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Dementia

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Case study and questions

Day 1 Mr LD, a 76-year-old retired sales manager, attended a memory clinic at his local district general hospital with his wife. He had a 2-year history of aphasia, mild memory difficulties and problems with activities of daily living (ADL). His wife reported that he needed help in dressing appropriately, often putting on pyjamas or suits at the wrong time of day unless she laid out his outfits each morning and evening. She said that he also used to be the one who looked after all the household bills, but now he just ignored bank statements and had also misplaced his chequebook and wallet.

His Mini-Mental State Examination (MMSE: Folstein) score was 27/30 and the ADL score was 17/20. He exhibited no extrapyramidal signs, had no medical history of note and scored 12 on the Hamilton Depression (HAMD) rating scale. His blood pressure was 135/75 mmHg, pulse 75 beats per minute (bpm), capillary blood sugar 4.6 mmol/L, and his urea and electrolyte levels were all within normal ranges. Tests for folate, B₁₂, haemoglobin, thyroid and liver function were also all within normal ranges.

- Q1** Briefly describe the purpose and function of the MMSE, ADL and HAMD rating scores.
- Q2** What is the purpose of the other baseline measures assessed for Mr LD?

Mr LD agreed to start an antidepressant and attend the memory clinic once a month for review. He was given information on ways in which he could improve his memory and a prescription for fluoxetine 20 mg each morning.

- Q3** What is the purpose of trying to improve Mr LD's memory?
- Q4** Was fluoxetine therapy appropriate for Mr LD?

Month 3 Mr LD arrived for the day dressed in his pyjama bottoms and a shirt and tie. He was adamant that he had been brought against his will and that there was nothing wrong with him, and he accused the ambulance driver of stealing his wallet. He became very agitated and displayed mild symptoms of aggression (shouting and pacing up and down) until one of the nurses distracted him with a photo-album depicting London in war time. Eventually he agreed to see the doctor. His MMSE score was now 25/30, the HAMD score 5, ADL rated 12/20 and his ADAS-cog score was 22.

A computed tomography (CT) scan showed enlarged lateral ventricles, widening of the sulci and atrophy of the medial structures, in keeping with a neurodegenerative disorder. No space-occupying lesions or cerebral ischaemia were seen.

- Q5** What is an ADAS-cog score, how is it calculated and what is the relevance of the final score?
- Q6** What is the relevance of the CT results?
- Q7** What is the probable diagnosis for Mr LD and how can it be confirmed?

Mr LD's wife was contacted and asked if she could accompany her husband to his next memory clinic appointment. At this appointment, they were both informed that Mr LD probably had Alzheimer's disease (AD).

- Q8** Why is an early diagnosis of AD better for the individual and family?
- Q9** What are the pharmacological treatment options for Mr LD?
- Q10** What therapy would you recommend? Outline a dosing and monitoring schedule.
- Q11** Outline a pharmaceutical care plan for Mr LD.

Month 7 Mr LD had his 3-monthly assessment after starting rivastigmine. He had complained of feeling nauseous and dizzy when the rivastigmine was initially started, but he had eventually tolerated the dose increases until the last increase to 4.5 mg twice daily, when he had begun to vomit and feel unwell. On observation he was lethargic and pale and reluctant to speak. He refused to complete any of the assessment scales because he was feeling so poorly.

- Q12** What is the possible cause of these side-effects and how might they be treated?

Mrs LD asked whether her husband should take any herbal remedies, as she had heard at the Alzheimer's Society carer support group that they could help.

- Q13** What is the role of ginkgo biloba and other dietary supplements in the symptomatic treatment of AD?

Month 8 Mr LD was looking much brighter and was telling the nursing staff about his day out to the zoo with his great-grandchildren at the weekend. His MMSE score was now 24/30, ADL rated 16/20 and the ADAS-cog score was 18. His wife thought that he ‘was doing brilliantly’, and that he seemed much happier and contented in himself.

Month 12 Mr LD was admitted to a general medical ward with deteriorating cognitive function and increasing confusion. That morning Mrs LD had woken up to find her husband was missing from their bedroom. She could not find him downstairs, then had heard ‘banging noises’ coming from the upstairs bedroom. She found Mr LD in the front bedroom wardrobe ‘hiding from the enemy soldiers outside’. Mr LD’s general practitioner (GP) arranged his admission to hospital for further investigation.

On examination Mr LD was increasingly confused and would not settle for a full physical examination. Observations noted were: a temperature of 39°C, an empty bladder and no signs of constipation. He had an increased respiratory rate, with a ‘chesty’ cough and crepitations at the left base.

He then became extremely anxious and ‘escaped’ from behind the curtains to the safety of the corridor near the nurses’ station. He now believed that he was back in the army and had to ‘take control of the lake’ to protect everybody. He would not allow anyone to come near him, and was having conversations with an imaginary person he referred to as ‘Captain’.

Q14 What is the likely diagnosis for Mr LD?

Q15 Would you recommend antipsychotic therapy for Mr LD at this point?

Two days later Mr LD’s cognitive symptoms had resolved and his temperature was now normal. Antibiotics had controlled his chest infection and he now wanted to go home to be with his wife. He complained that the ward was ‘full of old people’.

Month 24 Mr LD’s dose of rivastigmine had been increased 3 months earlier to the maximum licensed dose of 6 mg twice daily. This was in response to a fall in his MMSE, ADAS-cog and ADL scores. Since then there had been no improvement in the scores (MMSE 14/30, ADAS-cog 38 and ADL 8/20), but no further fall in scores. His wife was distressed because Mr LD was now very agitated and shouted at her for bringing ‘strangers into the house’. (The strangers were his grandchild and great-grandchildren.) He had started to wander aimlessly from room to room and seemed

unable to settle. He had also been having increasingly frequent episodes of urinary incontinence, and Mrs LD was feeling 'at the end of my tether'.

Q16 What are the next therapeutic options?

Q17 What care issues are necessary for Mrs LD?

Month 40 Mr LD was now very frail (he had lost 8 kg since the first diagnosis of probable AD). He had been admitted to a nursing home 3 months earlier when Mrs LD no longer felt able to cope. Although his medication of memantine 10 mg twice daily had been continued after admission, he now no longer seemed to be aware of his surroundings. He no longer recognised his wife or any of his family. Increasingly he had been calling for his mother, getting very agitated in the evenings, and had difficulty sleeping. He was often observed 'talking' to an imaginary person who sat at the end of his bed. His speech was rambling and confused, and mainly incoherent. He was also now doubly incontinent and unable to feed himself successfully.

Q18 How might Mr LD's increasing agitation and hallucinations be controlled?

Q19 Outline a pharmaceutical care plan for the treatment of double incontinence.

Q20 When might pharmacological treatment for Mr LD be withdrawn?

Answers

Briefly describe the purpose and function of the MMSE, ADL and HAMD rating scores.

