Prospects for Alzheimer's Disease Medicines

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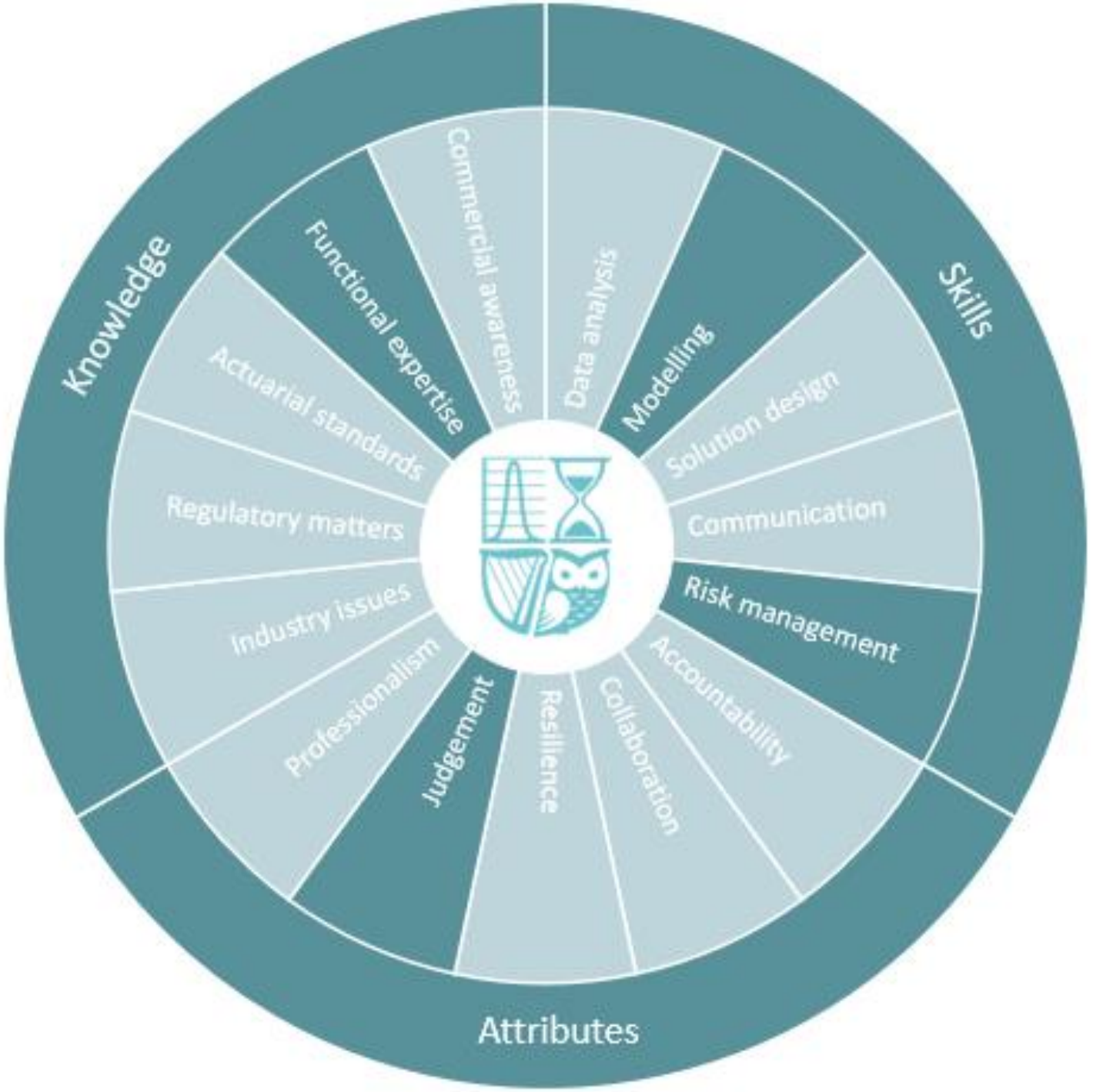
Disclaimer

The views expressed in this presentation – and the associated written paper – are my own and not necessarily those of the Society of Actuaries in Ireland. For the avoidance of doubt, I have no employer or clients. While I am an experienced biotech investor, I have no medical qualifications. I have held long and short investment positions in several biotech companies referenced in this presentation and the associated written paper (and may do so again after 22 March 2023).

