Dementia is a common condition. The average time from diagnosis to death is eight to 10 years. However, it may be many years from the time the first symptoms are noticed to the actual diagnosis. Dementia does not just affect memory; it has an impact on function, speech, swallowing, mobility and continence, which worsen as the condition progresses. The resulting care needs place huge social and economic costs on individuals and society.

At a dementia summit held in London in December 2013, leaders from the G8 countries — which include the UK and the US — recognised that 36 million people worldwide have the disease and predicted this number to double every two decades.

As well as agreeing to increase the amount spent on dementia research significantly, with the aim to identify a cure or a disease-modifying therapy by 2025, the G8 countries agreed the development of an international action plan for research, which will include the sharing of information and data.

Cost
In 2010, the total estimated worldwide cost of dementia was $604bn. This was around 1% of the world's gross domestic product, varying from 0.24% in low income countries to 1.24% in high income countries. If dementia care were a country, it would have the world's 18th largest economy.

In the UK, dementia costs were approximately £23bn per year by 2012. This did not include the cost borne by carers, which was estimated to be around £8bn.

Prevalence
By 2012, almost 800,000 people in the UK were living with dementia, equating to just over 1% of the population, with approximately 17,000 of patients being under the age of 65 years. This total is set to rise as the population ages and has been estimated to reach one million by 2021 and 1.7 million by 2051.

SUMMARY
The prevalence of dementia is increasing with age and the social, carer and economic effects of this are now being recognised worldwide. Alzheimer’s disease is the most common type of dementia and is characterised by atrophy and loss of neurones in the areas of the brain that are associated with memory and cognition. Symptoms of dementia include memory loss, disorientation and losing the ability to perform core activities of daily living.

The diagnosis of dementia is reached by the exclusion of other conditions, since there are currently no specific diagnostic investigations available. Although some risk factors are fixed, others may be modifiable. Since these modifiable risks are also implicated in other conditions such as cardiovascular disease and stroke, pharmacists can encourage their reduction as part of healthy lifestyle advice.

Nevertheless, a recent study in the UK indicates that the prevalence of dementia is falling. Figure 1 (p35) shows 2012 UK dementia prevalence by age group.

Two-thirds of people with dementia live in their own homes while the other third live in care homes. Some 64% of care home residents have dementia and around a quarter of hospital beds are occupied by people with some form of dementia.

Clinical features and diagnosis
The International Classification of Diseases 10th revision (ICD-10) defines dementia as “a syndrome due to disease of the brain, usually of a chronic or progressive nature, in
which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capability, language and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour or motivation."

The symptoms of dementia can be divided into three stages of severity (see Box 1). It should be noted that dementia involves more than forgetting; there must be at least two losses of higher functions and these must be affecting activities of daily living.

Behavioural and psychological symptoms of dementia (BPSD) occur in 90% of people with the condition at some point in their illness. BPSD is an umbrella term describing non-cognitive symptoms, such as verbal and physical aggression, agitation, psychotic symptoms (hallucinations and delusions), sleep disturbances and wandering. (See accompanying article, p40.)

A diagnosis of dementia is usually made by taking an accurate history from the patient and his or her carer, which can be supported with cognitive testing.

According to the National Institute for Health and Care Excellence, clinical cognitive assessment for people with suspected dementia should include examination of attention and concentration, orientation, short and long-term memory, language and executive function. Formal cognitive testing using a standardised instrument — such as the "mini mental state examination" (MMSE) — should take place as part of this assessment. Alternative tools include the "six-item cognitive impairment test" (6-CIT), the "general practitioner assessment of cognition" (GPCOG) and the "seven-minute screen".

NICE says that clinicians who interpret cognitive testing scores should take account of other factors that can affect performance, including educational level and skills, language and previous level of functioning, as well as any sensory impairments, mental illness or physical or neurological problems.

Despite advances in radiology and cerebrospinal fluid testing, there are no specific investigations that can be used to make a diagnosis of dementia. NICE recommends that a structural scan, using magnetic resonance imaging (MRI) or computed tomography, is taken to exclude space-occupying lesions and normal pressure hydrocephalus.

