Everyone reading this must wonder, from time to time, whether they are developing dementia. But forgetting where you put your glasses, or what you went upstairs to get, is normal and not unique to older people – and it is not usually a sign of early dementia. Memory loss is just one aspect of dementia, which can be defined as a progressive and significant deterioration in cognition that results in functional impairment and behaviours that cause distress to the individual and others.

Dementia is not one illness but a cluster of symptoms caused by damage to the brain. The commonest symptoms are memory loss in which events in the distant past become easier to remember than recent ones; problems with reasoning, making conversations hard to follow; and emotional distress with feelings of confusion, depression, anxiety and anger especially in unfamiliar environments.

**How common is dementia?**
The total population prevalence among people over 65 years in the UK is about 7 per cent, and there are estimated to be around 850,000 people with dementia. By 2051, the number of people with the condition is expected to rise to over two million in the UK. Dementia contributes to one in four hospital admissions and the health and social costs are more than the costs of caring for people with stroke, heart disease and cancer combined.

Historically, rates of diagnosis of dementia have been low, meaning many people have not received appropriate treatment to manage their condition. A government drive to improve rates of diagnosis has meant that in 2010/11, 42 per cent of people with dementia in England received a diagnosis and by June 2015, this had risen to 62 per cent.

**Is early diagnosis a good idea?**
The arguments for and against early diagnosis of dementia are complex. Early diagnosis means the person can be involved in planning their future care, potentially reversible causes can be identified and treated, other diagnoses...
like depression can be considered and vascular risk factors can be addressed. Nationally, services can be planned and funded. But sceptics argue that there is little evidence to support early diagnosis, it is a potentially distressing diagnosis, services are already overstretched, we may be overmedicalising a common consequence of ageing and we may raise an expectation of effective treatment, when there is none.

The drugs and interventions currently available may address symptoms, but there are no disease-modifying drugs reaching the market yet and certainly no prospect of cure.

**Types of dementia**

Alzheimer’s disease is the most common form of dementia. The relative proportions of the different types of dementia that are diagnosed are:5

- Alzheimer’s disease: 62 per cent
- Vascular dementia: 17 per cent
- Mixed dementia (Alzheimer’s disease and vascular dementia): 10 per cent
- Lewy-body dementia: 4 per cent
- Frontotemporal dementia (Pick’s disease): 2 per cent
- Parkinson’s disease dementia: 2 per cent
- Others: 3 per cent.

**What causes dementia?**

Most cases of dementia have neurodegenerative and vascular causes. Other rarer causes include infections, inflammatory diseases, cancer, toxins, metabolic disorders and trauma. Up to one in five cases of dementia are caused by potentially reversible conditions such as hypothyroidism, vitamin B12 deficiency and Lyme disease.8 A number of conditions can mimic dementia. These include normal ageing, depression, delirium and mild cognitive impairment.7 Validated tests and screening tools such as the General Practitioner Assessment of Cognition (CPCOG) and the Mini-Mental State Examination (MMSE; see Figure 1) are essential in making the diagnosis.

Alzheimer’s disease is characterised by the formation of amyloid plaques and neurofibrillary tangles – made up of amyloid-beta peptide and tau protein respectively – causing damage to neurones in the brain. Vascular dementia is associated with neuronal death in the frontal and/or temporal lobes of the brain.

**Predictive test may offer hope for early detection**

A possible explanation for how the characteristic build-up of amyloid plaques and neurofibrillary tangles progresses in the brain in Alzheimer’s disease has been reported recently.9 Vulnerable areas of the brain show characteristic patterns of proteins that modulate aggregation of amyloid plaques and neurofibrillary tangles.