A1 **These provide a baseline measurement of a patient's cognitive function, orientation in time, space and place and ability to carry out ADL. They also ascertain whether clinical depression is present.**

- (a) **MMSE.** The Folstein MMSE tests eight domains of cognitive function, including orientation, memory, recall, language and attention. It takes 10–15 minutes to complete. It is scored from 0 (lowest) to 30. A score of 27–30 = normal cognitive function, 21–26 = mild dementia, 10–20 = moderate dementia (10–14 = moderately severe dementia) and <10 = severe dementia.

In September 2006 the MMSE scoring outlined was proposed by a National Institute for Health and Clinical Excellence (NICE) health technology assessment as an indicator of when to start or to stop a person on a cholinesterase inhibitor (ChEI). In October 2006 the Royal College of Psychiatrists published guidance on behalf of

several parties reminding prescribers that MMSE scores can fluctuate from day to day, and that prescribing decisions should be made in 'the light of the individual patient's circumstances'. For people of previously low intellect the MMSE was ruled as discriminatory in England and Wales as it gave an inadequate reflection of cognitive status as individuals may end up with a score that reflected mild or even moderate dementia because they had never known the information. Increasing evidence from clinical practice demonstrates that its use in people of high intellect can give false negatives. More recently the Folstein MMSE has been copyrighted and is not as freely available for use.

Other tests with similar function include the Abbreviated Mental Test Score (AMTS), e.g. Hodkin's, which takes less than 4 minutes to complete. It is scored from 0 (lowest) to 10, with 7 or less indicating cognitive impairment. Also the HoNoS65+ (Health of Nations Outcome Scale 65+) is increasingly being used in practice.

The results of these tests help to establish the level of a person's cognitive impairment. Where a shortfall in performance is seen within a particular domain, the effect on day-to-day activities such as following commands, orientation to time, person and place or the ability to remember new concepts can be determined.

These tests are not without drawbacks. For example, English needs to be the patient's first language. Also, if patients being tested have learning difficulties or a poor educational background, they may never have known the answers to some of the questions. The tests are also relatively insensitive to change; however, there is proven sensitivity to the effects of ChEI therapy compared to placebo in mild to moderate AD. There is also a proven statistically significant inverse correlation between the MMSE score and the ADAS-cog score (see A5). This means that, as the MMSE score decreases (reflecting increasing severity of cognitive impairment and/or dementia), there is an increase in the ADAS-cog score (reflecting an increasing severity in the AD). However, a significant point is that people with dementia experience wide fluctuations in their day-to-day behaviour and cognitive function. Therefore, decision making purely on the results of a single test should be undertaken with great caution. Any clinical decision should also include the views of the person with dementia (if capacity for consent can be established) or carer (with the consent of the person with dementia). This is because the response to medicines can affect global aspects of the person's life, including language, speech, social interactions and ability to complete daily tasks.

- (b) **ADL.** In a clinical setting the Barthel Assessment scale rates the patient's ability to complete basic ADL. These include dressing, continence, grooming, eating, bathing and walking. It is scored out of a total of 20 (best outcome). A score <16 is associated with the need for care services or carer support. It must be remembered that, as cognitive function declines, the ability of the patient to perform physical tasks will also decline because the memory is no longer present for that particular task.

Complicated ADL can also be rated, and include shopping, cooking, finances and keeping appointments.

- (c) **HAMD.** Severe depression may present with the same symptomatology as a dementia (e.g. slowing down, memory loss, social withdrawal, low mood or personality change). These symptoms may also be reflected in low MMSE and/or ADL scores. When depression presents in this fashion it has often been referred to as a 'pseudo-dementia'. However, evidence suggests that it may in fact be a prodromal symptom of the onset of a dementia and regular follow-up and monitoring are advised. Because depression is eminently treatable and effective treatment reduces the associated morbidity and mortality, every patient suspected of having cognitive dysfunction, including dementia, should be assessed for depression. The HAMD scale rates a series of 17 domains ranging from mood to insomnia to anxiety and somatic symptoms. These are then attributed a score. A score of 0–7 = absence of depression, 8–17 = mild depression, 18–25 = moderate depression and >26 is associated with a severe depressive episode. Other scales include the Geriatric Depression Scale (GDS).

It is increasingly common that all people with a suspected dementia will undergo full psychological testing with an experienced clinician. The results from these in-depth tests can identify where the key deficits are in the individual's cognitive impairment and then recommend ways in which these could be addressed.

What is the purpose of the other baseline measures assessed for Mr LD?

A2 **These results (if normal) rule out the presence of a treatable cause for the cognitive disturbance.**

Cardiovascular assessment should include blood pressure monitoring, heart rate (undiagnosed arrhythmia), heart failure (possible hypoxia) and history of stroke or ischaemic disease (cause of cerebral ischaemic lesions associated with vascular dementia: VaD).

Biochemical monitoring should include blood glucose (to detect hypoglycaemia or untreated diabetes), serum urea and creatinine (renal

failure is a rare cause of cognitive decline), serum electrolytes (hyponatraemia and hypercalcaemia are a common cause of cognitive dysfunction, including delirium in the elderly, and are often medication-related), and haematological indices such as haemoglobin, folate and B₁₂ levels (severe anaemias of any type may produce cognitive impairment in the elderly, and these should be treated if detected). Thyroid function should also be assessed, as hypo- and hyperthyroidism can be associated with cognitive abnormalities. Liver function tests are generally done to complete the work-up and to establish baseline levels when starting certain pharmacological treatments.

A full physical and medical examination is also necessary, as making a diagnosis of probable AD is one of exclusion. All other possible causes for the symptoms observed should be eliminated. Common causes of cognitive dysfunction (especially delirium) in the elderly include infection (urinary, chest or skin); less common causes are human immunodeficiency virus (HIV) or syphilis and concomitant medication (especially on initiation or withdrawal of an agent). The use of alcohol or other illicit substances must also be asked about. Older people frequently self-treat with these agents.

Results from all of the above tests can help with the diagnosis of the type of dementia, which is increasingly reliant on the need for baseline criteria. AD is the most common form of dementia, with some sources stating it accounts for about two-thirds of all cases of dementia. New evidence suggests that it only accounts for 50% of cases, with VaD accounting for a further 25%. Furthermore, it is suggested that, included within these two categories, 25% will have a mixed AD and VaD picture. Dementia with Lewy bodies (DLB) accounts for 15% of all diagnoses and all other dementias account for the rest.

What is the purpose of trying to improve Mr LD's memory?

A3 **Memory dysfunction is a common complaint in ageing. This dysfunction may not be related to a neurodegenerative process.**

Often older people complain about changes in their memory. This may or may not be associated with changes after formal cognitive assessment. If minor changes are found but nothing else of note, the person is said to have age-related cognitive decline (ARCD). If slightly more abnormalities are found but insufficient to make a diagnosis of probable dementia, then the person is said to have mild cognitive impairment (MCI). There are two forms of MCI: non-amnesic (primarily affecting thinking skills) and amnesic (more associated with memory impairment). It has been

proposed that the prodromal period of AD is typically a 9-year decline in cognitive function, and part of that decline may possibly include a diagnosis of amnesic MCI.