Blood tests can be carried out to exclude hypothyroidism, vitamin B12 deficiency and more common comorbid conditions, such as diabetes or anaemia.

**Pathophysiology**

Figure 2 (p36) shows the proportions of people in the UK with the various forms of dementia, described in more detail below.

**Alzheimer’s disease** Alzheimer’s disease is the most common type of dementia. It is characterised by atrophy and a significant loss of neurones in areas of the brain primarily associated with cognitive function and memory, such as the cerebral cortex. Classic features are neuritic plaques and neurofibrillary tangles.

Neuritic plaques are spherical structures consisting of a central core of fibrous protein, known as amyloid, that is surrounded by degenerating or dystrophic nerve endings (neurites). The amyloid protein contains a 39–42 amino acid peptide, beta-amyloid (Aβ), that is derived from a larger amyloid precursor protein (APP) molecule. It is thought that abnormal processing of the APP molecule results in fragments, the most toxic of which is the Aβ1–42 peptide. This peptide readily forms insoluble clumps in the brain and it has been suggested that this triggers a cascade of events leading to neuronal dysfunction and death.

Neurofibrillary tangles are found inside neurones. They are composed of paired helical filaments of hyper-phosphorylated microtubule-associated tau protein. The
intracellular deposition may cause disruption of normal cell architecture, leading to cell death.

Until recently, most people received a putative diagnosis of Alzheimer's disease or vascular dementia. However, new research has changed the subtyping of dementia considerably. According to two large studies, most people who were found to have the pathophysiological indicators of Alzheimer's disease on post-mortem (ie, amyloid plaques and tau protein tangles) had not shown signs of dementia when alive.

In contrast, 80% of people who were found to have indicators of Alzheimer's disease, but who also had signs of vascular damage (especially deep white matter infarcts), had shown clinical symptoms of dementia when they were alive. This suggests that most patients diagnosed with Alzheimer's disease may have mixed Alzheimer's and vascular dementia, pathologically.11,12

Other studies, involving MRI and lumbar puncture, have found that most of the amyloid deposition predates the clinical diagnosis of dementia by years, sometimes even decades, leading to the theory that for a person to show the clinical syndrome of dementia there has to have been another insult to the brain such as vascular damage or delirium.13-15

Vascular dementia
The pathology of vascular dementia shows multifocal and diffuse lesions; damage can be caused by small strokes or injury to vessels from high blood pressure. Vascular dementia affects neuronal networks involved in cognition, behaviour, execution and memory.16,17

Where there is a series of strokes the condition may appear to progress in steps; decline may also appear gradual with progressive damage.

Memory may be more intact than in some other forms of dementia, depending on the area of the brain that is impaired. Emotional lability, including depression, may be seen, as well as physical symptoms such as apraxia, slurred speech, dizziness and inability to recognise objects.

Lewy body dementia
Pathologically, Lewy body dementia and dementia in Parkinson's disease can be considered the same condition. In Lewy body dementia, the cognitive signs start first; for dementia in Parkinson's disease, the motor symptoms of idiopathic Parkinson's disease predate the dementia. One-third of Parkinson's disease patients will develop dementia.18

The underlying brain changes of Lewy body dementia involve clumping of the protein alpha-synuclein in the brain. These clumps are the "Lewy bodies" that give the condition its name. The occurrence of Lewy bodies in the cerebral cortex of demented patients was first recognised in 1961.19

There are many features shared with Alzheimer's disease. The loss of cholinergic neurones is thought to be involved in problems with cognition, whereas the loss of dopaminergic neurones in the substantia nigra is postulated to account for the degeneration of motor control.

Unlike in Alzheimer's disease, memory impairment is not necessarily a prominent early feature of Lewy body dementia, but it will usually appear with progression of the disease. Instead, prominent early symptoms include confusion, as well as deficits in attention, executive function and visuospatial ability.20 These can lead to falls, visual hallucinations and other psychiatric symptoms.