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<table>
<thead>
<tr>
<th>ORIENTATION</th>
<th>What is the year? Season? Month? Date? Time? ./5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Where are we? Which country? Town? District? Hospital ward/floor? ./5</td>
</tr>
<tr>
<td>REGISTRATION</td>
<td>Examiner names three objects (eg apple, table, penny) and asks the patient to repeat (one point for each correct. Then the patient learns the three names, repeating until correct). ./3</td>
</tr>
<tr>
<td>ATTENTION AND CALCULATION</td>
<td>Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell “WORLD” backwards: DLROW). ./5</td>
</tr>
<tr>
<td>RECALL</td>
<td>Ask for the names of the three objects learned earlier. ./3</td>
</tr>
<tr>
<td>LANGUAGE</td>
<td>Name two objects (eg pen, watch). ./2</td>
</tr>
<tr>
<td></td>
<td>Repeat “No ifs, ands, or buts”. ./1</td>
</tr>
<tr>
<td></td>
<td>Give a three-stage command. Score 1 for each stage (eg “Place index finger of right hand on your nose and then on your left ear”). ./3</td>
</tr>
<tr>
<td></td>
<td>Ask the patient to read and obey a written command on a piece of paper. The written instruction is: “Close your eyes.” ./1</td>
</tr>
<tr>
<td></td>
<td>Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb. ./1</td>
</tr>
<tr>
<td>COPYING:</td>
<td>Ask the patient to copy a pair of intersecting pentagons ./1</td>
</tr>
</tbody>
</table>

**Figure 1.** Mini-Mental State Examination for assessing cognitive impairment (max. score 30)
Can dementia be prevented?

It would seem obvious that one of the ways to prevent dementia should be through the control of risk factors for cardiovascular disease, for example, using statins, antihypertensive drugs and aspirin, alongside lifestyle advice (not smoking, keeping active and a Mediterranean diet).

But the evidence is more complicated. For example, a recent Cochrane review investigating the efficacy of statins in the prevention of dementia concluded that: “There were limitations in the included studies involving the methods of assessment of cognition and the inclusion only of participants deemed to be of moderate to high risk of a problem with their vascular system. Nevertheless, there was good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia.”

In addition, a 2003 Cochrane review found: “No convincing evidence relating type or intensity of diabetic treatment to the prevention or management of cognitive impairment in type 2 diabetes.” The authors urged future research on diabetes treatments to include standardised assessments of cognitive function as outcome measures.

Does diet matter?

There is growing interest in the role of the microbes in our gastrointestinal tracts – the microbiome – and how this impacts on diseases including Alzheimer’s disease. The idea is that microbes break down food in the gut, producing molecules such as short-chain fatty acids that are essential for the health of our immune system and regulation of inflammation, appetite, mood and other processes. We need a healthy and diverse population of gut microbes to ensure good health. A poor diet that lacks variety, use of antibiotics and consumption of processed foods impair the quality of our microbiome.

However, questions remain; do pre- and probiotics that promote a healthy microbiome, decrease the risk of dementia? Which foods and in what amounts should we be recommending? We do not know the answers yet but a focus on encouraging healthy nutrition and avoiding inappropriate antibiotic prescribing is unlikely to do any harm.

What about vitamin supplements?

It is known that micronutrient status can affect cognitive function at all ages. Vitamin deficiencies could therefore influence memory function and dementia. The rationale for vitamin B6 supplementation for people at risk of dementia is that it is involved in the regulation of mental function and mood, and in the metabolism of homocysteine, a risk factor for vascular disease. A Cochrane review found two randomised placebo-controlled trials of vitamin B6 supplements for healthy elderly people but found no beneficial effects on mood or cognitive function, though they appeared to cause no harm either.

Drug treatments

There are currently no interventions that cure or alter the long-term progression of dementia. All of the available drugs offer symptomatic treatment and have modest efficacy but are generally well tolerated.

There are four approved and licensed drugs for Alzheimer’s disease; three are acetylcholinesterase inhibitors (AChEIs): donepezil, galantamine and rivastigmine. These are recommended by NICE as options for the management of mild to moderate Alzheimer’s disease. Memantine (an NMDA antagonist) is recommended by NICE as an option for the management of severe Alzheimer’s disease in those who cannot take AChEIs.

The severity of Alzheimer’s disease can be assessed using several methods, but is frequently defined by MMSE score (see Figure 1), which is scored out of 30 and interpreted as follows:

- Mild Alzheimer’s disease: MMSE 21–26
- Moderate Alzheimer’s disease: MMSE 10–20
- Severe Alzheimer’s disease: MMSE <10

NICE adds that treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global or behavioural symptoms. Treatment must be initiated by a specialist but can be continued by GPs under a shared-care agreement.