Giving people with ARCD or amnesic MCI guidance on how to remember things and/or improve memory allows them some control over their symptoms, but also these skills may normalise the initial symptoms. Such memory guidance includes:

- (a) The use of diaries or notebooks to act as memory aids.
- (b) Repeatedly practising a task.
- (c) Using alarm clocks or mobile phone alarms to remember appointments (with a note by the clock of the reason for the alarm). Advanced mobile phone technology means that daily activities can be structured into a routine using phone apps which include a prompt of what to do.
- (d) Using strategies such as mnemonics to remember an action plan (although sometimes only the mnemonic can be remembered, and not the reason why it is remembered).
- (e) When being introduced to new people, to repeat their name immediately once or twice to ensure that it enters the memory. Then, when speaking to the person, to use the person's name in the sentence.
- (f) To concentrate on things that are important to remember and ignore the less important, e.g. keep telephone numbers in a telephone book for referral.
- (g) Establish routines for placing frequently 'lost' items, e.g. always place car keys in a specific place, or carry spectacles on a neck chain so they cannot be lost.
- (h) There is increasing evidence that keeping the brain active by memory-enhancing activities such as crosswords and Sudoku-type puzzles, 'brain teasers' (computerised or written) and other activities can enhance cognitive function and improve memory.
- (i) Keeping physically active helps to restore cerebrovascular circulation.
- (j) To admit to others that there is a problem with short-term memory and ask for assistance and prompting.

Patients should be offered general public health advice which may also help, such as increasing exercise – improved cardiovascular function means improved cerebrovascular function – stopping smoking, maximising cardiovascular and diabetic medicines, reducing weight, improving diet and checking alcohol usage.

Was fluoxetine therapy appropriate for Mr LD?

A4 **Yes. An antidepressant is indicated. Mr LD had an HAMD score that indicated mild depression. The choice of an antidepressant in an elderly patient is dependent on comorbidity and concomitant medication. In patients with cognitive impairment it is best to select an agent with fewer anticholinergic side-effects, as these may enhance the impairment. Fluoxetine is thus an appropriate choice, but citalopram or sertraline could also be considered. Mirtazepine is licensed in the elderly but can cause excessive drowsiness due to its high anticholinergic activity. Poor memory processing is related to loss of cholinergic activity so any medicine which reduces this further, such as those with anticholinergic activity, should be minimised.**

Mr LD's HAMD score of 12 indicates mild depression, therefore it would be reasonable to initiate effective treatment to achieve resolution of his depressive symptoms.

There is little therapeutic difference in terms of efficacy between any group of antidepressants, especially between the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs). Treatment decisions are dependent on patient acceptability, tolerability, toxicity, suicide risk and cost. Owing to age-related changes in pharmacokinetic and pharmacodynamic parameters, the elderly are most susceptible to the adverse effects of any medication. These may also be exacerbated by concomitant medication and/or pathology.

In the elderly, pharmacokinetic changes markedly reduce clearance and the elimination half-life of TCAs. These changes can lead to increased plasma concentrations and an increased risk of dose-related toxicity. Pharmacodynamic changes in the elderly mean that organ sensitivity is increased to the adverse effects associated with these pharmacokinetic changes. The adverse effects of TCAs are well known, and the cognitive impairment resulting from their anticholinergic activity precludes their use in patients with dementia. This is also similar for mirtazepine (a noradrenergic and specific serotonergic antidepressant) which can cause drowsiness and some cognitive impairment.

Owing to the heterogeneity of the elderly and often the concurrent pathology and associated polypharmacy, it is appropriate to use an SSRI first, with the particular choice of agent governed by patient factors such as anticipated pharmacokinetic changes and tolerability. Mr LD has no cardiovascular disease, no history of movement disorders (which may preclude treatment with fluoxetine or paroxetine), and his renal and hepatic function (which may affect the clearance of citalopram, paroxetine and fluoxetine) is unremarkable. He is not on any other medication that might lead to the drug–drug interactions seen with many of the SSRIs. SSRIs have a selective effect on CYP isoenzymes, leading to

many pharmacokinetic interactions with other medicines. Paroxetine and fluoxetine are potent inhibitors of CYP2D6, whereas fluvoxamine mainly affects CYP1A2 and CYP2C19 activity, so it is safer to avoid these agents in older people taking concomitant medications that are substrates of these isoforms. The safest agents for older people with concomitant medications are those with a low propensity for drug interactions: citalopram and sertraline. Common side-effects on starting SSRIs are increased anxiety and/or nausea. These symptoms can be reduced by starting at half the recommended dose for the first 2 weeks (i.e. 10 mg citalopram) and then increasing to a maximum of 20 mg.

Fluoxetine is thus a reasonable choice for Mr LD; however, the time to therapeutic effect may be delayed because of the long half-life of the drug and its active metabolite norfluoxetine in the elderly. Therefore, the full therapeutic effect may not be attained for 1–3 months. Conversely, once stable plasma levels are reached a missed dose will have less of an effect than an agent with a shorter half-life.

It is important that the patient (and his wife) understands that it may take 4–6 weeks for a response to be noted and possibly 3 months for this response to be substantial (longer in older people). If there is some response at 6 weeks consideration should be given to increasing the dose; if there is no response, consideration should be given to changing to an alternative antidepressant. Once the depression has resolved, treatment at the dose which caused remission should be continued for at least 12 months.

What is an ADAS-cog score, how is it calculated, and what is the relevance of the final score?

A5 **ADAS-cog (the Alzheimer's Disease Assessment Scale – cognitive subscale) is a tool designed for research and clinical purposes to monitor the progression of disease, and also the response to pharmacological treatment.**

The ADAS-cog (there is also a non-cognitive subscale, which is used less frequently) was developed to measure all the major symptoms of AD and the severity and progression of the symptoms in a variety of settings and languages. It is a performance-based test that assesses 11 domains of cognitive function, including word recall, naming, orientation, commands, praxis, word recognition, spoken language and comprehension, word finding and recall. It takes about 1 hour to complete and is scored from 0 (no errors) to 70 (profoundly demented). Patients with moderate dementia (untreated) show an annual rate of change of about 13 points. In comparison, those who are mildly or severely affected have a point change of about 6 or 7, respectively. There are many other similar scales. Some centres use the Cambridge Mental Disorders of the Elderly Examination

(Camdex), others the Clinician's Interview-based Impression of Change (CIBIC) or the CIBIC-plus (includes caregiver input) for global outcomes; and the Global Deterioration Scale (GDS) for functional/quality-of-life measures. All scales have their limitations and some have wide inter-rater variability.

What is the relevance of the CT results?

A6 **A CT scan is used to eliminate reversible causes of dementia and can identify changes which require further investigation. It also acts as a baseline measurement for disease progression.**

The first purpose of a magnetic resonance imaging (MRI) or CT scan in AD is to rule out reversible causes such as tumours, strokes, haemorrhages, hydrocephalus, ischaemia and other lesions. The findings on CT of enlargement of lateral ventricles and sulci, and the appearance of cerebral atrophy are only supportive diagnostic indicators of dementia. In normal ageing, brain volume reduction is estimated at 5–10% at 80 years, with enlargement of the lateral and third ventricles and cortical cerebral sulci. False positives (apparent cerebral atrophy in normal subjects) and false negatives (appearances within the normal range in definite dementia) are frequently seen. MRI scanning can help to distinguish between the various dementias and normal ageing. It is increasingly used for people with a history of cerebrovascular ischaemic disease (i.e. stroke or transient ischaemic attacks) and early dementia (MCI) and is an important investigation to facilitate choice of appropriate therapeutic options. The use of follow-up rescanning and identification of progressive changes makes for a more accurate diagnosis.