There are three core diagnostic features:
Dosage and administration: Setofilm is indicated for oral use. The film should be placed on the tongue and will disintegrate without water in a few seconds. Setofilm may be recommended in patients with an enhanced risk of aspiration and in patients that experience difficulties in swallowing. Adults and elderly: The dose of ondansetron should depend on the indication. Emetogenic chemotherapy and radiotherapy. 8mg 1 to 2 hours before treatment, followed by 8mg 12 hours later. After 24 hours, 8mg twice daily may be continued for up to 5 days. Highly emetogenic chemotherapy 24mg taken with oral dexamethasone sodium phosphate 12mg, 1 to 2 hours before treatment. After 24 hours, this may be followed by 8mg twice daily for 5 days. Prevention of PONV 16mg one hour prior to anaesthesia or 8mg 1 hour prior to anaesthesia, followed by a further 2 doses of 8mg at 8 hourly intervals. There is limited experience on the use of ondansetron in elderly patients. Contraindications to Setofilm in patients with moderate to severe impairment of hepatic function. The maximum daily dose should not exceed 8mg. Children: The dose for treatment of CINV is calculated based on body surface area (BSA) or weight – see table 1. The dose may be continued for up to 5 days and must not exceed adult dose of 32mg. Selectively administered 4mg and 8mg orodispersible films. Abbreviated Prescribing Information PRESCRIBING

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Setofilm 4mg and 8mg orodispersible films. Ondansetron may reduce the analgesic effect of tramadol. Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Use with cardiotoxic drugs may increase risk of arrhythmias. Pregnancy and lactation: Use in pregnancy or breastfeeding is not recommended. Side effects: A very common side effect reported is headache. Common side effects are sensation of warmth or flushing and constipation. Other effects that have been reported are hypersensitivity reactions, including anaphylaxis, transient visual disturbances, QT prolongation, arrhythmias. For full list and frequency of adverse events, consult with the SmPC.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals Ltd on 01895 826606.

References:
2. MNS, May 2013.

Date of preparation: July 2013. SE/1650/JUL/13.
Fluctuating cognition with pronounced variation in attention and alertness

Recurrent visual hallucinations (typically well formed and detailed)

Spontaneous features of Parkinsonism

Two of these should be present for a diagnosis of probable Lewy body dementia, whereas one should be present for a diagnosis of possible Lewy body dementia. Supportive features are often present, but these alone are not sufficient for diagnosis. They include: repeated falls and syncope; transient, unexplained loss of consciousness; severe autonomic dysfunction (eg, orthostatic hypotension and urinary incontinence); non-visual hallucinations; systematised delusions; depression; and rapid eye movement sleep disorders.

Clinically, Lewy body dementia presents as a subcortical dementia with slowness of cognition. Rushing patients during testing can make them appear more impaired than they are and if given time they will often provide correct answers. Illusions are also common when the person misperceives visual cues; for example, seeing trees move in the wind could be perceived as green soldiers.

Frontotemporal dementias Frontotemporal dementias affect the front of the brain. They usually occur at an earlier age, the peak incidence being 55 to 65 years, and can present with disinhibitive, apathetic and language effects rather than memory loss. Primary progressive aphasia is the type of dementia where outward speech decreases; in semantic dementia there are failures in understanding language.

Other dementias Alcohol does not cause a progressive dementia but it can cause cognitive damage, particularly Korsakoff’s psychosis.

In mild cognitive impairment (described as mild cognitive disorder in ICD-10) there is subjective and objective loss of cognition, but no interference with functional ability. Mild cognitive impairment was originally suggested to be an early stage of dementia; however, it has an uncertain prognosis and can be associated with subsyndromal anxiety or depression, harmful alcohol use, concurrent medication and brain damage.

Risk factors

The chances of developing dementia increase with age. Except in the rare genetic forms of the illness, there is no single risk factor but rather an accumulation of factors that lead to dementia. Most risk factors are cardiovascular, because older people show mixed Alzheimer’s and vascular changes on post-mortem, and it is thought to be the latter that tips people from being asymptomatic to having clinical signs of dementia.

Genetic In some cases, early-onset Alzheimer’s disease is caused by mutations in the APP gene and the two presenilin genes PSEN1 and PSEN2. People with any of these extremely rare mutations tend to develop Alzheimer’s disease in their 30s or 40s.