Rivastigmine is also licensed for the treatment of mild to moderate dementia in idiopathic Parkinson’s disease (see Table 1).

Existing drug treatments that show promise

Dr Louise Walker of the Alzheimer’s Society says: “Where we really need a breakthrough is in the development of treatments that can modify the underlying causes of dementia, as opposed to those that help with its symptoms, which is all current treatments are able to do. Unfortunately, clinical trials of disease-modifying treatments have produced disappointing results so far, so we look forward to further developments in this area.”

A promising route is researching whether drugs currently used to treat other conditions may also be of benefit to people with Alzheimer’s disease. For example, the Alzheimer’s Society...
is involved in trials to find out whether the GLP-1 agonist lixoglutide used in the treatment of type 2 diabetes15 or the anti-TNF drug etanercept currently used for rheumatoid arthritis could benefit people with Alzheimer’s disease.16 In addition, the role of the phosphodiesterase (PDE) 5 inhibitor tadalafil, used in the treatment of erectile dysfunction, is being tested in an early-phase trial to see whether it leads to increased blood flow to the brain with potential benefits in vascular dementia.17

“There are also some trials that are looking at boosting the effects of existing Alzheimer’s disease treatments, for example donepezil, to help them to work better,” adds Dr Walker.

The role of genetic testing

There are many different forms of dementia and it is only in a very few cases – fewer than 1 in 1000 – that genes play a part, explains Dr Walker.

“The most common gene known to impact on someone’s risk of developing dementia is called APOE, and the way it does so is not straightforward. One variant of the gene, APOE4, is known to increase your risk of Alzheimer’s disease, but carrying it does not mean that you necessarily will develop the condition. There is therefore no sure-fire way of knowing via a genetic test whether you will develop the more common form of Alzheimer’s disease or not, and therefore this type of testing tends not to be recommended.”

What new drugs are there in the pipeline?

Excitingly, the number of clinical trials for new dementia drugs has almost doubled in three years, and there are currently quite a few drugs in various stages of clinical trials. One is solanezumab, a monoclonal antibody targeting amyloid-beta.18 Earlier trials showed promising results in Alzheimer’s disease; however, in the latest clinical trial, EXPEDITION 3, solanezumab failed to meet the primary endpoint of slowing cognitive decline.

Dr Walker also cites aducanumab, another monoclonal antibody that targets the aggregated form of amyloid-beta to clear amyloid plaques.19 “This drug has shown some promise but we need to wait for the results of an ongoing phase 3 clinical trial, due in 2018, to find out how effective it is and if its potentially serious side-effects can be controlled.” Recently, a phase 3 trial of the tau aggregation inhibitor drug LTMX produced disappointing results, with the drug failing to meet the primary endpoints as an add-on therapy, but further results of its efficacy as monotherapy are awaited within the next year.

“The main questions these drug trials aim to answer is what aspect of the condition to target and when. Some drugs target amyloid-beta, some target tau protein and others focus on targeting the immune system or the metabolism of glucose in the brain. All these are thought to be important factors in the development of dementia,” says Dr Walker.

Will there be a vaccine?

A clinical trial is underway to assess a potential vaccine that targets tau protein in the brains of people with Alzheimer’s disease.20 Scientists at the Research Institute for the Care of Older People (RICE) are hoping that the vaccine will prevent the build-up of neurofibrillary tangles in the brain and potentially remove them. The trial will look at whether the drug is safe for people with mild to moderate Alzheimer’s disease. Researchers hope that it could potentially slow or halt the progression of the condition.

The quest for disease-modifying drugs

Dr Walker points out that there is increasing evidence that Alzheimer’s disease may actually begin to develop decades before its symptoms start to show, which is why it is so important that we explore the opportunities to develop drugs that modify the disease itself and stop Alzheimer’s in its tracks.

GPs and other primary healthcare providers are well placed to encourage people at high risk or in the early stages of dementia to take part in clinical trials investigating new drugs and other interventions. The easiest way to get involved is by signing up to the NHS Join Dementia Research service.21

References


**Declaration of interests**
None to declare.

*Dr Robinson is a GP and health writer*