What is the probable diagnosis for Mr LD, and how can it be confirmed?

A7 **The diagnosis is probable AD. Confirmation is currently only possible via postmortem necropsy.**

Dementia has historically been defined as a syndrome consisting of progressive impairment in two or more areas of cognition (memory, language, visuospatial and perceptual ability, thinking and problem solving, and personality) which is sufficient to interfere with work, social function or relationships and represents a significant change from the previous level of function. It occurs in the absence of delirium or major non-organic psychiatric disorders such as depression or schizophrenia, or impaired consciousness. The *Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV* diagnostic criteria, which are American, or the *International Classification of Diseases-10 (ICD-10)* criteria, which is the World Health Organization classification system, are also used in diagnosis. In 2011 the National Institute on Aging and the Alzheimer's Association published

diagnostic criteria which increase specificity by including biomarkers such as MRI (disproportionate atrophy in medial, basal and lateral temporal lobe, and medial parietal cortex), positron emission tomography (PET) imaging (positive amyloid imaging and decreased fluorodeoxyglucose uptake on PET in temporoparietal cortex) and cerebrospinal fluid (CSF) assays (elevated CSF tau). Biomarkers are indicated for research but not for routine management as there is no standardisation between markers and evidence is still lacking in terms of the exact markers and levels which relate to a positive (rather than probable or possible) diagnosis of AD. For example, hippocampal atrophy is the first biomarker for probable AD with 80% sensitivity and specificity; however, it is also present in frontotemporal lobe dementia and other pathology. In DLB, there is relative preservation of the hippocampus (accurate in 60% of cases as a diagnostic marker), but atrophy in the medial temporal lobe.

The histopathological indicators of AD found at necropsy include significant loss of neurones and synapses and resultant neurochemical changes; intracellular neurofibrillary tangles; extracellular neuritic amyloid plaques; and, in some cases, the presence of Lewy bodies (however the presence of Lewy bodies is now thought to be indicative of DLB and/or Parkinson's disease dementia). Many of these findings cannot at present be detected by any visualisation techniques while the patient is still alive. Research is expanding in relation to developing less invasive biomarkers.

Why is an early diagnosis of AD better for the individual and family?

A8 It allows them the opportunity to arrange things such as wills, advance directives, power of attorney and long-term care arrangements while the patient has insight and can make informed choices.

An early definitive diagnosis is becoming more important, both for the person with dementia, the carers and loved ones and the patient's physician and multidisciplinary team. The Mental Capacity Act 2005 set out for the first time the legal rights of people with dementia to make decisions for themselves. The act assumes that people have the capacity to make decisions for themselves unless proven otherwise. For people with dementia this capacity may fluctuate on a day-to-day or moment-to-moment basis, so it is a reminder for all those involved in their care that capacity (or incapacity) to consent needs to be reassessed with each decision. An advance directive is also legally recognised and allows people with dementia to specify what types of treatment they do *not* want in the future. These advance directives need to conform to the specifications of the act, but are legally binding documents and must be followed by health professionals. The act also allows people with early dementia to decide on up to two

people with lasting power of attorney: the first for property and financial decisions and the second for personal welfare (health, day-to-day care). The act applies to England and Wales; Scotland has its own legislation. The British Medical Association has published guidance for healthcare professionals on assessing capacity for consent to treatment (including taking medication).

Other benefits of early diagnosis are:

- (a) Reversible conditions can be excluded.
- (b) It allows early access by the person with dementia and family to support groups (e.g. the Alzheimer's Society) for further information and planning purposes.
- (c) It helps to determine the prevalence of the disease.
- (d) It permits future research into treatments that may slow or halt the progression of the disease to be more effectively targeted to the right stage of the disease.
- (e) It enables the appropriate medical treatment to be started at the most beneficial time for the individual.

What are the pharmacological treatment options for Mr LD?

A9 **There are currently three licensed ChEIs for the symptomatic treatment of mild to moderate AD in the UK.**

ChEIs increase the bioavailability of acetylcholine, a neurotransmitter which is depleted in AD, by reducing its hydrolysis. All have shown statistically significant improvement in randomised controlled trials against placebo in patients with mild to moderate AD. However, not all patients will show a response to treatment, and some will have only a partial response. It is estimated that one-third of patients show a definite response, one-third respond to some degree and a further third may not respond at all. The reason for these findings is unclear, but is perhaps due to the heterogeneity of the dementias as diseases. Individuals with the apolipoprotein allele-4 (a genetic risk factor for AD) seem to have a different response rate from those without; however, this finding is inconsistent across studies.

The number needed to treat (NNT) with reference to a significant improvement in cognition, ADL or global functioning is relatively low (ranging from three to seven for a low dose of any ChEI), indicating that this is a clinically significant treatment. A higher NNT would also be acceptable in view of the chronic nature of the disorder.

Each of the agents available has a different side-effect profile and different cautions and contraindications to use. The choice of pharmacological agent is therefore dependent on the individual's concomitant pathology and medication.

Other agents have also been investigated. Long-term studies of patients taking non-steroidal anti-inflammatory drugs have shown a reduced incidence of dementia compared to normal population groups; however, there is currently no evidence for their use in established dementia, and the risk of adverse effects outweighs possible benefit.

What therapy would you recommend? Outline a dosing and monitoring schedule.

A10 A ChEI is justified. The choice and dose regimen is dependent on patient comorbidity and local prescribing guidance. For Mr LD, rivastigmine is an appropriate choice.

Mr LD is suitable for treatment with a ChEI because he has been diagnosed by a specialist physician as having probable moderate AD. The choice of ChEI depends on the patient's concomitant disease factors. The presence of severe hepatic or renal disease precludes the use of galantamine, and the presence of respiratory and cardiovascular disease is a caution against the use of ChEIs in general. Another consideration is that of adherence: once-daily dosing is often preferred by both the carer and the patient.

Rivastigmine is a reasonable choice for Mr LD. It is generally well tolerated, the most common side-effects being drowsiness, nausea, vomiting and diarrhoea, which occur most commonly with upward dose titration. Rivastigmine has a short half-life of about 2 hours but a prolonged action, as acetylcholinesterase is inhibited for up to 10 hours after the parent drug has been eliminated from the plasma. Excretion of inactive metabolites is via the kidney. There is no hepatic metabolism and little protein binding.

