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Clinical trials on Alzheimer's disease in Europe

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Alzheimer Europe gratefully acknowledges the grant provided by Janssen, which led to the production of this report.

Want to find out more about clinical trials at the 29th Alzheimer Europe Conference #29AEC in The Hague?

Join our special symposium SS3 "Clinical trials in Alzheimer's disease" on Thursday 24 October 2019, from 12.45–13.45 in room Princess Ariane.

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Foreword

> “Alzheimer Europe has started to cover this subject in 2014 with the aim to build an accessible, user-friendly, web-based resource that can help people with dementia and their carers to gain and share better information about clinical trials for the prevention and treatment of Alzheimer’s dementia and other types of dementia.”

I am very pleased to welcome our readers of our Dementia In Europe magazine to this special supplement about clinical trials.

Clinical trials represent an essential step toward the development of new ways to prevent, diagnose and treat dementia. A range of clinical trials is being conducted at a European level. People with dementia or those who are at risk of developing it and healthy volunteers are needed today to help advance Alzheimer’s disease research. However, the pathways to access to these clinical trials are complex. It is apparent that information about clinical trials is not easily accessible. People cannot find information on the clinical trials related to their own diseases.

For that reason, Alzheimer Europe has started to cover this subject in 2014 with the aim to build an accessible, user-friendly, web-based resource that can help people with dementia and their carers to gain and share better information about clinical trials for the prevention and treatment of Alzheimer’s dementia and other types of dementia. Alzheimer Europe reached out to both researchers and people with dementia and involved them in the provision of information on clinical trials in a language that is both understandable and accessible for people with dementia and scientifically accurate and checked by the researchers involved. This resulted in the launch in 2016 of our Clinical Trials Watch, a new service bringing together up-to-date information on clinical trials investigating drugs for the treatment and prevention of Alzheimer’s disease and other dementias in an accessible format. At that time, only Phase III clinical trials recruiting participants in at least two European countries were included. In 2018, thanks to the funding from the EU health programme, the resource was further expanded to include Phase II and III studies that are being conducted in all European countries.

The special supplement will give you a comprehensive insight into our Clinical Trials Watch and we hope that you will share our interest and commitment to this important research topic. The supplement begins with an introduction on and explanation of clinical trials. We have also included a section on the rationale behind the Clinical Trials Watch and how it was conceived. Next, Phase II and III clinical trials that are currently investigating drugs for Alzheimer’s disease and/or dementia in Europe are listed.

This is followed by an overview of the recent Phase III clinical trials that failed to show significant results supporting their clinical outcomes. Although pharmaceutical companies have invested heavily in various potential disease-modifying drugs for Alzheimer’s disease, the past years have brought some disappointing results.

We also feature an interview with Craig Ritchie in this special supplement. We are very grateful for his willingness to share his thoughts and experiences so far. It is evident that despite the many challenges that scientists are confronted with, there is a commonality in learning from these failed clinical trials. It is encouraging to see that new directions in Alzheimer’s disease research are being considered and that a major emphasis is placed on early intervention and prevention.

We hope you will find this special supplement helpful in outlining the Phase II and III clinical trials that are currently investigating drugs for Alzheimer’s disease and/or dementia in Europe, whilst also providing a useful reference for our member organisations wishing to promote clinical trials participation in their countries.

I want to acknowledge the contribution of the people involved in this work. My thanks go to Cindy Birck, Project Officer at Alzheimer Europe, who coordinates the Clinical Trials Watch and wrote this report. I would like to thank the European Group of People with Dementia (EWGPWD) and the pharmaceutical companies who are providing insightful feedback on the Clinical Trials Watch.

Lastly, if you are reading this during our 29th Alzheimer Europe conference (#29AEC) in The Hague, I would like to invite you to join the special symposium on “Clinical trials in Alzheimer’s disease” on Thursday 24 October from 12.45 to 13.45 pm. A special thanks goes to Janssen who provided a special grant for this supplement and the conference symposium.

Jean Georges
Executive Director, Alzheimer Europe

Understanding clinical trials

Relevance in the Alzheimer's disease field

To date there is no preventative or curative treatment for Alzheimer's disease. Some drugs exist for Alzheimer's disease that can, for some people, temporarily alleviate some of their symptoms, such as memory loss and confusion. There are currently four drugs approved and currently used in symptomatic treatment: donepezil (Aricept, 1996), rivastigmine (Exelon, 2000), galantamine (Razadyne, 2001) and memantime (Namenda, 2003). Three of the four available drugs – donepezil, rivastigmine and galantamine – are known as acetylcholinesterase inhibitors and are prescribed to treat symptoms related to memory, thinking, language, judgment and other thought processes in people with mild to moderate Alzheimer's dementia. The fourth drug, memantine, regulates the activity of a different neurotransmitter in the brain known as glutamate. Memantine is prescribed to improve memory, attention, reason, language and the ability to perform simple tasks in people with moderate to severe Alzheimer's dementia.

> "It is a long and difficult journey to bring new treatments to the market, involving decades of research and a series of clinical studies on human participants."

Clinical research is key for advancing medicine, leading to new interventions and improving medications - notably in the field of Alzheimer's disease research at a time when the disease is becoming more prevalent with the ageing of the world's population. There are several drugs currently in development and testing. However, it is a long and difficult journey to bring new treatments to the market, involving decades of research and a series of clinical studies on human participants, known as clinical trials.

What is a clinical trial?

A clinical trial (also called interventional study) is a biomedical/health-related research study conducted to evaluate the effects on humans of a new medical treatment. In most cases, clinical trials refer to a research study conducted in people to determine whether treatments are safe and effective. The word "treatment" most often refers to new drugs but may also refer to new technology, device, vaccine, surgical procedures, therapy or methods of prevention, screening and diagnosis of a disease.

> "Clinical research is key for advancing medicine, leading to new interventions and improving medications – notably in the field of Alzheimer's disease research at a time when the disease is becoming more prevalent with the ageing of the world's population."

Every product that is utilised in clinical practice has been rigorously tested. Clinical trials are carefully designed and reviewed with a number of parameters in order to generate meaningful results. In a clinical trial, participants receive the above interventions according to the protocol created by the investigators. Research participants can expect to receive either the drug being tested or a placebo treatment (a substance identical in appearance to the drug being tested with no active therapeutic effect; this refers to the control group). Every clinical trial follows a protocol that describes inclusion and exclusion criteria such as age, specific disease or health history to determine the target population that may participate in the trial. The protocol also outlines the design, methods, dosage, duration and target outcomes of the trial.

