amyloid (Soluble)	Amyloid (Soluble)	2020	2027	1	Pre-Clinical
Donanemab	Amyloid (Soluble)	Amyloid (Soluble)	2021	2028	1	Pre-Clinical

This table highlights several important points in current AD pharmaceutical research:

- Pharmaceutical companies are making heavy bets on the modified amyloid (soluble) hypothesis to develop effective new AD medicines. Given Leqembi's recent success, that approach now looks promising. However, amyloid in its soluble form goes through several molecular transformations, and not every medicine targets the same form of soluble amyloid.
- In light of the serial failures in relation to the original amyloid hypothesis, a separate and distinct hypothesis that focuses on various forms of chronic brain inflammation as an underlying root cause is also attracting some attention.
- The trend towards targeting earlier forms of the disease has continued and intensified. In particular, 3 trials are focussed on the previously unresearched pre-clinical phase in which no symptoms are observed, but the patient is at high risk of developing AD. These trials take more time to run because they are observing patients over multiple years to assess if there is a delay in developing visible AD cognitive decline symptoms. This approach is in contrast to observing patients who have already developed AD, in which case, clinical trials can use the less demanding approach of just assessing their rate of ongoing cognitive decline.

Pharmaceutical industry observers are relatively optimistic on the prospects for Donanemab as it is a very similar medicine to Leqembi. It may even incrementally outperform Leqembi in terms of reducing the rate of cognitive decline, but this remains to be seen.

None of the other medicines on this list are attracting similar levels of excitement or high expectations amongst industry observers. However, the utility of potential medicines under investigation at the pre-clinical stage represents an important wild card.

Pharmaceutical industry observers are relatively optimistic on the prospects for Donanemab as it is a very similar medicine to Leqembi.

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Prospects for Alzheimer's Disease (Agitation Symptoms)

Agitation in AD refers to a cluster of symptoms manifesting as inappropriate behaviours that include agitation, irritability, restlessness, wandering, repetition, aggression, and psychosis. Although such individual behaviours occur in many other mental illnesses, they collectively represent a hallmark symptom of AD. This collection is also referred to as behavioural and psychological symptoms in dementia (BPSD). About one third of AD patients living in the community and up to four fifths of patients living in institutional care facilities show signs of agitation.

The causes of such agitation are not fully understood but likely include a combination of the underlying biological degeneration of the brain and the psychological strain of patients dealing with their illness. Such agitation can be both distressing and demeaning to the dignity of the patients themselves but also is often highly challenging and draining for the patients' caregivers (whether family members or institutional care employees) to manage. In that context, such agitation represents a significant element of the burden, both emotional and financial, that AD places on patients themselves and on broader society.

Developing medicines to treat this agitation is therefore important. However, no such medicines have been approved to date by regulators, although the antipsychotic medicine risperidone is approved in European countries for the specific symptom of aggression. Nevertheless, for many years, other medicines have been used unofficially (so-called "off-label" use) to treat this agitation. In particular, powerful antipsychotic medicines intended to treat schizophrenia are in practice frequently prescribed to treat the agitation. Such medicines may provide a genuine benefit if the patient is experiencing delusions or paranoid beliefs. However, they appear to achieve their main apparent benefit by inducing sedation; that is, they are not so much treating the symptoms as smothering them. Besides the material reduction in quality of life to the patient, there is good evidence (Lenzer, 2005) these medicines substantially increase the risk of stroke and death (perhaps associated with 60%-70% higher mortality rates). There is even some evidence such antipsychotic medicines can accelerate the progression of AD. Despite this deeply unsatisfactory situation, some estimates place antipsychotic medicine prescription rates at about one third of all AD patients (Kirkham, et al., 2017).

Although no medicines have been approved that would treat the full spectrum of symptoms underlying the agitation, the structural difficulties in doing so are not as challenging as for AD itself. Examples supporting this are as follows:

- The specific brain circuitry that controls many of the individual symptoms of agitation are reasonably well understood. This understanding reflects the extensive level of research into other mental illnesses where such symptoms also occur. This fact is

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in sharp contrast to the general lack of biological understanding of AD.

