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New Drugs for Dementia

Dementia is a progressively debilitating condition that has been the focus of recent national and international political attention. Currently no drugs are available to treat the underlying diseases causing dementia. Recent policy has committed resources to fund more research and improve treatment and care. This POSTnote provides an overview of dementia, current treatments and potential new drugs. It examines the challenges involved in developing new drugs and in ensuring patient access. Finally, it considers prevention strategies.

Overview

- The number of dementia cases in the UK and the associated costs are predicted to more than double by 2050.
- Current drugs for dementia marginally alleviate symptoms.
- Developing drugs is challenging because of the complexity of the underlying diseases that cause dementia.
- Evidence shows that treatment in the early stages of dementia is important.
- New UK and international initiatives are accelerating research. Researchers call for more clarity over the future of funding.
- New drugs are likely to be expensive and will not treat all types of dementia. Providing patients with access to new drugs raises a number of challenges for the NHS.
- UK policy on preventing dementia is based on the premise that a healthy lifestyle may reduce the risk of developing dementia.

Background

Dementia is not a disease in itself, but a syndrome caused by one or more underlying diseases. The main feature is progressive damage to nerve cells (neurons) in the brain causing loss of cognitive function.[1,2] Symptoms include memory loss, confusion, difficulty with language, agitation and aggression.[3] Symptoms worsen over time and 24-hour care is needed in the latter stages.[4] Some people with dementia can be offered drugs to manage the symptoms (symptom-modifying), but there are no drugs that stop the underlying conditions from progressing (disease-modifying).

At least 800,000 people in the UK have dementia, with 1 in 14 over-65s affected.[5] Over 40,000 people have young-onset dementia, occurring before the age of 65. In 2013, dementia cost £22bn per year in social care and £4.3bn in health care, more than cancer and heart disease combined.[1,6,7] The number of people with dementia and associated costs are predicted to more than double by 2050, primarily due to population aging.[5,8]

Types and Causes of Dementia

Most people with dementia are aged over 75 and many have more than one dementia-causing disease (mixed dementia) alongside other illnesses.[6,9,10] Alzheimer's disease (AD) is diagnosed in 60 to 80% of cases and vascular dementia (VaD) in 10-17% of cases.[6,10] Rarer types include frontotemporal dementia, dementia with Lewy bodies and Parkinson's Dementia. All of these diseases are characterised by different biological changes and processes (pathologies) that are not fully under-stood.[11,12] The risk of developing AD or VaD doubles every five years after the age of 65.[13] Some rare dementias, particularly young-onset dementias, are inherited, and a number of genes have been identified that affect the risk of these conditions developing.[13,14] Lifestyle and other medical conditions may also increase the risk of developing dementia.[15]

UK Dementia Policy and Research Funding

There have been two Prime Minister's 'Challenges on Dementia' in 2012 and 2015, and dementia is a priority for the current government.[16,17,18] A G8 summit in 2013 committed to identifying a cure or disease-modifying therapy by 2025, although an independent report that followed the summit considered this goal challenging.[19,20] Dementia policy is detailed in a House of Commons Library briefing (March 2016).[5]

In 2010, research funding from charities and government was £61 per person with dementia compared to £295 per person with cancer.[7] This results in fewer research positions for dementia specialists in academia compared with other disease areas.[21] Since the first Prime Minister's Challenge on Dementia in 2012, government funding has doubled.[18] However, funding is largely pledged as one-off or short term contributions to projects and researchers call for continued investment to ensure that the projects can continue. Some researchers are concerned about the impact of Brexit on European dementia research funding.

Current Drug Treatments

Drugs that are currently available to treat dementia act to alleviate symptoms, but their benefits are limited. Non-drug interventions are described in Box 1.

Drugs for Cognitive Symptoms

There are two types of drug available on the NHS to treat cognitive symptoms for AD. They are prescribed based on the severity of symptoms:[22]

- **mild-moderate dementia** - donepezil, galantamine and rivastigamine aid communication between neurons and show modest but consistently positive effects on symptoms in clinical trials for AD.[23,24,25,26] Their side effects can be problematic for some people over 85.[26,27]
- **moderate-severe dementia** – memantine blocks the harmful effects of a chemical released in excess in AD.[23] It alleviates symptoms to a lesser extent than the other types of drugs but it has fewer side effects.[22,25]

The National Institute of Health and Care Excellence (NICE) is updating the drug guidelines, and will consider whether there is new evidence that supports their use in patients with VaD, for whom they are not currently recommended.[22,28] NICE will also review whether there is new evidence for whether taking both types of drug offers extra benefit.[28,29]