Competency Framework Wheel



Introduction

- Summarises written paper (on SAI website)

- Agenda
  - Define Alzheimer's Disease (AD)
  - Current sympomatic medicines
  - Difficulty developing new AD medicines
  - New breakthrough medicines
  - New medicines' potential impacts
  - Prospects for further new medicines

History of AD

Era	Development
c.2500 - 3000 BC	Egyptians describe AD in medical manuals
< 19th century	Generally viewed as natural impact of aging
19th century	Recognised as disease – but vascular/stroke in nature
1901-1907	Dr. Alois Alzheimer uncovers neurological nature based on unusual cases
1910 – 1970's	Accepted as distinct form of dementia – but a rare curiousity
1976	Dr. Robert Katzman identifies as dominant form of dementia
1976 - Today	Scientists and pharma companies seek to develop medicines
Today	Dementia is leading cause of death in developed countries (AD c.60%-80% of cases) and no effective medicines

Hallmarks of AD

Hallmark	Description
Amyloid Plaques	Amyloid is a benign brain protein. In AD, corrupts into 1) intermediate soluble form and then 2) clumps into plaques.
Neuronal Death	Neurons are at the core of cognitive ability. As AD progresses, neurons' functioning degrades, they lose connections to each other & eventually die.
Tau Tangles	Tau is also a benign brain protein (located inside neurons). In AD, again corrupts & clumps into tangles.
Brain Atrophy	As neurons die, brain atrophies. Very evident in advanced stages.

AD Stages

Disease Stage	Description
Pre Clinical	Starts two decades or more before symptoms manifest. Amyloid plaques visible on brain scans. Cause(s) currently unknown.
Prodromal (also MCI)	Minor symptoms but patients can still manage very well. Can be confused with other medical conditions. Diagnosis often deferred.
Mild Alzheimer's	Symptoms clearcut and most diagnoses made at this stage. But patients can still handle ADL's without much help.
Moderate Alzheimer's	Symptoms intensify and become more serious (e.g. may not recognise family). Need support with ADL's and require oversight.
Severe Alzheimer's	Ability to communicate & control of muscle function lost (e.g. swallowing). Bedridden and require total support. Death frequently arises from pneumonia and falls.

Key Demographic Statistics

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

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%

- Female rates (somewhat) higher than males
- Incidence rates are perhaps 20+ years earlier
- Typical lifespan of 8-10 years (ignoring background mortality)

- Mortality Table is Irish Life Table No. 17
- Lower female mortality ups female:male patient ratio
- Effective patient lifespan much lower at advanced ages

Falling AD Incidence Rates

- Meta-analyses suggest dementia incidence is falling (c.13% per decade)
- Table shows impact of 'modifiable' dementia risk factors (excludes age & genetic factors)
- Most risk factors improving for decades (e.g. education)
- Elderly AD demographic so risk factor gains have decades still to play out
- Plausible – but not categoric – explanation for falling incidence rates
- Aging in developed countries outweighs this issue

Modifiable Dementia 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%

Existing AD Drugs

- 1970's focus on "Cholinergic Hypothesis"
  - Acetylcholine (Acet.) = neurotransmitter pivotal to memory formation
  - Acet. formed in neurons which AD destroy (hence loss of memory)
  - Treating Acet. deficiency could halt AD progression???
- Japanese scientists found clever way to maximise Acet. in AD patients
- Resulted in drug Aricept
  - Improves memory for 5-18 months but no longevity gain
  - Neurons keep dying so eventually little Acet. left to maximise
  - 'Peak' $5.4bn yearly sales
- Similar "Glutamatergic Hypothesis" produced Memantine

2010 – 2023 : 39 Major Clinical Trial Fails!