Clinical trials can be sponsored and funded by government agencies, pharmaceutical or biotechnology companies, hospitals, academic institutions, other organisations or individuals. They are usually conducted at hospitals or clinics.

What are the types of clinical trials?

There are two main types of clinical studies: interventional and observational.

- Interventional clinical studies are clinical trials conducted to determine whether a candidate drug, a new combination of drugs, experimental treatment or therapy is safe and effective.
- Observational clinical studies investigate health issues and outcomes in large groups of people. The participants do not receive any investigational treatment or drug. Instead, researchers observe participants by monitoring their health over a period of time to collect data about the disease.

Different types of interventional clinical trials can be categorised according to their objectives and the way they are organised. Below are descriptions of some different types of clinical trials that exist in addition to treatment trials:

- Prevention trials involve tests to find ways to prevent particular diseases or medical conditions in people who have never had them or to prevent them from reoccurring. They can include the use of medicines, lifestyle changes or dietary supplements.
- Diagnostic and screening trials are aimed at finding new or better ways to detect and diagnose a particular medical condition.

What are the phases of clinical trials?

Clinical trials are conducted in a series of steps called Phases. They advance through four Phases (literally Phase I, II, III and IV) to test if a drug/treatment is safe and effective in humans, find the appropriate dosage and identify side effects. Each step has its own purpose and the number of people involved increases as the trial progresses from one Phase to the next one.

- Phase I trial tests an experimental treatment or a drug in a small group of people, often healthy people (20–80), for a short period of time. The purpose is to study the safety of the drug, identify side effects, determine a safe dosage range and see how the body reacts to the drug (e.g. how it is absorbed, distributed and eliminated from the body). It is the first investigation of a new drug in people after successful laboratory and animal testing.
- Phase II trial determines the right dosage and effectiveness of a drug in treating a particular disease and further studies its safety in a large number (100–300) of participants who have the disease/condition that the drug is intended to treat. The study typically assigns participants to different treatment groups, where each group can receive different doses.
- Phase III trial is performed on larger groups (1000–3000) of research participants with a disease/condition to confirm the effectiveness of the new drug, monitor its side effects and study different dosages. Phase III is the last stage before clinical approval for a new drug. These trials are longer in duration than Phase II trials, involve a much larger group of volunteers than Phase I and II trials and are often multinational.
- Phase IV trial is also known as post-marketing study. The aim is to monitor the long-term safety and effectiveness of a drug in large populations once it is approved by regulatory authorities and made available to the public.

There are also some clinical trials that have an extension trial. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate. Participants are usually informed at the time they are recruited into the main trial that they may be eligible to participate in an extension study. After the completion of the main trial, some research participants may be invited to enrol in the extension study. In most cases, during an extension trial, participants receive the drug over a long period to gather information about long-term safety and tolerability.

> “To date there is no preventative or curative treatment for Alzheimer’s disease. Some drugs exist for Alzheimer’s disease that can, for some people, temporarily alleviate some of their symptoms.”

Figure 1. Overview of the four clinical trials Phases

Phase I

Safety & Dosage
- 20–80 healthy volunteers
- Several months

Phase II

Efficacy & Side effects
- 100–300 people with the disease
- Several months to 2 years

Phase III

Safety & Efficacy
- 1000–3000 people with the disease
- 1–4 years

Phase IV

Post-market safety monitoring
- All people using the treatment after it has been approved

Clinical Trials Watch

Background and objectives of the database

Only a small body of research exists that has examined the personal experiences of participants enrolled in a clinical trial. In particular, research on people with dementia and their experiences of taking part in a clinical trial, their needs and problems encountered is very limited.

Information about clinical trials and experimental treatments is very relevant for people living with dementia, their families and also for the general public. The demand from people for information about ongoing clinical trials has been growing for many years. Many people are willing to participate in clinical trials and for many this opportunity should be a right (Locock et al, 2011).

> In 2018, the Harris Poll conducted the largest global survey about Alzheimer's disease on behalf of Novartis, Amgen and Banner Alzheimer's Institute and in association with Alzheimer's Disease International. The survey was conducted among 10,095 adults living in 10 countries and highlighted the importance of raising awareness on how to get involved in Alzheimer's disease research. Findings reported that a majority of participants (79%) would be willing to participate in medical research specifically about Alzheimer's disease but 70% said it is difficult to find out about the latest developments in medical research and 75% had no idea how to get involved with medical research.

The accessibility to clinical trials remains problematic and very much dominated by the medical profession. These issues become even more complex in dementia as often people with dementia experience difficulties for accessing, understanding information or making informed decisions. Moreover, often, the carer has to be involved at some level.

Although new regulations have been put in place in Europe about transparency and the type of information that should be accessible to the public, user-friendly information about clinical trials is scarce and participants are confronted with a number of practical and emotional challenges. It is very limited for people to find a clinical trial that may be suitable for them. This type of information is often difficult to find and generally written in language that is difficult to understand (e.g. large amount of complex information, jargon).

Considering the above, Alzheimer Europe decided in 2014 to propose the development of a user-friendly web-based resource that can help people with dementia and their carers to gain and share better information about clinical trials for the prevention and treatment of dementia. In September 2016, Alzheimer Europe announced the launch of the resulting Clinical Trials Watch - a service bringing together up-to-date information on clinical trials investigating drugs for the treatment and prevention of Alzheimer's and other dementias, in an accessible format. The Clinical Trials Watch is not an exhaustive resource of information. It contains information about clinical trials that are:

- Currently recruiting participants
- Conducted in at least one European country
- In phase II and phase III.

Since its development, Alzheimer Europe continues to develop and improve its innovative online resource providing dementia-friendly information on clinical trials.

Methodology

Who is involved in this work?

For this new resource, Alzheimer Europe collaborated closely, with members of its European Working Group of People with Dementia (EWGPWD) from 2014–2016 and also asked several pharmaceutical companies conducting trials feedback on how to present basic information. Five members of the European Working Group of People with Dementia, all living with dementia, were involved in the development of an easy-to-read template with information about trials and in helping to ensure that the information provided in each template is understandable for a lay person, regardless of whether the person has (or not) a diagnosis of dementia.

Once a new trial is identified, Alzheimer Europe develops a table containing basic information about it. The contents are based on the information available on public registries, such as the US and EU Clinical Trials Registries. ClinicalTrials.gov and the EU Clinical Trials Database (EudraCT) provide the

The European Working Group of People with Dementia – EWGPWD – was launched by Alzheimer Europe and its member associations in 2012. The group is composed entirely of people with dementia who are nominated by their national Alzheimer associations. They work to ensure that the activities, projects and meetings of Alzheimer Europe duly reflect the priorities and views of people with dementia.