The starting dose is generally 1.5 mg twice daily, increasing slowly by steps of 1.5 mg twice daily at monthly intervals to a maximum of 6 mg twice daily. This is in an attempt to increase the tolerability to rivastigmine and to determine the most effective response to a particular dosage. Rivastigmine is marketed in 1.5, 3, 4.5 and 6 mg strengths to aid flexibility in titration. Some patients may need a longer titration interval, e.g. by increments of 1.5 mg daily at monthly intervals. A long-acting patch formula is now available which can minimise side-effects in some individuals.

In some centres the propensity of rivastigmine to cause severe vomiting and diarrhoea, plus its twice-daily dosing regimen, which means its use requires greater input from carers to ensure the medication is taken and not forgotten, has made this a second- or third-line agent.

The monitoring requirements of the ChEI selected will be guided by local policy, but will generally include a barrage of cognitive, physical and psychological assessments to assess continuing efficacy and guide the need for continued treatment.

In 2001, NICE suggested that prior to initiation of therapy a mutually agreeable endpoint for withdrawal of therapy be agreed with the individual and carer. With emerging evidence of rapid deterioration on withdrawal, this is increasingly hard to establish. Therapy is usually reassessed during titration of dosing every 2–4 months until an appropriate maintenance dose is achieved. Often it takes longer than 3 months to achieve a therapeutically effective maintenance dose owing to the patient's inability to tolerate dose increments. Current advice is to titrate to the maximum tolerated licensed dose as soon as possible to help preserve cholinergic functioning for as long as possible. Once reached, assessment can be made every 6 months and the agent continued if the MMSE remains >10; however, overall benefit is still judged in terms of behaviour, global functioning and ADL in patients with MMSE scores <10.

In those who demonstrate no therapeutic response, or who cannot tolerate the adverse effects of a first-line agent, evidence shows that they may respond to an alternative ChEI. If ChEIs are contraindicated then memantine is now licensed for moderate to severe dementia. Current NICE guidance does not recommend memantine for the treatment of moderately severe to severe dementia except as part of well-designed clinical studies; however, it says that 100% of people with moderate illness should be offered suitable treatment. NICE did not comment on the suitability of memantine in moderate dementia.

There is no currently available guidance on when to withdraw treatment in patients who have previously demonstrated a therapeutic response but have since shown no improvement. One could argue that, if the disease progression itself is being held static and no deterioration is shown, then the treatment should continue. Recent evidence demonstrates that stopping ChEIs can result in a dramatic decline in individual functioning and behaviour. In practice, if the decision is made to withdraw the ChEI then the person is carefully monitored over a 2-week period, and if there is a substantial decline in behaviour or symptoms, or if a previously unappreciated benefit emerges, then treatment is reinstated as soon as possible. In 2008 Ballard and Fossey found that in postmortem tests on the brains of people prescribed ChEIs there was a dramatic (70%) fall in the levels of the β -amyloid and τ proteins associated with the cause and progression of AD. This evidence supports the hypothesis that ChEIs slow progression of the illness at a cellular level.

Outline a pharmaceutical care plan for Mr LD.

A11 The pharmaceutical care plan for Mr LD should include the following:

- (a) The person with dementia and, with the patient's consent, the carer's understanding of the illness and its treatment should be fully assessed with reference to local support services.
- (b) All members of the team providing healthcare to the person with dementia should be identified within the pharmaceutical care plan.
- (c) Prior to starting the ChEI a full medication history should be taken, and if possible all medicines with highly anticholinergic side-effects should be withdrawn/changed to agents with lesser effects. This is because dementia is associated with reduced levels of cerebral acetylcholine, so that medicines with anticholinergic side-effects will make this imbalance worse.
- (d) Pharmaceutical needs may include the need for concomitant medication, advice and treatment about adverse effects, titration schedule, medicine reminder devices, patient and carer information, medication reminder aids, patient and carer agreement with the treatment plan and monitoring of efficacy. It is increasingly important to ask the person with dementia and the carer about what outcomes are important for them. Often memory is not helped that much but ADL, preservation of personality and social skills improve and this can be more important to harmonious relationships.
- (e) At each dose titration a medication review may aid the early detection of intolerable adverse effects which could lead to the suggestion of treatment options for adverse effects or a switch to an alternative ChEI.
- (f) Identification of main carer and relevant carer needs. (The National Dementia Strategy (2009) provides further information.)
- (g) Generally the aim of a pharmaceutical care plan is to achieve concordance. It must be taken into account that people with dementia will probably not remember what is said, or even that anything has been said. There should therefore be written supporting information at each consultation, even if the carer is present. A difficult thing to take on board for many pharmacists is that true concordance may never be achieved between the person with dementia and the health professionals. The best to aim for is adherence, and to achieve this the pharmacist needs to involve the main carer in charge of medication and explore medication issues in general. Once-daily dosing regimens are often preferred, and donepezil and long-acting galantamine preparations may be beneficial if there are issues regarding multiple dosing regimens. Liquid formulations should be considered if there are swallowing difficulties, which are common in advancing illness.

What is the possible cause of these side-effects and how might they be treated?

A12 They are probably due to the cholinergic side-effects of the increasing rivastigmine dose.

Susceptible patients may find it increasingly difficult to tolerate dose increases because of increased vomiting and nausea, which may be so severe that the patient loses a clinically significant amount of weight. If there is no evidence of a movement disorder such as Parkinson's disease or DLB, then prescribing a long-acting form of metoclopramide for 2 days prior to the dose increase and the first week of the increased dose may help. Staggering the upward titration over a longer period may also help (e.g. 4.5 mg each morning and 6 mg each evening for 4 weeks prior to a final increase to 6 mg twice daily). In patients with movement disorders domperidone 10 mg four times daily as a regular medication, again starting 2 days prior to dose increases and continuing until tolerance is achieved, may help. If diarrhoea is a problem then loperamide can be used. Other alternatives include changing the formulation to a long-acting patch or switching to another ChEI.

What is the role of ginkgo biloba and other dietary supplements in the symptomatic treatment of AD?

A13 There is some evidence to support their efficacy but few robust data are available.

- (a) ***Ginkgo biloba***. The *Ginkgo* (sometimes spelled *Gingko*) *biloba*, or maidenhair tree, dates back some 200 million years. Its leaves have been used in the treatment of asthma and as a memory enhancer for perhaps 5000 years in Chinese medicine. It is licensed in Germany for the symptomatic treatment of cognitive disorders, intermittent claudication and vertigo of vascular origin. It is becoming increasingly popular in the USA and UK as a dietary supplement to enhance memory.

The active ingredients are unknown and may include one or all of the following: flavonoids, terpenoids, organic acids. This means that there is no product standardisation, and different formulations have different ingredients and dosage specifications. This factor contributes to the inconsistency of results in clinical trials.

Ginkgo biloba is thought to produce a vasoregulatory effect on arteries, capillaries and veins, which improves blood flow, and to antagonise platelet-activating factor. There is a theoretical increased risk of adverse bleeding events if it is taken by patients on either aspirin or warfarin; however, there are only isolated case reports in

the literature. A Cochrane Review updated in April 2009 suggests that overall the evidence for the use of ginkgo for people with dementia is inconsistent and unconvincing. The Scottish Intercollegiate Guidelines Network (SIGN) guidelines in 2006 suggested that people wanting to use ginkgo should consult a qualified herbalist and be made aware of possible interactions with other prescribed medicines.