Around 10% of people with a diagnosis of dementia have a prescription for one of these drugs.[30] A study found that prescription rates are lower in deprived areas of England for several reasons.[31] For example, in deprived areas people attend relatively under-resourced practices. They are also more likely to have other chronic conditions that preclude the use of dementia drugs due to potential side effects.[31]

Drugs for Behavioural Symptoms

Antipsychotics can help control behavioural symptoms like aggression and delusion, but can have serious side effects and increase the risk of premature mortality. Their use is only recommended as a last resort for severe behavioural symptoms.[16,22,30,32,33]

Development of New Drug Treatments

Symptom-Modifying Drugs

Of the 187 new drugs for dementia in development in 2014/2015, 31% were classified as symptom-modifying.[34] A new drug, idalopirdine is being tested in combination with donepezil to see if it provides additional benefit.[35] Early results are expected in late 2016.[59,60] Development of new antipsychotics is also ongoing, such as aripiprazole and brexpiprazole.[60,61]

Disease-Modifying Drugs

No disease-modifying drugs have yet shown significant clinical benefit in trials. However, subsequent analysis of two phase III trials (clinical trial phases are explained in Box 2) of the compound Solanezumab (produced by Eli Lilly) found that the drug may have worked in patients with mild but not moderate Alzheimer's disease (AD).[62] Pathologies can form more than ten years before symptoms emerge, and once a person exhibits moderate symptoms their brain may be too damaged for treatment to have an effect.[63] There is increasing consensus that treatment needs to begin as early as possible, even pre-symptomatically. Trials now focus on early stages of dementia.[64,65,66] Of the potential disease modifying drugs in research and development, over ten are in phase III trials and may become available in the next five years.[60]

Box 1. Non-Drug Interventions

There are a range of cost-effective non-drug interventions to improve the quality of life of people with dementia and reduce the need for long-term residential or hospital care.[10,36,,37,38] The National Institute of Health and Care Excellence (NICE) recommends that support is also offered to the estimated 700,000 unpaid carers of people with dementia in the UK, to support their psychological and physical health.[1] GPs or NHS dementia clinics recommend suitable interventions according to individual needs and preferences. NICE recommends that individual care plans are developed and regularly reviewed. The interventions are commissioned and delivered by the NHS, local authorities, charities such as Alzheimer's Society and Age UK, and private providers.[22,39,40] NICE recommends that these agencies work together to provide a variety of options:

- **Psychological Support** - counselling, cognitive behavioural therapy, and peer support for those with anxiety and depression, including carers.[36,41,42]
- **Functional Support** – approaches that support functional ability to help people with dementia maintain independence and social participation. These include cognitive rehabilitation, occupational therapy and assistive technologies such as memory and communication aids.[37,41]
- **Cognitive Symptom Management** - a number of approaches to support memory, orientation, language skills and well-being, including Cognitive Stimulation Therapy, which uses group activities and physical exercises.[22,41,43]
- **Behavioural Symptom Management** – Person Centred Care to improve communication so that the wishes of the person with dementia are understood.[44,45] NICE recommends that factors causing symptoms such as agitation and aggression should be evaluated and addressed.[22,45,46,47]

Access to Effective Non-Drug Interventions

The British Psychological Society argues that national guidance on what should be available is lacking, leading to local variation and gaps in provision.[36,48] More robust research is emerging about the benefits of non-drug treatments.[46,49,50] New interventions and improved delivery methods are under development.[51,52,53,54,55]The Scottish Government aims to provide at least one year of support to those newly diagnosed with dementia. In England, Government and partners including those from health, social care and the third sector have set out their ambition to 'deliver better quality diagnostic care'.[56,57] The Royal College of Psychiatrists runs a Memory Services National Accreditation Programme to improve services.[17,58]

Box 2. Research and Development Phases of New Drugs

- **Preclinical phases** involve researchers working to understand the disease, identify potential drugs, and test them for safety and efficacy using computational models, cells and animals.
- **Phase I trials** usually focus on the safety of the treatment, tests involve small numbers of people.
- **Phase II trials** test dosage levels and efficacy. They use between twenty and a few hundred patients.
- **Phase III trials** assess the treatment's efficacy in comparison to the best existing treatment, and spot uncommon side effects. They involve large numbers of people.
- **Licensing approval** involves the submission of evidence to regulatory agencies for approval.
- **Phase IV trials** take place once a drug is approved and in use. Trials continue to detect long-term safety and to compare against competitors' products or current medical practice.[67,68]

Potential Treatments

Although several other approaches are in early development,[69,70,71] key treatment areas that scientists are pursuing are:

- **Amyloid β plaques** - the formation of plaques in the brain made from a protein called Amyloid β are a key feature of AD.[62,72] Drugs are intended to break down or prevent build-up of the plaques. A number of phase III trials are underway in patients with mild and pre-symptomatic AD for drugs including Solanezumab (Eli Lilly), Aducanumab (Biogen) and Verubecestat (Merck). The earliest of these trials will report in late 2016.[60]
- **The immune system** - inflammation in the brain and elsewhere in the body triggered by the immune system may cause dementia and also speed up the progression of other features of the diseases.[73,74,75,76] It may be possible to re-purpose anti-inflammatory drugs that are already on the market. Pioglitazone (used for diabetes) is in phase III trials for AD and Etanercept (used for rheumatoid arthritis) is in phase II.[60,77]
- **Tau tangles** - Tau is a protein that supports the structure and function of neurons. In some dementias, such as AD and certain types of frontotemporal dementia, Tau accumulates in tangles, disrupting brain cell function.[78,79] In mice, targeted treatment reduces Tau tangles and prevents cognitive decline.[80] Two drugs, including one that also treats inflammation, are in phase III trials.[60,81,82]

Scientific Challenges of Developing New Drugs

Developing drugs for dementia is challenging because:

- the brain is protected by a barrier that prevents some drugs from reaching it. This means that innovative compounds are required.[12]
- there are different diseases and multiple pathologies (for example tau tangles and amyloid β plaques) involved.[83]

Further research is required to understand them and several initiatives have been established (Box 3).

The Importance of Biomarkers

A successful disease-modifying drug will influence the course of dementia by affecting one or more of the pathologies causing the condition.[84,85] This can be demonstrated using biomarkers – measurable biological indicators of the presence and severity of a disease.[86,87]

Box 3. Examples of Dementia Research Initiatives

New Academic Institutes in the UK

- **UK Dementia Research Institute**[88] - with £150m of government funding and £100M in charitable contributions, it will focus on innovative discovery science to improve understanding of biological mechanisms and support research into diagnosis, treatment, care and prevention.
- **Drug Discovery Alliance**[89] - founded by Alzheimer's Research UK, this three-institute network will take promising targets, confirm their role in dementia and develop treatments to act upon them.

Trials with People who are Pre-symptomatic

- **Dominantly Inherited Alzheimer Network**[90] - an international project pooling people with familial dementia around the world so that sufficient numbers can be recruited. The UK base is at University College London.
- **European Prevention of Alzheimer's Dementia Consortium**[91] - a European register of around 24,000 people known to be at risk of developing AD. Around 1,500 will be selected to take part in clinical trials of preventative drugs.

Co-ordination initiatives in the UK

- **Dementias Platform UK**[92] - a public/private research partnership led by the Medical Research Council using data from 2m people.
- **Dementia Consortium**[93] - a collaboration between third and private sector stakeholders. The consortium accelerates promising research to bridge the gap between academia and industry.

In dementia, biomarkers include levels of amyloid and tau that can be measured in cerebrospinal fluid and with brain imaging.[86] However, it is not yet possible to correlate biomarker measurements with symptoms. Some drugs have been shown to reduce amyloid levels in small phase II trials and so progressed to large phase III trials. However participants did not then see cognitive improvements, suggesting that the change in amyloid level was not sufficient to have an impact on symptoms.[94]

Accurate biomarkers are an essential tool in order to:

- **identify and group suitable participants for trials**. Earlier trials did not screen participants. Some subsequently found that a quarter of participants did not have the expected amyloid pathology meaning that they would not be expected to benefit from a drug targeting amyloid.[62] The different diseases and pathologies mean that drugs will have different outcomes for different people. Trials are increasingly grouping people with specific dementia pathologies so that results can be interpreted with confidence.[34,95]
- **identify people who are at risk of developing dementia**, so that they can be treated pre-symptomatically.[10] This requires ethical consideration as the use of tests to identify pre-symptomatic people is not recommended until a treatment is available.[12]

Some studies working to develop biomarkers focus on inherited (familial) dementias (Box 4). People with a mutated gene known to cause dementia will almost certainly develop dementia at a similar age to their parent. They can be monitored before they develop symptoms to identify biomarkers that represent different symptomatic stages of the disease.[90,96] Researchers warn that caution should be exercised in applying the evidence from familial dementias to other types of dementia.[12,83,97,98]

Box 4. UK Patient Recruitment Initiatives

- **Join Dementia Research**[99] - encourages people to register interest in taking part in research. It is run by the National Institute for Health Research and almost 20,000 people have registered.
- **Cognitive Health in Ageing Register for Investigations, Observations & Trials in Dementia Research**[100] - matches suitable participants recruited through GP practices in London with appropriate trials. It is led by Imperial College London. Over 25,000 people have registered.