European Working Group of People with Dementia
ALZHEIMER EUROPE

major source of information for the Clinical Trials Watch. They are the largest registries of clinical trials that should give complete, accurate and updated information about trials. We use the public registries labelling interventional Phase II and III trials that are recruiting participants in Europe.

The pharmaceutical company or study sponsors running the trial are asked to provide feedback on the contents of the table and to check that the information included are scientifically accurate. In the meantime, each easy-to-read document is reviewed by a member of the European Working Group of People with Dementia to ensure that the information provided is understandable for a lay person before being published on the Alzheimer Europe website.

What do the tables contain?

The tables provide information on active phase II and III clinical trials for Alzheimer's disease and/or dementia. All the clinical trials included are currently recruiting participants in at least one European country. However, it is important to bear in mind that recruitment may not happen in all countries at the same time. The content is updated regularly, based on information available on public registries. Each table contains the following sections:

1. Study information
2. Information about the drug that will be tested in the study
3. Information about participating in the trial
4. Who can participate in this study?
5. Where and when will the study be conducted?
6. Information for your doctor

All tables can be found on the Alzheimer Europe website. In addition, an accessible easy read version of each study is also available as a pdf. One easy list provides the names of all studies currently being conducted in Europe. However, a better way to find relevant information on trials is by searching by country or condition. This allows users to only find those studies that are currently recruiting or planning to recruit participants in their country or for their condition (at risk, prodromal, mild, moderate, severe dementia, agitation).

Taking part in research as an expert by experience means that you need correct information about all clinical trials that might be relevant, what is required and expected, from all involved, which is accessible, easy to read and understand, that is exactly what Alzheimer Europe has produced with their dementia friendly resource on clinical trials. A dementia diagnosis does not mean we are all suddenly at the later stage of dementia, there is a beginning and middle before the end, the later stages. It also doesn't mean we have to sit back, waiting to die and exist with no chance of a useful life. We all need a future, a purpose, a focus, and a life full of hope. And this is what taking part in research, gives us! This is what research gave me, it gave me the hope and knowledge we needed to carry on living our life with dementia. We all need to work together if any progress is to be made in research, for us to take part, we might need extra support. The professionals involved, also need support to work with us and to better understand what's going on with regards to our diagnosis. Being enabled and supported, not disabled, is just what is needed, this dementia-friendly information resource on clinical trials does just this, it helps make possible to still contribute and live alongside dementia.

Chris Roberts,
Vice-chair, EWGPWD

How many trials are reported in the CTW?

The CTW was developed three years ago (at the time of print) and 37 clinical trials have already been reported via this service. Although some trials have been removed since they are no longer recruiting participants, new trials have also been added, resulting in 17 clinical trials currently reported in the database (as of 25 September, 2019).

Phase II trials

As part of our Clinical Trials Watch, we identified eight Phase II clinical trials currently recruiting participants for the treatment of Alzheimer's disease and /or dementia in Europe. They are investigating eight different agents (ABvac40, ACI-24, CPHPC, ORY-2001, RO7105705, LM11A-31-BHS, IONIS-MAPTRx, Valaciclovir).

We also identified seven compounds (BIIB092, RO7105705, ABBV-8E12, BI 425809, Neflamapimod, Liraglutide, Lemborexant) that are being investigated in Phase II clinical trials, those are European ongoing studies but new participants are not currently being recruited or enrolled.

Smart-Age is another active Phase II trial investigating the effects of polyamine supplementation on cognition and biomarkers in older adults with subjective cognitive decline. This trial is listed as recruiting participants in Germany on the public registry clinicaltrials.gov but the recruitment status has not been updated since March 2017. At the time of print, this trial is suggested to be an ongoing study that has completed its recruitment.

The detailed list of active Phase II clinical trials can be found in table 1.

"You need information that is correct, accessible and easy-to-read and understand, about all clinical trials that might be relevant, and to know what is expected - that is exactly what Alzheimer Europe has produced."

Chris Roberts

Table 1. Agents in Phase II of Alzheimer's disease drug development in Europe

Name of the drug	Name of the study	Target	Condition	Study sponsor	Recruitment status
ABvac40	/	Amyloid-related (immunotherapy)	Amnestic mild cognitive impairment or very mild Alzheimer's disease	Araclon Biotech	Recruiting
ACI-24	ACI-24-1801	Amyloid-related (immunotherapy)	Mild Alzheimer's disease	AC Immune	Recruiting
CPHPC	DESPIAD	Amyloid-related (small molecule)	Mild Alzheimer's disease	University College London	Recruiting
ORY-2001	ETHERAL	Epigenetic (small molecule)	Mild-moderate Alzheimer's disease	Oryzon Genomics	Recruiting
RO7105705	LAURIET	Tau (immunotherapy)	Moderate Alzheimer's disease	Genentech	Recruiting
LM11A-31-BHS	/	Neuroprotection (small molecule)	Mild-moderate Alzheimer's disease	PharmatrophiX	Recruiting
IONIS-MAPTRx	MAPT-CS1	Tau (RNA-based)	Mild Alzheimer's disease	Ionis Pharmaceuticals	Recruiting
Valaciclovir	VALZ-Pilot	Neuroprotection & inflammation (antiviral agent)	Early Alzheimer's disease	Hugo Lovheim	Recruiting
Polyamine	SmartAge	Neuroprotection (dietary supplement)	People with subjective cognitive decline	Charite University Berlin	Recruiting
BIIB092	TANGO	Tau (immunotherapy)	Mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease	Biogen	Active, not recruiting
RO7105705	TAURIEL	Tau (immunotherapy)	Prodromal to mild Alzheimer's disease	Genentech	Active, not recruiting
ABBV-8E12	AWARE	Tau (immunotherapy)	Early Alzheimer's disease	AbbVie	Active, not recruiting
BI 425809	/	Neurotransmitter based (small molecule)	Cognitive impairment due to Alzheimer's disease	Boehringer Ingelheim	Active, not recruiting
Neflamapimod	REVERSE-SD	Inflammation (small molecule)	Mild Alzheimer's disease	EIP Pharma	Active, not recruiting
Liraglutide	ELAD	Metabolic function (small molecule)	Mild Alzheimer's dementia	Imperial College London	Active, not recruiting
Lemborexant	/	Neurotransmitter based (small molecule)	Mild to moderate Alzheimer's disease dementia	Eisai	Active, not recruiting

> “Accessibility to clinical trials remains problematic and is dominated by the medical profession. These issues become even more complex in dementia as often people with dementia experience difficulties accessing and understanding information.”