- (b) **Lecithin supplementation.** A Cochrane Review found no evidence to support the use of lecithin in the treatment of people with dementia.
- (c) **Vitamin E supplementation.** Although one large randomised controlled trial of vitamin E supplementation demonstrated a slowing in the decline of cognitive function associated with a reduction in numbers of patients reaching an endpoint of severe dementia in the active supplementation arm, an increased number of falls was also noted in the active group of the study. Subsequently a Cochrane Summary in July 2008 stated there was no evidence for the use of vitamin E in people with MCI or dementia.
- (d) **Melatonin.** A Cochrane Summary in March 2011 suggested that melatonin may be effective for the treatment of dementia-related psychopathologic behaviour disturbances. Studies suggest there is a relationship between the decline of melatonin function and the symptoms of dementia.
- (e) **Other supplements or interventions.** The NICE Dementia Guidelines, published in 2007, outlined a number of non-pharmacological interventions to help in the treatment and/or support of cognitive or behavioural problems in dementia. Cochrane have also completed a number of summaries in this area. There has been increasing evidence for the use of bright light therapy (>1000 lux) to help improve some cognitive and non-cognitive symptoms of dementia. This has been shown to be especially beneficial in the winter months. Lemon balm (*Melissa officinalis*) or lavender is used in aromatherapy interventions to induce sleep or to calm behaviour.

It is also pertinent to remember that the environment in which the person is cared for contributes a great deal to mood and behaviour. Cochrane and the Dementia Guidelines both uphold the importance of the environment, including its design, content, accessibility, the use of colour, and access to garden and walking areas.

What is the likely diagnosis for Mr LD?

A14 Infection-induced delirium superimposed on a background of dementia. Supporting factors include signs of infection, sudden onset and both visual and auditory hallucinations.

Delirium is extremely common in this age group, affecting as many as 24% of all hospital admissions. There are many triggers for delirium and the reader is referred to the DSM-IV criteria, which aid in the final diagnosis by outlining the exclusions and investigations that need to be made. The most common triggers for delirium are:

- (a) Infection, especially of the urinary or lower respiratory tract (the elderly have a delayed immune response to infection and can become systemically very unwell before changes in X-rays, temperature or blood cultures are seen), but also skin infections and, more rarely, neurosyphilis or HIV.
- (b) Metabolic and endocrine disorders, especially thyroid disorders, dehydration and electrolyte disturbances.
- (c) Neurological disorders, especially stroke and transient ischaemic attacks.
- (d) Cardiovascular disease, especially heart failure (poor cerebral perfusion) and arrhythmias.
- (e) Medication toxicity, including intoxication, withdrawal effects and side-effects of certain pharmacological classes. Alcohol or nicotine withdrawal should be considered, as well as the starting and stopping of any pharmacological agent.
- (f) Other medical conditions, such as chronic constipation, chronic pain or urinary retention.
- (g) Changes in environment (transfer to ward/nursing home), poor lighting and staff or carer changes can also exacerbate confusion as reference points are no longer present.

Impairment of consciousness is defined in DSM-IV terminology as 'reduced awareness of the environment'. In delirium this fluctuates throughout the day, with the intensity of the impairment generally greater at night. This can often present as a disturbance in the sleep-wake cycle, where the patient experiences daytime sleepiness and night-time agitation. Sometimes complete reversal of the sleep-wake cycle can occur. The patient's behaviour and thought processes are often slow and muddled, visual perception is distorted and hallucinations are frequently noted. The patient can present with mood changes, disorientation for time and place and memory disturbance. Emotional disturbances such as anxiety, fear, depression, irritability, anger, euphoria and apathy may also be demonstrated, with a rapid and unpredictable shift from one emotional state to another. Fear may distress patients to such an extent that they try to climb out of bed while still attached to medical equipment such as intravenous lines and urinary catheter bags. They may also attack those who are falsely perceived to be threatening, e.g. the nurse trying to get them back into bed.

Would you recommend antipsychotic therapy for Mr LD at this point?

A15 **No. Antipsychotic therapy is only indicated if Mr LD's behaviour puts either himself or others at risk of physical harm.**

The underlying principle for the successful treatment of delirium is to treat the physical condition or the underlying cause. During the acute phases of cognitive impairment it is important to relieve patients' distress and to prevent behaviour that may result in an injury to themselves or others. The NICE Guidance CG103 outlines strategies to prevent delirium and also manage its treatment.

Where possible, non-pharmacological methods should be employed to treat behavioural disturbances in this age group. Patients who have poor concentration are often easily distracted, and behavioural intervention methods are recommended. These include:

- (a) Creating a calming environment.
- (b) Providing activities to reduce boredom and loneliness.
- (c) Providing a regular routine.
- (d) Providing proactive non-confrontational care.
- (e) Ensuring the physical environment is optimal, i.e. temperature control, space to walk, good lighting.
- (f) Ensure sensory function is optimal, i.e. if appropriate, check glasses are on, clean and the correct prescription, ensure hearing aid is switched on and batteries are functional, check teeth are in.

Other psychological strategies include the ABC analysis, where the patient is carefully observed over a 2-week period for:

- (a) Antecedents (television programme, meal times, nurse of the opposite sex involved in bathing routine).
- (b) Behaviour (clear description of behaviour exhibited).
- (c) Consequences (if the consequence is unimportant, does the behaviour require treatment?).
- (d) The next step is to record what stops the behaviour (so that it can be used again if necessary).

Recent research has demonstrated a statistically significant association between the rate of cognitive decline, pneumonia and/or death from cerebrovascular or cardiovascular disease and the prescribing of antipsychotics. Current advice is not to use antipsychotic medication unless the behavioural symptom places the individual and/or others at risk of injury.

The Omnibus Budget Reconciliation Act (OBRA), legislated in the USA in 1998, recommends that behaviour be observed for up to 1 month in patients with neurodegenerative disease before any pharmacological

treatment is initiated. This is to ensure that the behaviour is not just a short-term manifestation of disease progression. Unnecessary medication puts the elderly person at risk of increased morbidity and mortality from iatrogenic illness.

In the UK a report by Professor Sube Bannerjee in 2009 on the inappropriate prescribing of antipsychotics in people with dementia stated that up to 1800 unnecessary deaths and 1620 cerebrovascular events were caused by these agents each year. This led to a National Dementia Strategy and was followed in 2011 by the Alzheimer's Society publishing guidelines on 'Optimising treatment and care for behavioural and psychological symptoms of dementia: A best practice guide' to reduce the inappropriate prescribing of antipsychotics.

