07 - Alzheimers disease (AD)

Alzheimer’s disease (AD)

630 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Dementia Dementia is a progressive syndrome affecting around 5% of those aged over 65 years, rising to 20% in the over 80s. The disorder is characterised by cognitive decline, impaired memory and thinking and a gradual loss of skills needed to carry out activities of daily living (ADL). Changes in mood, personality and social behaviour are frequent.1 The various types of dementia are classified according to the different disease processes affecting the brain. The most common cause of dementia is Alzheimer’s disease (AD), accounting for around 60% of all cases. Vascular dementia (VaD) and dementia with Lewy bodies (DLB) are responsible for most other cases. AD and VaD may coexist and are often difficult to separate clinically. Dementia is also encountered in about 30–70% of patients with Parkinson’s disease1 (see Chapter 10). Alzheimer’s disease (AD) Mechanism of action of cognitive enhancers used in AD Acetylcholinesterase (AChE) inhibitors The cholinergic hypothesis of AD is predicated on the observation that the cognitive deterioration associated with the disease results from progressive loss of cholinergic neurons and decreasing levels of acetylcholine (ACh) in the brain.2 However, it is no longer widely believed that cholinergic depletion alone is responsible for the symptoms of AD.3 Three inhibitors of AChE are currently licensed in the UK and elsewhere for the treatment of mild to moderate dementia in AD: donepezil, rivastigmine and galantamine. These three drugs are also recommended in severe AD. In addition, rivastigmine is licensed in some countries for the treatment of mild to moderate dementia associated with Parkinson’s disease. Both AChE and butyrylcholinesterase (BuChE) have been found to play an important role in the degradation of ACh.4 Cholinesterase inhibitors differ in pharmacological action: donepezil selectively inhibits AChE, rivastigmine affects both AChE and BuChE and galantamine selectively inhibits AChE and also has nicotinic receptor agonist properties.5 To date, these differences have not been shown to result in important differences in efficacy or tolerability (see Table 6.1 for a comparison of AChE inhibitors). Memantine Memantine is licensed in the UK and elsewhere for the treatment of moderate to severe dementia in AD. It is believed to exert its therapeutic effect by acting as a low to moderate affinity, non-competitive N--methyl-D-aspartate (NMDA) receptor antagonist that binds preferentially to open NMDA receptor--operated calcium channels. This activity- dependent binding blocks NMDA-mediated ion flux and is thought to mitigate the effects of sustained and pathologically elevated levels of glutamate (and this excitotoxicity) that may lead to neuronal dysfunction (Table 6.1).6

Prescribing in older people CHAPTER 6 Table 6.1 Characteristics of cognitive enhancers.7–14 Characteristic Donepezil Rivastigmine Galantamine Memantine Primary mechanism AChE-I (selective and reversible) AChE-I (reversible, non- competitive inhibitor) AChE-I (competitive and reversible) Glutamate receptor antagonist Other mechanism None BuChE-I Nicotine receptor

agonist 5HT3 receptor antagonist Starting dose 5mg daily 1.5mg bd (oral) (or 4.6mg/24 hours patch) 8mg XL daily (or 4mg bd solution) (immediate-release tablets largely discontinued) 5mg daily Usual treatment dose 10mg daily 3–6mg bd (oral) (or 9.5mg/24 hours patch) 16–24mg XL daily (or 8–12mg bd solution) 20mg daily (or 10mg bd) Recommended minimum interval between dose increases 4 weeks (increase by 5mg daily) 2 weeks for oral (increase by 1.5mg twice a day) 4 weeks for patch (increase to 9.5mg/24 hours) Consider increase to 13.3mg/24 hours after 6 months 4 weeks (increase by 8mg XL daily or by 4mg bd for solution) 1 week (increase by 5mg weekly) Adverse effects7–13 (*very common: ≥1/10 and common: ≥1/100) Diarrhoea,* nausea,* headache,* common cold, anorexia, hallucinations, agitation, aggressive behaviour, abnormal dreams and nightmares, syncope, dizziness, insomnia, vomiting, rash, pruritis, muscle cramps, urinary incontinence, fatigue, pain, falls Anorexia,* dizziness,* nausea,* vomiting,* diarrhoea,* decreased appetite, nightmares, agitation, confusion, anxiety, headache, somnolence, tremor, abdominal pain and dyspepsia, sweating, fatigue and asthenia, malaise, weight loss (frequency of adverse effects with the patch may differ) Nausea,* vomiting,* decreased appetite, hallucination, depression, syncope, dizziness, tremor, headache, somnolence, lethargy, bradycardia, hypertension, abdominal pain and discomfort, diarrhoea, dyspepsia, muscle spasms, fatigue, asthenia, malaise, weight loss, fall, laceration Drug hypersensitivity, somnolence, dizziness, balance disorders, hypertension, dyspnoea, constipation, elevated liver function test, headache Half-life (hours) ~70 ~1 (oral) 3.4 (patch) 7–8 (oral solution) 8–10 (XL capsules) 60–100 Metabolism CYP3A4 CYP2D6 (minor) Minimal involvement of CYP isoenzymes CYP3A4 CYP2D6 Primarily non-hepatic Drug–drug interactions Yes (see Table 6.2) Interactions unlikely Yes (see Table 6.2) Yes (see Table 6.2) Effect of food on absorption None Delays rate and extent of absorption Delays rate but not extent of absorption None AChE-I, acetylcholinesterase inhibitor; bd, twice a day; BuChE, butyrylcholinesterase.