It is possible to rank European countries as indicated in figure 2, which shows the number of active Phase II clinical trials recruiting research participants in Europe. There is no country where it is possible for research participants to enrol in all eight identified Phase II clinical trials. Only 11 European countries (Austria, Czech Republic, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, UK) are recruiting participants in Phase II trials. Sweden, Spain, UK and France are among the countries with most phase II trials. In all other European countries, it is impossible for volunteers to enrol in Phase II clinical trials, as none of the identified clinical trials are recruiting in those countries.

Phase III trials

A number of Phase III clinical trials investigating drugs for Alzheimer’s disease and/or dementia are also being conducted. As indicated in table 2, Alzheimer Europe has identified 9 Phase III clinical trials investigating different compounds (Brexpiprazole, Gantenerumab, TRx0237, Guanfacine, Mirtazapine, AVP-786, Omega-3 treatment, COR388) that are currently recruiting research participants in at least one European country (as of 25 September, 2019).

Furthermore, three other compounds (Masitinib, ALZT-OP1 and Pimavanserin) are being examined. AB Science completed Phase III recruitment of masitinib in people with confirmed mild to moderate Alzheimer’s disease in mid-2018. In June 2019, AB Science reported that their pre-planned interim analysis of the Phase III study data had detected a positive trend of efficacy in one of the masitinib doses tested. Final analysis are expected by the end of 2019. In August 2019, AZTherapies announced that the company completed enrolment for its Phase III COGNITE trial, testing the safety and efficacy of its investigational drug ALZT-OP1 for the treatment of early Alzheimer’s disease. The study is still ongoing, participants are receiving an intervention or being examined, but no new participants are being enrolled. In September 2019, Acadia Pharmaceuticals announced that the HARMONY Phase III study will be stopped early for positive efficacy as Pimavanserin met its primary endpoints on people with dementia-related psychosis.

Besides that, in March 2019, Eisai began a Phase III trial called Clarity AD in the US. It aims to enrol people with early Alzheimer’s disease who will receive BAN24-01 or placebo for 18 months. The company expects to expand the recruitment in Europe in the coming months and the trial is set to run until 2024. As can be seen from figure 3, there are significant differences between European countries in terms of number of Phase III clinical trials open for recruitment. There is no country where it is possible for research participants to enrol in all 9 recruiting Phase III clinical trials. UK, Spain, France and Poland are among the countries with most Phase III trials. In a number of smaller and mostly Eastern European countries (Albania, Austria, Bosnia & Herzegovina, Cyprus, Estonia, Greece, Iceland, Israel, Ireland, Jersey, Latvia, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Romania, Slovakia, Slovenia, Switzerland), it is impossible for volunteers to enrol in Phase III clinical trials, as none of the identified clinical trials are recruiting in those countries. Details of possible participation of research participants in Phase III clinical trials can be found in table 3.

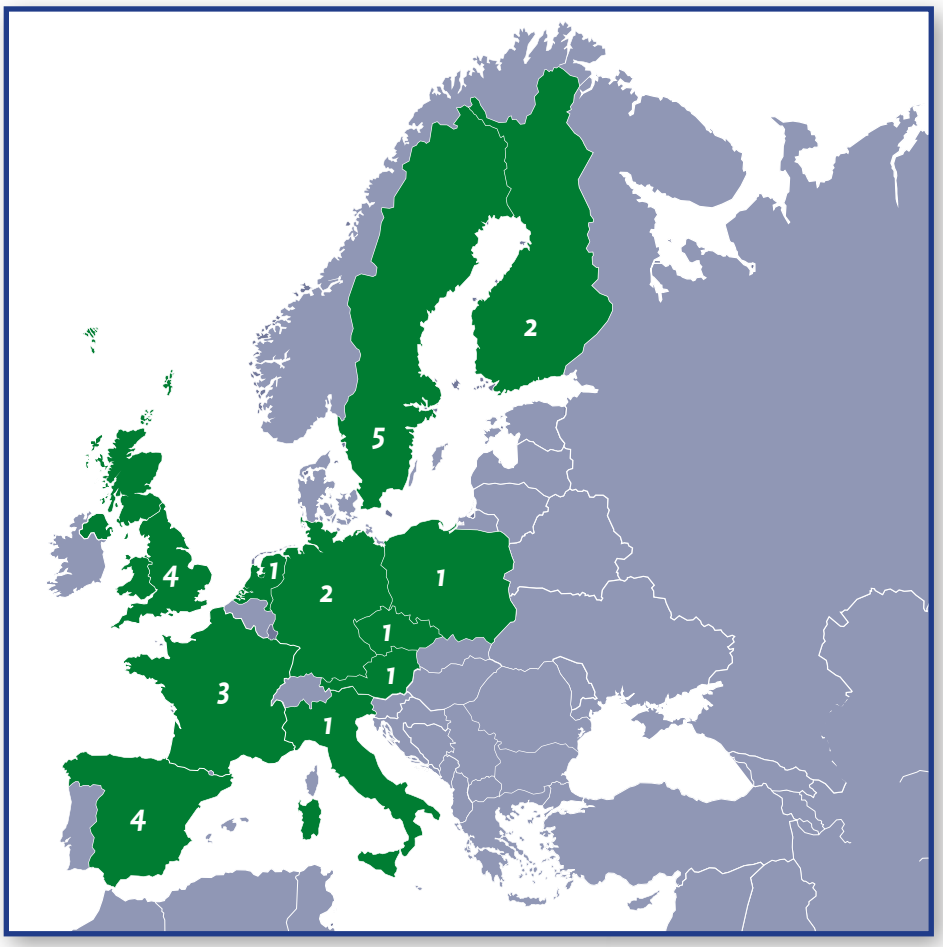


Figure 2. Phase II clinical trials open for recruitment in Europe – numbers shown per country refer to number of trials currently open (as of 25 September 2019)