The Need for Co-ordination and Data Analytics

Understanding dementia requires analysis of large amounts of data.[9] International collaboration is required due to the resources needed.[97] Trials take place over a long period and must involve large numbers of people if they are to capture the role of different contributory factors. Extensive infrastructure is needed to store and process the data.[9,12,97] A robust regulatory and legal framework is needed for privacy, data access and data standardisation so that study outputs can be shared.[12,101] Future treatment will involve patients taking combinations of drugs targeting multiple pathologies at the same time, meaning that collaboration will be needed between different drug developers.[83,94,102] Box 4 details collaborative initiatives.

Participation in Research

Recruiting people with dementia to clinical trials is challenging. People may not know that they can participate or may be put off by invasive procedures and possible side effects.[103] However those who do agree to take part may do so because they have experience of dementia through friends and family. They may also be motivated to take part in research to help others in the future, to try new treatments, and to learn more about their condition.[104] Alzheimer's Disease International recommends enhancing the connection between NHS clinical practice and research, so that practitioners know about and actively refer patients to trials.[21,103] Two UK recruitment initiatives are described in Box 4. Since participants are selected on the basis of biomarkers that indicate whether the disease of interest is present, not everyone who wishes to participate in a trial will be chosen. For example one study estimates that in order to find 1,000 suitable participants, 5,000 need screening.[83,105]

Risks and Incentives for Pharmaceuticals

Drug development is expensive and takes on average 12.5 years.[67] A recent study found that 0.5% of drugs for AD made it to market compared with the industry average of 4.1%.[106] This makes dementia financially risky for the pharmaceutical industry.[34,107] However, there are over 46m people with dementia worldwide and this figure is expected to rise, meaning that the potential market for a successful drug is very large.[108] Industry research tends to focus on AD as more people are diagnosed with dementia caused by AD.[34] Public-private partnerships, risk sharing agreements and patent extensions can reduce financial risks.[12]

Patient Access to New Drugs

Once a drug is successful in phase III it must be submitted to regulators for approval. It is then usually evaluated by NICE to determine its cost-effectiveness for the NHS. It is likely that the first disease-modifying drug on the market will be for people with mild AD with Amyloid β pathology.[109]

Expediting Drug Licensing Approval

The OECD argues that governments should accelerate dementia research by establishing supportive regulatory pathways to expedite clinical trials and licensing.[12] In 2014, the Medicines and Healthcare products Regulatory Agency (MHRA) launched the Early Access to Medicines Scheme. The scheme enables use of unlicensed drugs for life-threatening or debilitating conditions in areas of high unmet need, and may be appropriate for dementia treatment.[110]

Challenges for Clinical Practice

A disease-modifying drug for dementia is likely to be complex to implement in practice for various reasons:

- **Translation of Efficacy** - efficacy seen in clinical trials may not translate into practice. Trial participants are carefully selected and are often around 70 years old, whereas the median age of dementia onset is 80, and people in this age group often have other diseases that may complicate their treatment.[111]
- **Cost** - new diagnostics and new drug treatments are likely to be more expensive than current symptom-modifying drugs as they are more complex compounds. They will be an additional financial burden on the NHS.[112,113] It falls to NICE to evaluate cost-effectiveness and make comparisons with existing options.[114]
- **Delivery of Care** - some trial drugs, such as Solanezumab, are given as a monthly infusion, which is not a standard procedure for dementia clinics.[115] It is particularly difficult for the NHS to adopt new drugs when service redesign is required.[116]
- **Diagnosis** - biomarkers are needed to identify people suitable for treatment. Amyloid imaging is expensive and cerebrospinal fluid extraction is invasive.[117,118] Research is underway to develop a blood test which would be a cheaper and less invasive test for a first diagnostic test.[9]

Preventing Dementia

Research shows that a third of dementia cases may be attributable to modifiable risk factors.[15] There is some evidence that good vascular health - resulting from regular physical exercise, a healthy diet and not smoking - could reduce the number of new dementia cases.[119] A few studies show that educational level, occupation and engagement in cognitively stimulating activities may have a preventative effect.[120,121] The incidence of dementia is stabilising in the UK. The reasons are not fully understood but could arise from post-war improvements in education and public health. However, rising levels of obesity and type 2 diabetes could reverse this progress.[122,123] Research is ongoing to understand the underlying mechanisms of these contributory factors and how they influence the course of the disease.[124] Public Health England recommends the integration of brain health into prevention programmes for other non-communicable diseases.[124,125]

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