- Patients need only be followed for 3-6 months in clinical trials to assess whether a potential medicine can alleviate agitation symptoms. AD clinical trials often need patients to be followed for 18 months or longer to determine whether a medicine is beneficial in mitigating cognitive decline. That time difference is a considerable advantage in terms of clinical trial cost and elapsed time.
- Patients in most stages of AD (typically mild, moderate, and severe) are suitable to be enrolled in clinical trials for agitation. Conversely, disease-modifying AD clinical trials are typically confined to just one or two stages of the disease. This restriction considerably slows down recruitment to clinical trials and adds to cost.

Near Misses

Over the past decade or so, pharmaceutical companies have started in earnest to develop medicines to manage the symptoms of agitation but without resorting to methods like sedation. Although to date no medicine has been approved from these efforts, there have been an encouraging number of "near misses"':

- Neudexta is an approved medicine owned by the Japanese pharmaceutical company Otsuka to treat pseudobulbar affect (an inability to control emotions for patients with various neurological disorders or traumas). In March 2019, Otsuka announced positive results from one of two drug dose levels in a key clinical trial for AD patients with moderate to advanced agitation. However, Otsuka did not state the specific clinical benefit or statistical *p* value for the successful dose level. In September 2019, Otsuka announced the results of a second key clinical trial in AD patients with moderate to severe agitation across two drug dose levels. This time, neither drug dose level produced positive results. However, this disappointing outcome has not deterred Otsuka's interest in AD agitation. As will be discussed later in this section, they have invested in three separate key Neudexta agitation clinical trials that are all underway at the time of writing.
- Nuplazid is an approved medicine owned by the U.S. pharmaceutical company Acadia to treat hallucinations and delusions suffered by Parkinson's disease patients. In December 2019, Acadia announced positive results for reducing the risk of relapsing psychosis in a Phase III clinical trial of patients with AD, Parkinson's disease, and other forms of dementia. The headline results looked impressive: The risk of relapsing psychosis was reduced by an impressive 65%, and the reported *p* value was a strong 0.23%. However, U.S. regulators in both April 2021 and August 2022 refused to approve Nuplazid for AD patients with psychosis. Their concerns focussed on the fact that most of the generated benefit came from the subset of Parkinson's disease patients in the trial. In contrast, AD patients showed only a minor response level that was not statistically significant and deemed clinically insignificant as well.
- Rexulti is an approved medicine owned by both the Japanese and Danish pharmaceutical companies Otsuka and Lundbeck, respectively, to treat schizophrenia and depression. In May 2017, both companies announced results from two Phase III clinical trials for AD patients with agitation. In the first Phase III clinical trial (in which patients were given dose levels of either 1 mg or 2 mg of Rexulti per day), only the higher 2 mg dose produced positive results. In the second Phase III trial (in which patients could be given flexible doses of 0.5 mg, 1 mg, or 2 mg per day), the outcome was a failure. Despite these mixed

Over the past decade or so, pharmaceutical companies have started in earnest to develop medicines to manage the symptoms of agitation but without resorting to methods like sedation. Although to date no medicine has been approved from these efforts, there have been an encouraging number of "near misses"

results, Otsuka and Lundbeck invested in another key clinical trial.

Breakthrough

In June 2022, there was finally a clear breakthrough in finding a medicine to treat AD agitation. As mentioned above, a third Phase III clinical trial had been started to assess Rexulti's ability to treat the indication. The third Phase III clinical trial incorporated key lessons from the previous two Phase III trials:

- The previous trials had shown higher dose levels were correlated with an improved ability to treat the agitation symptoms. Accordingly, the third key clinical trial tested two higher dose levels of 2 mg and 3 mg per day.
- Patients were now required to have undergone a brain scan that produced results consistent with having AD. As noted previously in this paper, a problem with many AD clinical trials in recent years has been ensuring enrolled patients actually have the disease.

These changes evidently improved the clinical trial design since the trial was a clear success. Patients on the combined 2 mg and 3 mg dose levels demonstrated a strong reported *p* value of 0.26%. Patients on each of the individual 2 mg and 3 mg dose levels also demonstrated positive *p* values of 2.4% and 0.5%, respectively.