Behavioural problems can include restlessness, irritability, nocturnal waking, aggressive behaviour and resistive behaviour. The first course of action is to attempt to identify any underlying treatable cause. The following questions should be considered:

- (a) Is the patient in pain? (Remember, these patients have reduced visuospatial awareness and are often confused, and therefore at greater risk of falls or walking into things.)
- (b) Is there an underlying depression causing the apathy and lethargy?
- (c) Is there a superimposed delirium due to infection or some other cause?
- (d) Is the patient's communication hampered by visual or hearing or speech difficulties? Always remember to check for glasses, hearing-aids or false teeth when communicating with an elderly patient.
- (e) Has the patient recently moved from another care environment? Changes in environment can greatly distress patients with dementia as they no longer have familiar items by which to reorientate themselves.
- (f) Does the patient become more distressed in certain situations, such as when being bathed by a member of the opposite sex, or at meal times? If so, try to establish the causative factor.
- (g) Ask yourself: 'Is the patient really wandering or actually just walking?' People need exercise and mental stimulation. The National Dementia Strategy in 2009 found that the typical person in a care home spent just 2 minutes interacting with staff or other residents over a 6-hour period of observation (excluding time spent on care tasks). Medication should not be a substitute for inappropriate staffing levels or lack of activities.

Each problem should be analysed to identify causality if possible, and specific procedures for assessment and treatment should be agreed so that

all members of the multidisciplinary team and any visitors can handle the problem in the same manner.

In 1998, the *Expert Consensus Guidelines for the Treatment of Agitation in Older Persons with Dementia* (updated annually) were first published, giving guidance on two treatment strategies: environmental intervention and the use of medication. The guidelines describe mild agitation as behaviour which is somewhat disruptive but not aggressive, such as moaning, pacing, crying or arguing. They describe severe agitation as behaviour that is aggressive or endangers others (or the patient), e.g. screaming, kicking, throwing objects, scratching others or self-injury. Their first recommendation is that the family and/or carer(s) should be educated about dementia and agitation and encouraged to join a support group. The most important aim is to identify the trigger for any problem behaviour.

Efforts should be made to reduce disorientation, e.g. at night try using low lights so that the patient can orientate to place, and to avoid sensory over- and under-stimulation. It may be easier to care for restless agitated patients in a side room where there is less disturbance from noise and other patients.

Carer (and healthcare professional) education groups on dementia are often provided by the Alzheimer's Society or the local memory clinic. These groups can help carers to understand changing/challenging behaviour and learn how to cope with it. This greatly increases the support mechanism for the caring process, and also ensures people with dementia are cared for appropriately.

What are the next therapeutic options?

A16 **Memantine, a novel N-methyl-D-aspartate (NMDA) antagonist, is licensed for the symptomatic treatment of moderate to severe AD.**

Transfer to an alternative ChEI may be tried at this point, but it would seem more logical to initiate (or co-prescribe, depending on local policy) the non-competitive NMDA receptor antagonist memantine. Memantine is licensed in the UK for the symptomatic treatment of moderate and moderately severe to severe AD. When patients are classified as having a moderate to moderately severe dementia it is often difficult to assess their cognitive function owing to reduced attention span and poor memory. Therefore, the burden on the carer is also measured in relation to assisting the patient with ADL.

Double-blind placebo-controlled studies have demonstrated significant improvements in cognitive impairment, lack of drive, motor dysfunction, ADL and elevation of mood, with reduced lability of affect also reported. In two double-blind placebo-controlled randomised trials,

memantine demonstrated statistically significant improvement in the following domains of ADL, as measured by the Global Deterioration Scale: overall behaviour and ability to move, to wash and to dress.

Memantine targets excitatory amino acids such as glutamate. A chronically released high level of glutamate is associated with the pathomechanism of neurodegenerative dementia. An excess of glutamate causes over-stimulation of NMDA receptors, which allows the free flow of calcium into the cell. Sustained elevation of glutamate leads to a chronic overexposure to calcium, which in turn leads to cell degeneration and ultimately neuronal cell death. Memantine is thought to bind to NMDA receptor sites, thereby reducing this overexposure to calcium. However, although memantine blocks the glutamate-gated receptor channels allowing the physiological activation of the receptors (involved in memory formation), it blocks the pathological activation. Owing to the pharmacological effects and mechanism of action of memantine, there are several drug–drug interactions and the reader is advised to refer to the agent’s latest Summary of Product Characteristics for further information.

The initial dose is 5 mg once daily, increasing to twice daily, then 10 mg each morning and 5 mg in the evening, eventually leading to the maximum dose of 10 mg twice daily. Dose increments should be made at weekly intervals. Memantine is available as 5 mg tablets or a solution to aid dosing regimens. This slow upward titration is to reduce the incidence of side-effects. The most common side-effects are hallucinations (5% versus 2.1% in placebo); confusion (1.3% versus 0.3%); dizziness (5% versus 2.8%); headache (5% versus 3.1%) and tiredness (1% versus 0.3%). Uncommon adverse reactions include anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.

Anecdotal evidence shows that some people respond extremely well to memantine, often those with driven and agitated behaviours. A Cochrane Summary highlighted its possible usefulness in treating vascular and mixed dementias as well as AD. Increased efficacy and safety have also been demonstrated when this drug is used concomitantly with ChEIs.

What care issues are necessary for Mrs LD?

A17 Mrs LD requires a personal care plan that meets her emotional, physical and psychological needs.

Carers of people with AD need a great deal of support to ensure that their own physical, mental and social needs are met. The institutionalisation of patients with AD is generally dependent on when the carer feels unable

to cope with the demands of a 24-hour, 7-day week regimen of caring (consult the National Dementia Strategy (2009) for further detail).

Early intervention for carer needs is vital, as many will suffer from depression, and many will be frail and elderly themselves, with concomitant healthcare needs. Frequently the stress associated with caring can lead to physical and mental ill health. Healthcare professionals need to be aware that many people are completely unaware of any services and appreciate actually knowing that they are a carer. The Carer Rights Act aims to support all carers appropriately; however, many healthcare trusts and organisations suggest that there is insufficient funding to support its recommendations, and this is why support is often not proactively offered.

It is advised that each carer has a care plan agreement which outlines respite care needs, additional service needs, community psychiatric nurse monitoring, psychiatric care support programme, carer and patient counselling/support/stimulation activities and local day hospital services. There should also be a social worker assessment. The Alzheimer's Society and the local memory clinic are useful first contacts for any carer.

How might Mr LD's increasing agitation and hallucinations be controlled?

A18 **The treatment of agitation and hallucinations should be by non-pharmacological methods if possible; however, if these fail, an atypical antipsychotic may be warranted.**

Patients with AD are often reported to have associated psychotic presentations such as persecutory delusions and hallucinations. When these occur with behavioural changes (e.g. agitation, aggression) they are termed behavioural and psychological symptoms in dementia (BPSD). A recent study demonstrated that the incidence of visual hallucinations in dementia was actually 3%, compared to the more accepted 40%. Researchers found that poor lighting, combined with ageing eyesight, onset of cataracts, glaucoma and/or macular degeneration, resulted in an interaction where the person made mistakes in seeing what was there, and also had errors in perception of what was there. For example, seeing little people in the corner of the room was actually linked to the television being on at the other end of a room!