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
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
Solanezumab	Amyloid	Amyloid	2014	2023	1	Pre-Clinical

Failed Trial Issues

- 13/20 medicines used “Amyloid Hypothesis”
  - Removing amyloid plaques from brain deemed pivotal to treatment
  - Discredited by persistent failures
- Aduhelm & Gantenerumab=modified “Amyloid (Soluble) Hypothesis”
  - Response to persistent trial failures
  - Holds that intermediate corrupted & soluble form of amyloid is pivotal
- General trend to focus on earlier AD stages

Aduhelm Controversy

- Failed combined interim “futility” test in 2019
- 1 trial later surprisingly passed at high dose but
  - Only a post-hoc statistical outcome
  - In other trial, performed worse than placebo
  - >50% patients on high dose had serious ARIA side effect
- In 2021, US regulator controversially approved Aduhelm
- US Aduhelm launch disastrous & withdrawn in 2022
  - Stakeholders sceptical Aduhelm worked & wary of ARIA
  - Initially cost $56k a year and Medicare/insurers refused to cover
- No other regulator approved Aduhelm

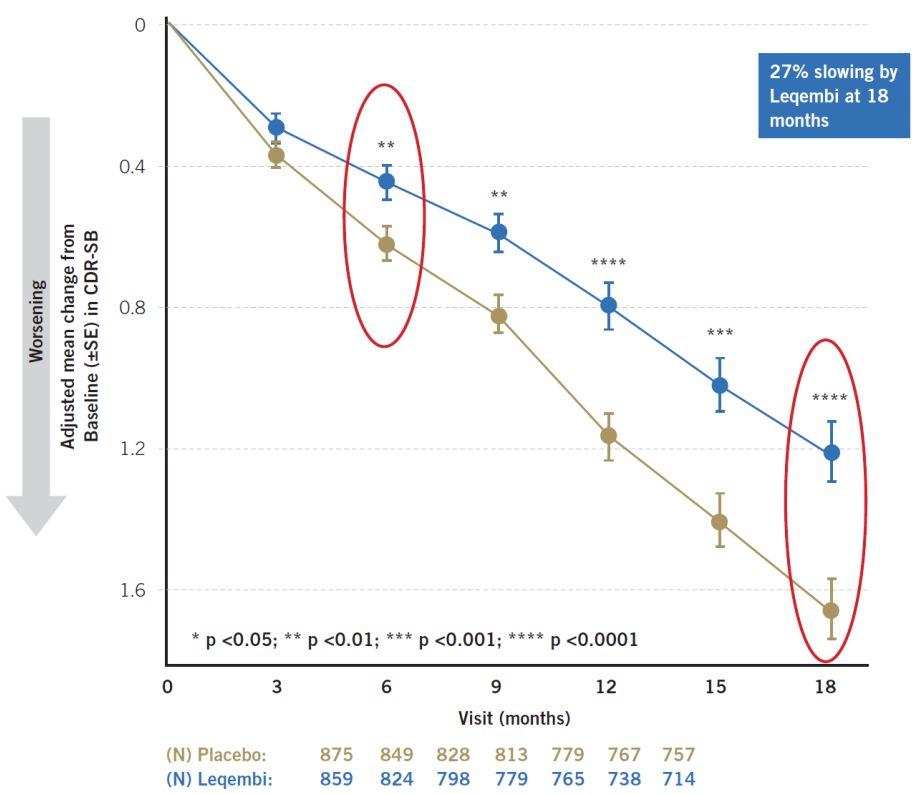
Medicine Development Issues

Facet	Covid-19	Alzheimer's Disease
Disease Understanding	SARS-Cov-2 coronavirus root cause	Not understood
Accessing the Disease	Readily accessible to immune system	Blood-brain barrier formidable obstacle
Animal Model	Infects many animals	Only humans get AD
Tissue Sample	Multiple viable & practical tissue types	Not practical
Clinical Trial Duration	Quick in a pandemic!	Typically 18 months
Recruiting Trial Patients	Easy	Surprisingly difficult

Recent Research Advances

Year	Research Advance
2012	Improved diagnosis by PET brain scans
2015	Original “Amyloid Hypothesis” discredited
2018	Clinical trial success bar lowered
2023	Diagnosis possible through blood samples

Leqembi - Breakthrough!