 Efficacy of cognitive enhancers used in AD Currently, no treatments exist that unequivocally reverse disease progression in dementia. Therapeutic interventions are therefore targeted at specific symptoms or at improving or slowing the decline in cognitive function. AChE inhibitors (AChE-Is) may provide some modest cognitive, functional and global benefits in mild to moderate AD.15 The three AChE-Is seem to have broadly similar clinical effects; estimates of the number needed to treat (NNT) (for an improvement of >4 points in the AD Assessment Scale – cognitive subscale [ADAS-cog]) range from 4 to 12.16 An analysis of memantine studies found estimated NNT ranged from 3 to 817 for improved cognitive function. A Cochrane review of memantine in dementia confirmed that there was a small clinical benefit of memantine in people with moderate to severe AD, which occurs irrespective of whether they are also taking a cholinesterase inhibitor, but no benefit in people with mild AD.17 A 2021 study18 investigated the ‘real world’ effectiveness of cholinesterase inhibitors and memantine. The study found that, in general, the initial decline in Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores occurred approximately 2 years before medication was eventually initiated. Medication stabilised cognitive performance for the ensuing 2–5 months. The effect was enhanced in more cognitively impaired cases and attenuated in those taking antipsychotics. Importantly, patients who were switched between agents at least once tended to continue to decline at their pre-medication rate (i.e. did not benefit from pharmacological interventions). Those who remained on the same agent tended to respond better and to stabilise in respect to cognitive changes for a period once the medication was prescribed. Of course, switching might be more common in non-responders, so the act of switching

itself may not be detrimental to outcome. Overall, 68% of individuals experienced a period of cognitive stabilisation before continuing to decline at the pre- treatment rate. Other studies have found similar benefits alongside evidence that AChE-Is may reduce overall mortality.19 Switching between drugs used in dementia The benefits of treatment with AChE-Is are rapidly lost when drug administration is interrupted20 and may not be fully regained when drug treatment is reinitiated.21 Poor tolerability with one agent does not rule out good tolerability with another.22 The British Association for Psychopharmacology (BAP) guidelines for dementia confirm that previous comparative trials have failed to consistently demonstrate any significant differences in efficacy between the three AChE-Is, the main differences found being in frequency and type of adverse events. As a result, their recommendation remains valid that a significant proportion of patients (up to 50%) appear to both tolerate and benefit from switching between AChE-Is if they cannot tolerate one.23 Several cases of discontinuation syndrome upon stopping donepezil have been published24,25 suggesting that a gradual withdrawal should be carried out where possible. However, a study comparing abrupt versus stepwise switching from donepezil to memantine found no clinically relevant differences in adverse effects despite patients in

Prescribing in older people CHAPTER 6 the abrupt group experiencing more frequent adverse effects than the stepwise discontinuation group (46% vs 32%, respectively).26 (For switching to rivastigmine patch see ‘Tolerability’ later in this chapter.) Following a systematic review of the literature,27 a practical approach to switching between AChE-Is has been proposed. In the case of intolerance, switching to another agent should be done only after complete resolution of side effects following discontinuation of the initial agent. In the case of lack of efficacy, switching can be done overnight, with a quicker titration scheme thereafter. Switching to another AChE-I is not recommended in individuals who show loss of benefit several years after initiation of therapy. Other effects AChE-Is may also affect non-cognitive aspects of AD and other dementias. For more information about the management of these symptoms, see ‘Management of behavioural and psychological symptoms of dementia (BPSD)’ later in this chapter. Dosing and formulations For dosing information see Table 6.1 and up-to-date manufacturers’ literature. Rivastigmine transdermal patches (9.5mg/24 hours) have been shown to be as effective as the highest doses of capsules but with a superior tolerability profile in a 6-month double-blind placebo-controlled randomised controlled (RCT).28 This has been confirmed in a Chinese study.29 A nasal spray has also been developed.30 The US Food and Drug Administration (FDA) has approved a higher daily dose of donepezil sustained release (23mg) for moderate to severe AD. In the approval trial there was a small statistically significant improvement in cognition (a 2.2 improvement over the 10mg dose on the Severe Impairment Battery [SIB] scale) but no difference in global functioning (a 0.06 improvement on the Clinician’s Interview-Based Impression of Change plus caregiver input [CIBIC--plus] scale). Furthermore, the higher dose was not superior on either of the prespecified secondary outcome measures and the rate of gastrointestinal adverse effects was over three times higher (21%) in the first month in the group receiving donepezil 23mg than in the 10mg group (5.9%).31 The memantine extended release (ER) 28mg once-daily capsule formulation was approved in the USA in 2010. Its efficacy was demonstrated in a large, multinational, phase III trial which showed that the addition of memantine ER to ongoing cholinesterase inhibitors improved key outcomes compared with cholinesterase inhibitor monotherapy, including measures of cognition and global status. The most common adverse events were headache, diarrhoea and dizziness.32 While the FDA chose to approve memantine ER based on efficacy data from this study, the European Medicines Agency decided against approval. It questioned the clinical relevance of the drug given