As noted previously, repurposed schizophrenia medicines generally have a dark history when used off-label to treat AD patients with agitation. However, Rexulti does not appear to be similarly concerning for several reasons:

- Unlike many other schizophrenia-related medicines, Rexulti is known not to induce sedation. This was corroborated in all three Phase III clinical trials in AD patients with agitation where sedation was not an observed side effect. The clear implication is Rexulti is achieving its benefit by treating at least some of the affected brain circuitry underlying the agitation.
- No cases of stroke or death appear to have occurred in all three key clinical trials in AD patients with agitation.
- Rexulti has been approved for prescribing since 2015. Sometimes, important side effects emerge only after a medicine has finished its clinical trials and has been approved for general prescription. To date, no unexpected new side effects have emerged since Rexulti's approval.

One critical point to note here is Rexulti will not at all alter the progression of the disease. It is simply helping to manage some of the serious symptoms associated with the disease. However, there may be a weak second-order mortality benefit if Rexulti is successful in materially reducing the off-label, and often deeply unsatisfactory, use of antipsychotic medications.

U.S. regulators are scheduled to approve Rexulti for prescription for AD agitation in May 2023. Assuming it is approved, U.S. AD patients, their caregivers, and their doctors will finally have a reasonably effective and relatively safe option to treat the often difficult-to-manage agitation issues. One issue to watch is that neither company has, at the time of writing, yet indicated when they will file for approval with European regulators.

The Future

Finally, the table below shows my own compilation of Phase III trials for run by pharmaceutical companies AD agitation-modifying potential medicines that are underway at the time of writing.

There are a much lower number of trials underway, at the time of writing, for agitation than for the disease itself. However, the success of Rexulti and the aforementioned less-challenging background to medicine development for agitation means it is not implausible there will be another success here in 2024-2025 when the trial results are due to be released.

In particular, Rexulti's mechanism of action is via the neurotransmitters serotonin and dopamine. This, in

Medicine Name	Company	Medicine Mechanism	Year Trial(s) Launched	Year of Trial Results	Number of Trials
Auvelity	Axsome	NMDA & Sigma-1	2022	2024	1
AVP-786	Otsuka	NMDA & Sigma-1	2017	2025	3
Masupirdine	Suven Life	Serotonin	2022	2025	1

theory, should boost Masupirdine's chances of success. However, it would be preferable if AVP-786 or Auvelity were to succeed. Their different mechanisms of action open the possibility of patients taking them in addition to Rexulti because, generally speaking, two medicines with varying mechanisms of action can have a synergistic impact on the target illness if taken in combination. From a commercial standpoint, it is interesting to see Otsuka (one of the developers of Rexulti) is also the developer for AVP-786. It is unusual to see one pharmaceutical company back two distinct medicines for the same target illness because there is a real commercial risk one medicine will cannibalise the sales of the other. The company's motivation is not clear here: It may just want multiple shots on target for a serious and underserved target illness, or it may indeed believe both medicines could ultimately be taken in combination for a synergistic outcome.

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Concluding Thoughts: Longevity Shock?

A final point of deliberation in this paper relates to actuarial considerations of longevity improvements, or more specifically, a longevity shock scenario. Such a scenario would relate to a sudden and substantive discontinuity in future assumed mortality improvements stemming from the idea of, "What if they find a cure for Alzheimer's?". Such a scenario would logically require the following elements:

- A new medicine is developed that halts all cognitive decline in nearly all AD patients.
- This new medicine has no substantive side effects.
- This new medicine is taken as a simple pill or, at worst, by self-injection like insulin medicines.
- In parallel with the medicine breakthrough, AD diagnosis rates substantially improve and all AD cases are uncovered by the mild disease stage at the latest.
- The pharmaceutical company that develops the new medicine charges a low enough price so national health systems do not explicitly or implicitly slow down the medicine's adoption.
- The new medicine breaks the pharmaceutical industry's pattern that new medicines take 6 years or so to reach peak sales.

My own view on such a "cure" scenario is that it is, in practical terms, a near impossibility. Put another way, I would argue it is an idea that belongs more in the realm of science fiction than hard-headed scenario modelling. In support of such a view, consider the totality of the issues raised in this paper:

Such a scenario would relate to a sudden and substantive discontinuity in future assumed mortality improvements stemming from the idea of, "What if they find a cure for Alzheimer's?".