- In July 22, Leqembi is 1st drug to treat AD in key trial
- 27% relative reduction in cognitive decline after 18 months
- Triumph for modified ‘Amyloid (Soluble) Hypothesis’
- ‘ARIA’ side effect a concern
- Full approval due in July ‘23 in US & Q4/Q1 ‘23/’24 in EU
- US cost is $26,500 per year

Medicine Development – A Hard Business

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%

- All 3 medicines based on same modified 'Amyloid (Soluble) Hypothesis'
- Only Leqembi showed efficacy with lowest ARIA rate
- Leqembi may get $5bn-10bn 'peak' yearly sales – other 2 are c.$500m+ write-offs
- Microscopic improvements in drug design = profound efficacy & commercial benefits

Leqembi - Impact

- Modelling from Phase IIb trial implies net c.1 year longevity gain
  - More time in prodromal & mild stages vs. less in moderate & severe stages
  - Bigger gains in insurance & pension portfolios
- Leqembi patient take-up difficult to model
  - Cost, ARIA side effect & dosing relevant factors
  - Will patients be diagnosed earlier?
  - Perhaps 35%-50% take-up in prodromal & mild stages
  - Also correlated with socio-economic status
- Longevity impact felt throughout 2030's
  - c.6 years to 'peak' sales & c.8-10 year current lifespan

Leqembi - Impact

- Healthcare
  - Model implies institutional care utilisation lowered by c.30%
  - c.50%-70% institutional care patients have dementia
  - Institutional care usage also correlated with socio-economic status
  - Institutional care impact bigger than longevity?
- Ongoing Clinical Trials
  - Self-injection (replace IV dosing in medical facilities?)
  - Less frequent dosing (lower cost/side effects with same efficacy?)
  - Longitudinal (more benefit after 18 months?)
  - Pre-clinical stage (more benefit if taken earlier?)

Leqembi - An Interim Milestone

- 27% benefit => Amyloid (Soluble) Hypothesis isn’t full root cause
- Don’t know why amyloid gets corrupted
- Don’t know if Pre-Clinical use of Leqembi beneficial
- ARIA side effect significant drawback
- No treatment for one-fifth AD patients with “mixed dementia”
- Don’t know if treating ‘tau tangles’ is beneficial

Current Key Trials

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
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

- Donanemab mechanism similar to Leqembi & success is plausible
- Chronic brain inflammation emerging as a popular hypothesis
- 2 Pre-Clinical stage trials important wildcards

Agitation - Background

- Agitation is hallmark cluster of AD symptoms
  - Includes agitation, irritability, wandering, repetition, aggression & psychosis
  - Prevalence = 1/3rd in community & 4/5^{ths} in institutional care
  - Challenging & draining for caregivers
- Widespread use of ‘off label’ potent antipsychotic drugs
  - ‘Work’ by sedation & erode quality of life
  - Aggravate stroke risk & mortality
- Developing medicines simpler than for AD itself
  - Root causes better understood & trials quicker/cheaper
  - Several recent ‘near misses’ in key trials

Agitation - Breakthrough

- In July 2022, Rexulti clearly passed key agitation trial
  - Failed prior agitation trials but lessons learnt
  - Strong *p* value of 0.26%
  - Already approved for schizophrenia but no sedation side effect
  - No signs of elevated stroke or mortality risk
  - US approval in May 2023 (European timelines unclear)
- List of current key agitation trials is short but promising

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

‘Curing’ AD Causes Longevity Shock?

- Characteristics of an ideal ‘cure’ medicine:
  - 100% reduction in cognitive decline
  - Simple pill with no serious side effects
  - 100% diagnosis by Mild stage
  - Instant rise to ‘peak’ sales & full take-up
- Totality of paper makes this highly unbelievable scenario
- Scenario of gradual incremental gains much more plausible
  - Implies gradual multi-decade longevity gains from 2030’s
  - Underpins standard long-term longevity improvement assumptions
- After c.50 centuries of documenting AD, this is profound change

Q&A

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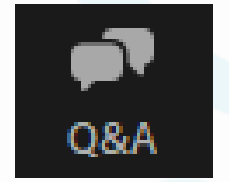
Use the **Q&A function** to ask a question



Appendix A : Syphilis – A Treatable Dementia

- Syphilis : Historically very common STD where advanced form of neurosyphilis causes progressive dementia

Era	Development
1494-1495	Syphilis first recorded in Europe
16th-19th Century	Mercury ointment is standard treatment – some efficacy but severe side effects
1904	Treponema pallidum bacteria identified as root cause
1909-1910	Salvarsan drug developed – much better efficacy but can't treat neurosyphilis
1943	Newly isolated penicillin excellent syphilis treatment – including neurosyphilis
1943-1945	Penicillin drug mass produced by US & UK
1950's onwards	New antibiotics & chemotherapies treat patients allergic to penicillin

- Discovering root cause was essential to developing effective drugs
- Still a multi-decade iteration to develop fully curative drugs