For later onset Alzheimer’s disease, the gene with the most known impact on the risk of development is apolipoprotein E (APOE). There are three isoforms of this gene: APOE-ε2, APOE-ε3 and APOE-ε4. Everyone has two copies of the APOE gene, which means that there are six genetic combinations. Having one copy of APOE-ε4 increases the risk of developing dementia fourfold compared with the average, but having two copies increases it 10-fold. In contrast, APOE-ε2 may be protective, and people carrying this gene are less likely to develop dementia until late in life.

Down’s syndrome People with Down’s syndrome often develop the plaques and tangles commonly seen in Alzheimer’s disease. One in three people with Down’s syndrome will show symptoms of dementia by the age of 60 years.

People with learning disabilities are also at higher risk of displaying early-onset dementia (three to four times more likely than the general population) and having a rapid progression of the condition. Men with limited education may be at increased risk of developing dementia.

Hypertension The vascular dementia arm of the “systolic hypertension in Europe” (Sys-Err) trial investigated whether antihypertensive drug treatment could reduce the incidence of dementia. The results showed that such treatment was associated with a lower incidence of dementia, suggesting that if 1,000 patients with high blood pressure were treated with antihypertensive medicines for five years, 19 cases of dementia might be prevented.

Cholesterol Elevated levels of low-density lipoprotein cholesterol have been shown to be an independent risk factor for the development of dementia with stroke. However, no association has been found between lipid levels and the risk of Alzheimer’s disease, suggesting that cholesterol might be more closely linked with dementia that has a vascular component.

Diabetes Diabetes is associated with a reduction in cerebral perfusion due to micro- and macrovascular changes, often resulting in infarctions. People with diabetes are therefore considered to have an increased risk of developing vascular dementia.

Obesity Obesity is a risk factor for cardiovascular disease and stroke, which impacts on the chances of developing dementia from vascular damage.

Depression People who experience depression in later life, or have a history of depression, are more likely to develop dementia. However, the relationship between depression and dementia remains unclear. Some researchers consider that depression is a risk factor for dementia, whereas others believe it may be an early symptom of the disease. Depressive symptoms have been shown to increase the risk of subsequent cognitive decline. Nonetheless, although depression is common in early dementia it is not a predictor of Alzheimer’s disease.
disease.16 High levels of cortisol might be associated with depression, and indeed stress, and might also cause neuronal death.18

Alcohol Several studies have shown an increased risk of vascular dementia in patients with a history of alcohol misuse, but not all research supports this. Some studies have shown that a light to moderate consumption of alcohol could have a protective effect.19,20

Smoking Smoking was shown to be a risk factor for dementia in one major study;21 whereas another did not show any association.22 However, the latter could be explained by the decreased life expectancy of smokers offsetting the raised prevalence of dementia with increasing age.

Aluminium The relationship between Alzheimer's disease and aluminium is difficult to assess. Epidemiological studies were instigated in response to the observation of aluminium within plaques and tangles.23 Aluminium can cause abnormal phosphorylation of tau protein. Although initial studies linked aluminium toxicity with Alzheimer's disease, the link has not been proven increases despite continuing investigation. Importantly, there is no evidence to suggest that aluminium exposure increases the overall risk of dementia.24

Exercise Exercising three times a week or more reduced the incidence of dementia from 19.7 to 13 per 1,000 person years.25 This may be due to increased blood flow and perfusion to the neurones and improved neuronal connectivity. Brain cognitive networks studied using functional MRI show improved connectivity after six to 12 months of exercise.26

Delirium Delirium is common on acute wards and in intensive care settings, and diagnosis should be differentiated from dementia to ensure appropriate management. There is possibly an increased risk of developing dementia where delirium has been diagnosed, especially in older people, among whom an eightfold increase in the diagnosis of dementia after delirium has been found; this is also associated with faster cognitive decline.27

Reducing risk Growing evidence suggests that brain health is closely linked to heart and blood vessel health. The risk of developing dementia appears to increase as a result of many conditions that damage the heart or blood vessels. These include high blood pressure, heart disease, stroke, diabetes and high cholesterol levels. Therefore, the prevention and treatment of modifiable risk factors will be important in the future for reducing the impact of dementia on individuals and on society.

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