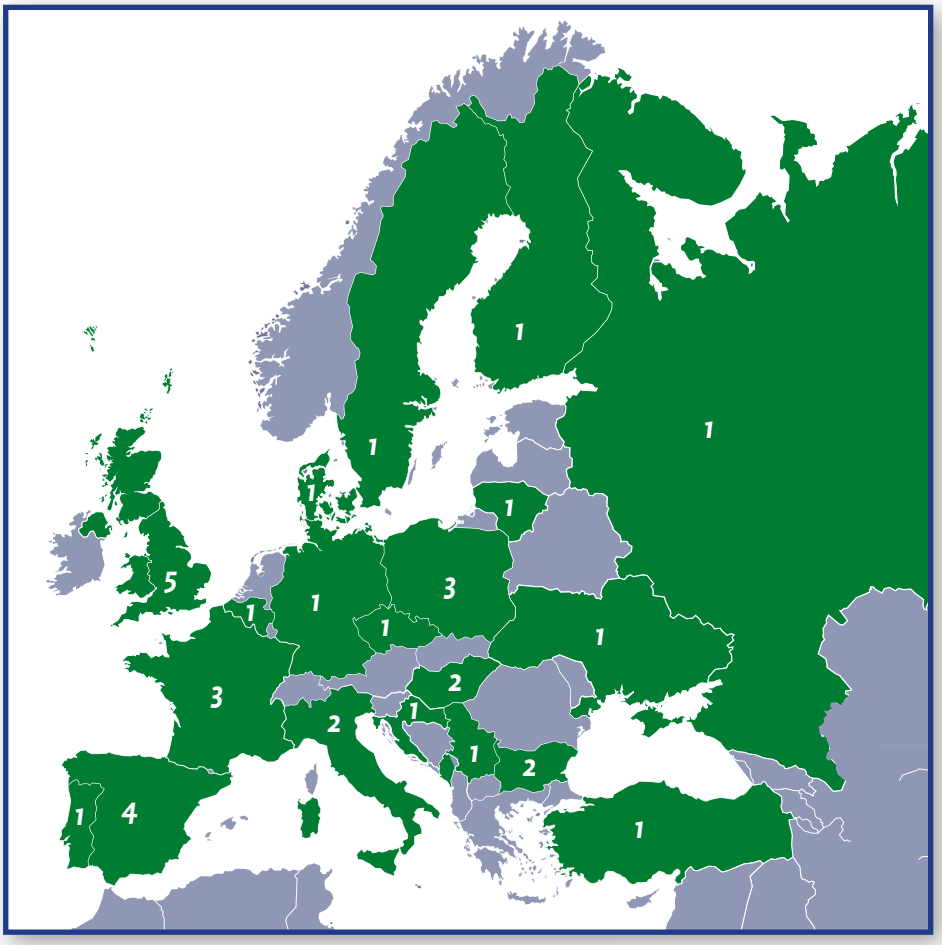
Table 2. Agents in Phase III of Alzheimer's disease drug development in Europe

Name of the drug	Name of the study	Target	Condition	Study sponsor	Recruitment status
Brexpiprazole	/	Neurotransmitter based (small molecule)	Agitation associated with dementia of the Alzheimer's type	Otsuka Pharmaceutical	Recruiting
COR388	GAIN	Inflammation (small molecule)	Mild to moderate Alzheimer's disease dementia	Cortexyme	Recruiting
Gantenerumab	GRADUATE1	Amyloid-related (immunotherapy)	Early (prodromal to mild) Alzheimer's disease	Hoffmann-La Roche	Recruiting
Gantenerumab	GRADUATE2	Amyloid-related (immunotherapy)	Early (prodromal to mild) Alzheimer's disease	Hoffmann-La Roche	Recruiting
TRx0237	LUCIDITY	Tau (small molecule)	Early Alzheimer's disease	TauRx Therapeutics	Recruiting
Omega-3 treatment	LO-MAPT	Neuroprotection (dietary supplement)	Subjective memory complaints or family history of Alzheimer's disease	University Hospital, Toulouse	Recruiting
Guanfacine	NorAD	Neurotransmitter based (small molecule)	Mild to moderate Alzheimer's disease	Imperial College London	Recruiting
Mirtazapine	SYMBAD	Neurotransmitter based (small molecule)	Agitation in people with dementia	University of Sussex	Recruiting
AVP-786	17-AVP-786-305	Neurotransmitter based (small molecule)	Agitation associated with dementia of the Alzheimer's type	Avanir Pharmaceuticals	Recruiting
Pimavanserin	HARMONY	Neurotransmitter based (small molecule)	Dementia-related psychosis	ACADIA Pharmaceuticals	Active, not recruiting
ALZT-OP1	COGNITE	Amyloid-related & Inflammation (small molecule)	Evidence of early Alzheimer's disease	AZTherapies	Active, not recruiting
Masitinib	/	Inflammation (small molecule)	Mild to moderate Alzheimer's disease	AB Science	Active, not recruiting
BAN2401	Clarity AD	Amyloid-related (immunotherapy)	Early Alzheimer's disease	Eisai	Planned

Table 3. Phase III clinical trials open for recruitment in European countries (R: Recruiting, ANR: Active not recruiting P: Planned)

	Brexpiprazole	GAIN	GRADUATE1	GRADUATE2	LO-MAPT	LUCIDITY	NorAD	SYMBAD	17-AVP-786-305
Belgium				R		P			
Bulgaria	R								R
Croatia				R					
Czech Republic									R
Denmark				R					
Finland				R					
France			R		R	P			R
Germany			R						
Hungary			R						R
Italy			R			P			R
Lithuania			R						
Netherlands				ANR					
Poland		R		R		P			R
Portugal				R					
Russia			R						
Serbia	R								
Spain	R		R	R		P			R
Sweden				R					
Turkey				R					
Ukraine	R								
United Kingdom				R		R	R	R	R

Figure 3. Phase III clinical trials open for recruitment in Europe – numbers shown per country refer to number of trials currently open (as of 25 September 2019)



Mechanisms of actions

As described above, the Clinical Trials Watch currently reports on 8 Phase II and 9 Phase III clinical trials recruiting research participants in Europe.