- Section 5: The serial failure of multiple apparently promising AD experimental medicines since 2010, including the dispiriting story of Aduhelm.
- Section 6: The multiple inherent difficulties of developing medicines for AD that make progress materially harder than for most other illnesses.
- Section 7: There are useful ongoing advances being made in AD research, but these are happening gradually and at an incremental pace.
- Section 9: Leqembi is a milestone as the first medicine to treat AD successfully, but it only reduces the rate of cognitive decline by less than a third, is currently difficult to administer, and has a significant and dangerous side effect.

- Section 10: Peak patient take-up of Leqembi will likely take over 5 years and will be considered a success if used by half of eligible AD patients. Related to this, its mortality benefits will not show up until the 2030s. Several more multi-year clinical trials are needed to establish the full utility of Leqembi to treat AD.
- Section 11: There are multiple grounds for considering Leqembi only a moderate step on the journey to "curing" AD.
- Section 12: None of the clinical trials in progress at the time of writing offer real confidence of demonstrating anything more than perhaps an incremental improvement over Leqembi.

Instead, in terms of considering future AD related longevity shocks, it is much more plausible to think of gradual and moderate longevity gains, starting in the 2030s and persisting for several more decades as additional incremental advances are made in treating AD. In that context, this much more plausible future scenario of incremental progress over several decades could be better seen as underpinning and buttressing current standard long-term longevity improvement assumptions used in actuarial work.

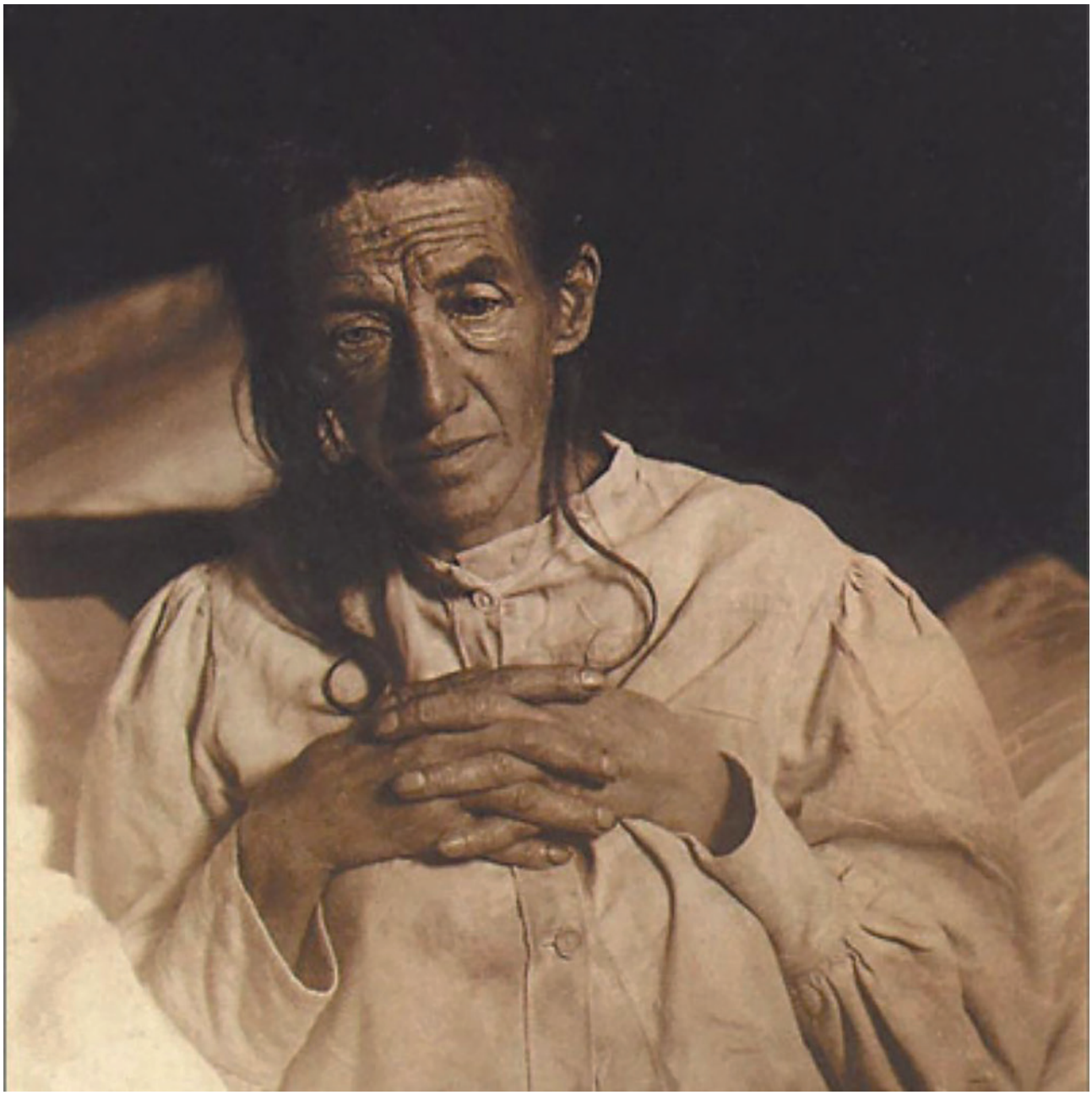
However, none of this is to take away from Leqembi being the first medicine to unambiguously demonstrate an ability to partially treat AD. As stated in the opening section of this paper, after perhaps 50 centuries since humanity starting recording its understanding of AD and dementia in general, we are now entering an era where the leading cause of death in many developed countries is finally starting to become treatable. There is much to be thankful for to be living in an era of such gradual but cumulatively profound change.