Historically such symptoms were often treated first by the use of antipsychotic medication. We now need to be more circumspect about prescribing, and determine whether patients are actually distressed by these hallucinations or whether they can be distracted from them or they can be ignored. All antipsychotics are known to increase morbidity and mortality in older people. Stroke is increased more than threefold with risperidone or olanzapine, and more than doubled with any other atypical

antipsychotic agent. This does not mean that typical (conventional) antipsychotics should be used indiscriminately. Two large epidemiological studies have demonstrated that the safety profiles of typical and atypical antipsychotics are similar. The consensus on safe prescribing in older people with dementia is that any antipsychotic should be used with caution under specialist supervision and for a short period of time, with regular review. A full risk assessment should be made before deciding to prescribe an antipsychotic and should be documented in the patient's notes. It should state clearly all factors that were considered in the decision-making process.

An added concern is that people who have DLB or Parkinson's disease dementia show an exaggerated sensitivity to the extrapyramidal side-effects (EPSE) of antipsychotics and an increased risk of morbidity and mortality. Conventional antipsychotics should not be used in these people (because of the increased risk of EPSE) and atypical antipsychotics should be used with extreme caution. Finally, two recent studies have shown that when antipsychotics are withdrawn there is no change in the amount of behavioural disturbances in individuals, illustrating that generally they seem to be ineffective. When withdrawn from antipsychotics, 70% of people require no further treatment.

In June 2008 the US Food and Drug Administration alerted prescribers to the increased risk of mortality in people treated for dementia-related psychosis with both conventional and atypical agents, and that this increased risk of mortality should be discussed with the patient, the patient's family and carers prior to commencing treatment. A similar report was published in the UK in 2009 (see A17).

Alternative approaches may instead be more appropriate. Increasingly, studies in the treatment of BPSD are showing clinically significant reductions in behavioural problems following treatment with a ChEI, memantine, sodium valproate, citalopram or carbamazepine.

Despite these concerns, in some situations an antipsychotic may be warranted. If the decision is taken to prescribe, the following factors need to be taken into account. Pharmacokinetic changes in the elderly lead to higher plasma concentrations at low doses of antipsychotics, thereby increasing susceptibility to side-effects, which will occur at much lower doses than in younger patients. The elderly have reduced lean body mass, with a corresponding increased lipophilic store and decreased serum albumin, all of which affect the distribution and transportation of a pharmacological agent. Clinically this means that when dosing with a lipophilic agent it may seem to take an unexpectedly long time before therapeutic effect is reached. Ageing also results in decreased renal and hepatic mass (indeed, all organ mass is reduced), which affects the body's ability to metabolise and then excrete medicines. A corresponding

reduction in hepatic and renal blood flow also exacerbates this delay in clearance.

At the time of writing low-dose quetiapine is the antipsychotic drug of choice; however, quetiapine clearance rates are reduced by 30–50% in the elderly, so it is recommended that dosing is started at 12.5–25 mg once daily, increasing by 12.5–25 mg increments every 1–3 days until a therapeutic effect is reached. Quetiapine is well tolerated in the elderly, has a low incidence of seizures, no anticholinergic activity and sedative effects similar to those of chlorpromazine; however, postural hypotension can be a problem if titration is too rapid. Risperidone, used short term (maximum 6 weeks) and at a low dose (start at 250–500 micrograms at night, increasing in 250–500 microgram increments) is the only licensed antipsychotic for persistent aggression in moderate to severe AD unresponsive to non-pharmacological strategies.

Increasing side-effects (EPSEs and postural hypotension) are seen at doses >2 mg daily. Risperidone does not reduce the seizure threshold or block histamine receptors, and has no anticholinergic side-effects. However, the cerebrovascular and cardiovascular risks need to be discussed with the patient's carer and the agent withdrawn as soon as possible.

Olanzapine has been used extensively for the treatment of psychoses in the elderly. Fewer EPSEs have been reported than with risperidone, but there is a 10% incidence of drowsiness, anticholinergic effects and weight gain. Therefore, it is less useful in elderly patients with worsening cognitive dysfunction. Olanzapine is also associated with cerebrovascular and cardiovascular risks.

The efficacy of clozapine is well documented in this age group but its use is associated with many side-effects, including sedation, hypersalivation, tachycardia, hypotension, hypertension, constipation and urinary incontinence. Its propensity to cause fever and agranulocytosis also necessitates mandatory monitoring of blood cell counts on a regular basis. It also has high anticholinergic activity and will therefore adversely affect cognitive function. It is generally only considered as a last resort.

Low-dose haloperidol (250–500 micrograms once daily, adjusting the dose accordingly) seems to be used increasingly for agitation and rapid tranquillisation with or without lorazepam (500 micrograms to 1 mg). In 2005 Schneider *et al.* demonstrated an increased risk of mortality of 107% with the use of haloperidol in particular.

Whatever agent is chosen, if an antipsychotic is being prescribed, its dose, frequency and continued use should be reviewed daily. As the patient responds to the treatment of the behavioural disturbance, antipsychotic therapy should be reduced and withdrawn as soon as possible. It is also prudent to remember that the neurodegenerative process will be ongoing, and that as this progresses the observed behaviour will change in response.

Outline a pharmaceutical care plan for the treatment of double incontinence.

A19 **Double incontinence puts the patient at risk of infection and skin problems. It is often a leading reason for institutionalisation of the patient by carers.**

As social awareness declines and patients no longer remember how to find the toilet, or that they actually physically need to go to the toilet, alternative measures are needed. Behavioural treatment suggests a toilet training regimen, e.g. taking the patient to the toilet at regular intervals during the day, such as on waking, after breakfast, lunch and dinner, and then again before going to bed. The co-prescription of agents such as oxybutynin is not to be recommended as they have anticholinergic side-effects and may exacerbate confusion and cognitive functioning. Continence pads are also an option. Catheterisation is generally not acceptable because of problems with bladder infections and the distress associated with changing the catheter; however, it may be an option if the patient is bed-bound and has no bladder control and/or a permanent catheter *in situ*.

If the patient is doubly incontinent a 'constipating and laxative' regimen is often employed. This is where the patient is kept deliberately constipated using codeine or loperamide, and then has a stimulant laxative or enema once or twice weekly so that bowel actions can be controlled. Toilet training options involve less medication and less distress and discomfort for the patient. Dietary interventions are often less effective owing to the reduced appetite of the individual.

It is also important to be aware of the risk of the skin breaking down and leading to chafing or pressure areas. The use of a good barrier preparation, such as Morhulin, calendula or Drapolene, will help to protect vulnerable areas.

When might pharmacological treatment for Mr LD be withdrawn?

A20 **When there is no halt in progression of baseline disease-monitoring scales for at least 3 months.**

There is no current guidance for the withdrawal of memantine or ChEIs from patients with end-stage AD. However, it would seem obvious that if there is no halt in the progression of the disease, and if patients are requiring full nursing care and are unaware of their surroundings, a full review of all pharmacological agents should be completed with a view to stopping all except those that are essential. Death is commonly due to bronchopneumonia or embolism (as a result of reduced mobility). Also, loss of awareness of hunger and thirst often results in profound weight loss and/or dehydration. At this stage of the illness the principles of palliative medicine should apply.

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