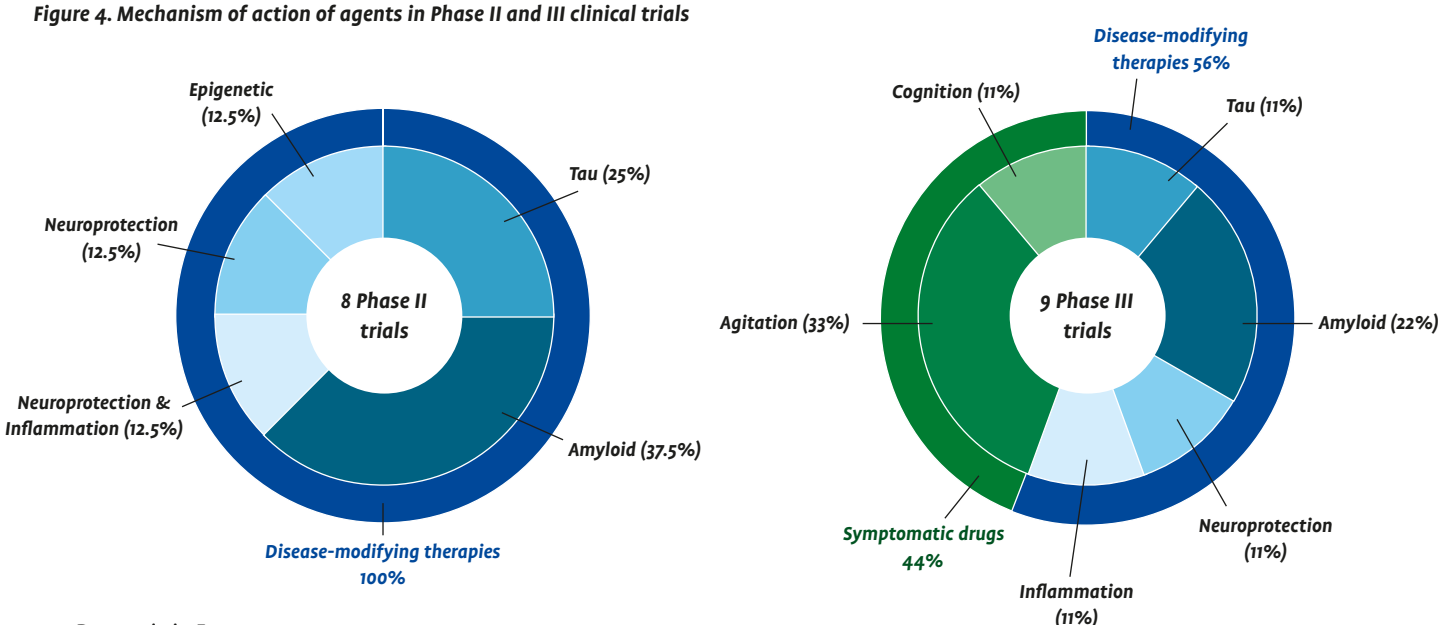
8 agents are investigated in 8 Phase II clinical trials and 8 agents in 9 Phase III clinical trials. There are 12 agents that intend to achieve disease modification as they attempt to alter the pathophysiology of Alzheimer's disease. Misfolded proteins such as Amyloid and Tau are the most common specific targets in Phase II and Phase III studies as they can accumulate into plaques, tangles and other forms in the brain and become toxic. However, new compounds are being studied based on other mechanisms including neuroprotection, anti-inflammatory approaches, synaptic activity, metabolic and genetic interventions.

All 8 compounds in Phase II clinical trials are disease-modifying drugs. In Phase III, there are 4 symptomatic agents and 4 compounds that are targeting disease modification.

Figure 4 shows a breakdown by mechanisms of action of agents in Phase II and III clinical trials recruiting research participants in Europe. The data presented here focus on agents currently reported in the Clinical Trials Watch resource.

> "The Clinical Trials Watch is a service bringing together up-to-date information on clinical trials investigating drugs for the treatment and prevention of Alzheimer's and other dementias, in an accessible format."

Figure 4. Mechanism of action of agents in Phase II and III clinical trials



Recent failed disease-modifying treatment trials

Although there are four compounds on the market that treat symptoms of Alzheimer's disease, there are currently no approved disease-modifying drugs that stop the progression of the disease.

No new disease-modifying treatments have been successful in Phase III clinical trials for Alzheimer's disease underlying the very high rate of failures in Alzheimer's disease drug development programmes which is estimated at a 99.6% failure rate during 2002–2012 (Cummings et al, 2014). According to the recent report published by the Biotechnology Innovation Organization, the clinical development success rates for Alzheimer's disease programmes is among the lowest found in any therapeutic area.

> "Clinical development success rates for Alzheimer's disease programmes are among the lowest found in any therapeutic area."

Most Phase II clinical trials ending with a positive outcome do not succeed in Phase III, often due to adverse effects or failure to meet pre-specified primary endpoints. Table 4 provides an overview of phase III clinical trials investigating drugs for Alzheimer's disease that have recently failed along with their sponsor and the indication of why the clinical trial failed.

There have been many failures in attempts to develop new drugs for Alzheimer's disease targeting the neuropathological findings of the disease. These investigations that have failed to date include acetylcholinesterase inhibitors (encenicline), agonists and antagonists of neurotransmitter receptors (idalopirdine, azeliragon, intepirdine), molecules acting on neuronal pathways (ITI-007), agents related to mitochondria and metabolic function (AC-1204), β-secretase inhibitors (verubecestat, lanabecestat, atabecestat, CNP520, elenbecestat) and vaccines or antibodies targeting Aβ clearance (crenezumab, gantenerumab, solanezumab, aducanumab).

> "Lessons have been learned from failed and discontinued clinical trials offering opportunities to improve the development of new disease-modifying therapies."

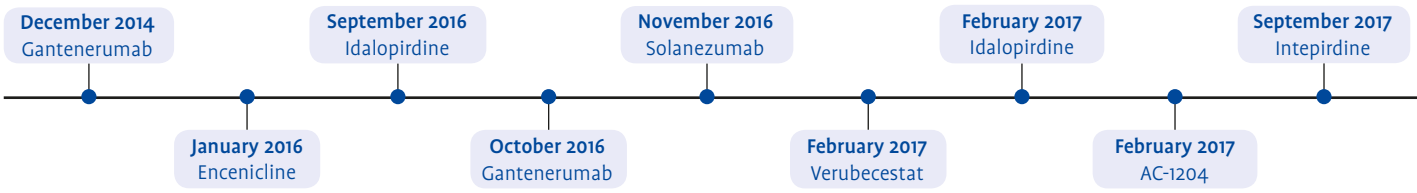
Over the last decade, advances have been made in understanding the biological mechanisms underlying Alzheimer's disease. Furthermore, lessons have been learned from failed and discontinued clinical trials offering opportunities to improve the development of new Alzheimer's disease–modifying therapies.

> "Most Phase II clinical trials ending with a positive outcome do not succeed in Phase III, often due to adverse effects or failure to meet pre-specified primary endpoints."