Appendix A
Dr. Alzheimer's Interview Notes

Dr. Alois Alzheimer took detailed notes of his interviews with his first AD patient, Auguste Deter. Once considered lost, Auguste Deter's medical records, including these notes, were rediscovered in 1996. These interview notes were subsequently published, including a translation into English (Maurer, et al., 1997). The following are some excerpts from these notes on 26 November 1901, the day after Auguste was admitted to the asylum.

As background, Auguste Deter was married to Carl August Wilheim Deter, a railway clerk. The Deter family lived in Frankfurt, the same city as the asylum to which she would later be admitted. Some comments made by Dr. Alzheimer as he was recording the interview are shown in parentheses, and separate explanatory notes are shown in square brackets.

Dr. Alzheimer:	"What is your name?"
Auguste Deter:	"Auguste."
Dr. Alzheimer:	"Family name?"
Auguste Deter:	"Auguste."
Dr. Alzheimer:	"What is your husband's name?" (She hesitates, finally answers.)
Auguste Deter:	"I believe ... Auguste."
Dr. Alzheimer:	"Your husband?"
Auguste Deter:	"Oh, my husband."
Dr. Alzheimer:	"How old are you?"
Auguste Deter:	"Fifty-one."
Dr. Alzheimer:	"Where do you live?"
Auguste Deter:	"Oh, you have been to our place."
Dr. Alzheimer:	"Are you married?"
Auguste Deter:	"Oh, I am so confused."



Photograph of Auguste Deter, while admitted to the Frankfurt asylum

Dr. Alzheimer: "Where are you right now?"

Auguste Deter: "Here and everywhere, here and now, you must not think badly of me."

Dr. Alzheimer: "Where are you at the moment?"

Auguste Deter: "We will live there."

Dr. Alzheimer: "Where is your bed?"

Auguste Deter: "Where should it be?"

(Around midday, Auguste Deter ate pork and cauliflower.)

Dr. Alzheimer: "What are you eating?"

Auguste Deter: "Spinach." (She was chewing meat.)

Dr. Alzheimer: "What are you eating now?"

Auguste Deter: "First I eat potatoes and then horseradish."

Dr. Alzheimer: "Write a '5.'" [The German word for "5" is *fünf*.]

Auguste Deter writes: "A woman." [The German word for "woman" is *frau*.]

Dr. Alzheimer: "Write an '8.'" [The German word for "8" is *acht*.]

Auguste Deter writes: "Auguse."

(While Auguste Deter is writing, she repeatedly says, "I have lost myself, so to say.")

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