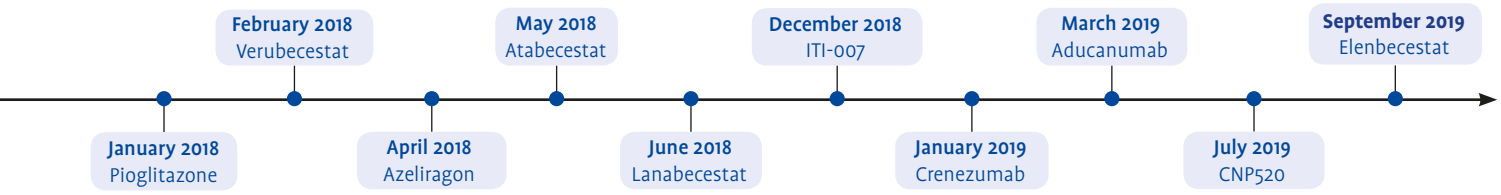
Table 4. Overview of Phase III failures over the past years in Alzheimer's disease-drug development

Name of the drug	Name of the study	Target	Condition
Elenbecestat	MISSIONAD1 MISSIONAD2	Amyloid-related (small molecule)	Early Alzheimer's disease
CNP520	Generation S1 Generation S2	Amyloid-related (small molecule)	Risk to develop clinical symptoms of Alzheimer's disease
Aducanumab	EMERGE ENGAGE	Amyloid-related (immunotherapy)	Early Alzheimer's disease
Crenezumab	CREAD1 CREAD2	Amyloid-related (immunotherapy)	Prodromal to mild Alzheimer's disease
ITI-007	ITI-007-201	Neurotransmitter based (small molecule)	Agitation in patients with dementia
Lanabecestat	AMARANTH	Amyloid-related (small molecule)	Early Alzheimer's disease
	DAYBREAK-ALZ		Mild Alzheimer's disease dementia
Atabecestat	EARLY	Amyloid-related (small molecule)	Risk for developing Alzheimer's dementia
Azeliragon	STEADFAST	Amyloid-related & Inflammation (small molecule)	Mild Alzheimer's disease
Verubecestat	APECS	Amyloid-related (small molecule)	Prodromal Alzheimer's disease
Pioglitazone	TOMMORROW	Inflammation (small molecule)	Risk of mild cognitive impairment due to Alzheimer's disease
Intepirdine	MINDSET	Neurotransmitter based (small molecule)	Mild to moderate Alzheimer's disease
AC-1204	NOURISH AD	Mitochondrial metabolism (dietary supplement)	Mild to moderate Alzheimer's disease
Verubecestat	EPOCH	Amyloid-related (small molecule)	Mild to moderate Alzheimer's disease
Idalopirdine	STARBEAM STARBRIGHT	Neurotransmitter based (small molecule)	Mild to moderate Alzheimer's disease
Solanezumab	EXPEDITION-3	Amyloid-related (immunotherapy)	Mild Alzheimer's disease
Gantenerumab	MARGUERITE RoAD	Amyloid-related (immunotherapy)	Mild dementia due to Alzheimer's
Idalopirdine	STARSHINE	Neurotransmitter based (small molecule)	Mild to moderate Alzheimer's disease
Encenicline	COGNITIV AD	Cholinergic system (small molecule)	Mild to moderate Alzheimer's disease
Gantenerumab	SCarlet RoAD	Amyloid-related (immunotherapy)	Prodromal Alzheimer's disease

Timeline of failed drug trials



Study sponsor	Results
Eisai	September 2019 - Discontinuation based on data safety monitoring board recommendation due to an unfavourable risk-benefit ratio.
Novartis	July 2019 – Discontinuation based on a planned analysis. The review of unblinded data reported that participants receiving the experimental drug worsened in some measures of cognitive function.
Biogen	March 2019 – Halt based on results from a futility analysis conducted by an independent data monitoring committee, which reported that the trials were unlikely to meet their primary endpoint upon completion.
Roche	January 2019 – Discontinuation based on the results from a pre-planned interim analysis. An independent data monitoring committee reported that crenezumab was not expected to meet its primary endpoint.
Intra-Cellular Therapies	December 2018 – Discontinuation based on a data monitoring committee who recommended to stop the trial for futility. The study was not likely to meet its primary endpoint upon completion.
Eli Lilly	June 2018 – Discontinuation based on an independent data monitoring committee who reported that lanabecestat was unlikely to meet its primary endpoints.
Janssen	May 2018 – Discontinuation due to serious elevations of liver enzymes observed in some research participants who received atabecestat. The company concluded that the benefit-risk ratio is no longer supported to continue the development of the study.
vTv Therapeutics	April 2018 –Failure to meet the co-primary endpoints.
Merck	February 2018 – Discontinuation based on recommendation by the external data monitoring Committee reporting that verubecestat was unlikely to demonstrate a positive clinical effect if the trial continued.
Takeda	January 2018 – Discontinuation based on a planned interim futility analysis showing an inadequate treatment effect with pioglitazone in delaying the onset of mild cognitive impairment due to Alzheimer's disease.
Axovant Sciences	September 2017 –Failure in demonstrating a statistically significant improvement in cognition and measures in daily activities (co-primary endpoints).
Accera	February 2017 – Failure in demonstrating a statistically significant improvement at 26 weeks (primary endpoint).
Merck	February 2017 – Discontinuation based on recommendation of an external data monitoring committee who determined no chance of a positive result and recommended ending the study.
Lundbeck	February 2017 – Failure in demonstrating efficacy.
Eli Lilly	November 2016 – Failure to meet primary endpoint. Solanezumab did not experience a statistically significant slowing in cognitive decline.
Roche	October 2016 – Discontinuation based on a planned futility interim analysis showing low probability of meeting the primary outcome measure with the doses studied.
Lundbeck	September 2016 – Failure in showing efficacy and significant improvements.
FORUM Pharmaceuticals	January 2016 – Discontinuation following reports on gastrointestinal side effects.
Roche	December 2014 – Discontinuation based on an interim futility analysis made by an independent data monitoring committee. The company noted that no new safety signal arose.



The academic perspective on recent clinical trials and on the future of AD research

Alzheimer Europe interviewed Professor Craig Ritchie from the Centre for Dementia Prevention (Edinburgh, Scotland) to discuss the recent clinical trials' results and the future directions of Alzheimer's disease (AD) research.

Recently there have been quite a few high profile failures of Phase III clinical trials of disease-modifying treatments. What have we learned from these failed clinical trials?

One of the things we have learned over the past several years is that Alzheimer's disease starts to develop in the brain decades before dementia symptoms appear, probably starting in mid-life and with as yet not fully understood disease processes. Given that, recent trials have been showing us that better targeted populations should be considered for inclusion in studies and that intervention may be required before clinical symptoms are apparent. We should of course try to target individuals with earlier stages of disease rather than those in the advanced stages of Alzheimer's disease.

It is worth mentioning of course that these trials, despite not being successful in achieving their primary objective, are still teaching us and help us develop knowledge. Maybe the lesson is as much what not to do in the future as well as what to do. There will have been a point in the course of all recent trials when the sponsor could have known and perhaps should have known that the intervention was highly unlikely to be successful. In that regard, the other lesson that is very important to learn is the value of adaptive trial design whereby data from the trial is regularly reviewed. Therefore, as the trial progresses, researchers and companies can actually make early decisions about whether or not there is any opportunity or any chance that the drug is going to be successful. If the drug is not statistically likely to be successful, they could stop that trial and move the resources elsewhere and more importantly not continue to expose research participants to the risk of taking a drug which is unlikely to show success.

One thing I would say though is that I don't think that the targets for these drugs are necessarily the wrong targets. There is still a lot of promise there and these approaches like anti-amyloid therapies for instance are going to be useful in the future. Key though is to understand 'when' and in 'who' the drug should be tested rather than what remains a little bit of a 'one-size-fits-all' approach too late in the disease course. We have fundamentally reassessed how we approach clinical trials in Alzheimer's disease by establishing projects like EPAD to find solutions to these key challenges.

Looking at the current compounds in the Alzheimer's disease development pipeline, what is coming up next?

First of all, a lot of compounds that have been tested recently are intended to modify the course of disease and this encompasses the challenges mentioned above. Companies and drug developers have recognised these challenges as well as the unmet clinical needs for people with later stage disease where other, non-cognitive, symptoms have a major impact on a person's well being. Many investigators and companies are already adding a new direction by looking at drugs that have a particular effect on the behavioural symptoms such as agitation, psychosis or sleep disturbances. Several clinical trials are underway with agents designed to address behavioural symptoms associated with Alzheimer's disease we see in practice. As a clinician, I recognise that a lot of the challenges that people with dementia encounter are not just around their memory impairment but also on what we call neuropsychiatric symptoms. New approaches for managing neuropsychiatric symptoms in Alzheimer's disease are needed and I think we are going to see new developments in this area both with pharmacological and non-pharmacological interventions.

In terms of disease-modifying agents, the drug development pathway is complicated by the fact we are recognising that Alzheimer's disease is an incredibly complex disease that can be initiated and driven by multiple genetic and non-genetic factors. At a biological level it is no longer helpful to think about the disease just in terms of Amyloid and Tau pathology as there are many other pathological processes (both upstream and downstream) that affect brain health and which lead to the person having symptoms. Researchers are now focusing on drugs for a multitude of biological targets moving beyond Amyloid and Tau for instance. Although a new breadth of approaches may over time yield advances, we still have the problem of when do we intervene. This can be only informed by much better disease models being developed that confirm the biology of a range of neurodegenerative brain diseases at their earliest stages of development.

Last but in no ways least, it's worth noting the value of combining therapies as a method of gaining greater effectiveness in what is after all a very complex disease with numerous interacting biological processes. This area has been slow to gather pace but is beginning to get some attention. It is not without substantial challenges e.g. the safety of combinations of novel treatments needs to be understood before embarking on large scale trials – though the scale of the problem of Alzheimer's disease should convince sponsors to find ways to rise to

these challenges. Given the complexity of the disease including interactions of many different processes, we want to consider the use of combination therapies to try to address these in relevant, specific, well characterised populations; as we do in cancer interventions currently. I think personally it would be a huge leap forward for the Alzheimer's disease community and may hold the greatest promise for disease modification. We still need those early disease models though!

You are leading several programmes aiming to prevent the disease such as the PREVENT Dementia study and the European Prevention of Alzheimer's Dementia (EPAD) project. Should we prioritise prevention over disease-modifying treatments?

I'm pleased to be part of the leadership of a couple of major projects working with people at varying risks of dementia so together we can identify risk factors for neurodegenerative diseases and how this is expressed and progresses decades before dementia develops. These are the disease models I keep referring to. The value of the PREVENT Dementia project and the EPAD Longitudinal Cohort Study amongst others projects across the world is really being able to improve the knowledge and understanding of the disease processes which left alone would lead years later to the development of dementia. For this, we need to have the highest quality of longitudinal data including multiple different measures such as brain imaging, spinal fluid assays, cognitive testing, genetic analysis and blood proteomics. Over time, we will generate wonderful and much needed disease models that will give us the knowledge regarding why some people develop the disease, what the diseases are and what we can do to mitigate the effects of these dreadful brain diseases.

In my opinion, there is a consistency between pharmacological and non-pharmacological interventions. We should pursue both strategies as at the end of the day the prevention of Alzheimer's dementia is going to require both. The first step is always related to risk modification and building resilience for any individual to do the best they can to maintain their brain health from childhood onwards. Public health interventions will also play a vital role to enhance well being and therein brain health. If, despite this, the disease develops, then at that point people may want to consider a specific pharmacological intervention. It is part of the process of first lifestyle changes, early detection and then intervention with or without pharmacological agents. To be fair, I think that the priority in the early stages of the disease would be lifestyle changes.

What other promising research leads are there?

There is a massive amount of research going on in terms of early detection, blood biomarkers, genetics, imaging and others markers. There is also a number of studies in progress on the pharmacology front. Firstly, we will definitely need more collaborative approaches. We should find an effective mechanism to bring all the current research together and engineer future research to be contributing to coordinated action. It would indeed be more effective to use all the knowledge and data generated to develop statistical models and methods that allow individuals to be assessed accurately for what their risk of developing dementia or brain disease in the future is, so that we can intervene and prevent disease taking hold. The second area I would like to highlight is that we should all make sure that all these research findings are rapidly implemented into clinical practice. It is essential that this happens and researchers have to give priority and plan how to ensure that research rapidly, effectively and responsibly transitions into practice.

EPAD team working with Craig Ritchie, March 2019, Centre for Dementia Prevention, Edinburgh, Scotland

Profile

Prof. Craig Ritchie is the Professor of Psychiatry of Ageing and Director at Edinburgh Dementia Prevention, the University of Edinburgh. He is also a visiting Professor at Imperial College, London. Prof. Ritchie is the Chief Investigator of numerous dementia research projects and these include the EPAD, PREVENT Dementia Programme and the Scottish Dementia Research Consortium. He is also the Founding Director of Brain Health Scotland. He has authored almost 200 publications in the area of dementia research.

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Further information and references

Please note that the information provided in the Clinical Trials Watch service should not be interpreted as a recommendation to use a particular treatment, nor to participate in a particular study.

Further information on clinical trials and on the studies appearing in the Clinical Trials Watch is available at: http://www.alzheimer-europe.org/Research/Clinical-Trials-Watch

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ClinicalTrials.gov https://clinicaltrials.gov/

European Union Clinical Trials Register (EudraCT) https://www.clinicaltrialsregister.eu/

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