the small differences on the co-primary endpoints and the non-significant differences on the functional measure. In addition, since no comparison studies were performed between memantine immediate release (IR) and memantine ER, the risk–benefit ratio could not be fully evaluated.33

634 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 These high doses of donepezil and memantine have not yet been approved in the UK and many other countries. In addition, most older people seen in practice with AD are likely to be frailer and have more comorbidities than patients in clinical trials and may therefore be less likely to tolerate the higher doses. Combination treatment Guidelines and the UK's National Institute for Health and Care Excellence (NICE)1 recommend the use of a combination of AChE-I plus memantine rather than AChE-I alone in patients with moderate to severe AD. A network meta-analysis of 54 trials found that memantine plus donepezil showed superior outcomes for cognition, global assessment, daily activities and neuropsychiatric symptoms, but lower acceptability than monotherapy and placebo. A 2022 analysis observed broadly similar outcomes.34 Combination therapy may be more cost-effective because memantine slows the progression of AD.35 A Cochrane review has confirmed these recommendations for combined therapy.36 Studies have also shown that there are no pharmacokinetic or pharmacodynamic interactions between AChE-Is and memantine.37,38 Drug tolerability Drug tolerability may differ between AChE-Is, but, in the absence of sufficient direct comparisons, it is difficult to draw conclusions. Overall tolerability can be broadly evaluated by reference to the numbers withdrawing from clinical trials. Withdrawal rates in trials of donepezil39,40 ranged from 4% to 16% (placebo 1–7%), 7% to 29% (placebo 7%) with rivastigmine41,42 and 7% to 23% (placebo 7–9%) with galantamine.43–45 These figures relate to withdrawals specifically associated with adverse effects. The number needed to harm (NNH) has been reported to be 12.16 A study of the French pharmacovigilance database identified age and the use of antipsychotic drugs, antihypertensives and drugs targeting the alimentary tract and metabolism as factors associated with serious reactions to AChE-Is.46 It has also been suggested that donepezil and rivastigmine are active centrally (CNS events, extrapyramidal symptoms, sleep disturbances and cardiorespiratory events), in contrast to galantamine, which is more active peripherally (muscle cramps and weakness, cardiorespiratory events and urinary incontinence).47 Tolerability seems to be affected by the speed of titration and, perhaps less clearly, by dose. Most adverse effects occurred in trials during titration, and slower titration schedules are recommended in clinical use. This may mean that these drugs are equally well tolerated in practice. Rivastigmine patches offer convenience and a superior tolerability profile to rivastigmine capsules.28,29 Data from three trials found that rivastigmine patches were better tolerated than the capsules with fewer gastrointestinal adverse effects and fewer discontinuations due to these adverse effects.48 Data support recommendations for patients on high doses of rivastigmine capsules (>6mg/day) to switch directly to the 9.5mg/24 hours patch, while those on lower doses (≤6mg/day) should start on 4.6mg/hour patch for 4 weeks before increasing to the 9.5mg/hour patch. This latter switch is also recommended for patients switching from other oral cholinesterase inhibitors to the

Prescribing in older people CHAPTER 6 rivastigmine patch (with a 1-week washout period in patients sensitive to adverse effects or who have very low body weight or a history of bradycardia).49 It is possible to consider increasing the dose to 13.3mg/24 hours after 6 months on 9.5mg/24 hours if tolerated and cognitive or functional decline occurs on the lower dose. A 48-week RCT found the higher-strength patch (13.3mg) significantly reduced deterioration in instrumental activities of daily living (IADL) compared with the 9.5mg/24 hours patch and was well tolerated.50

Patients and caregivers should be instructed on important administration details for the rivastigmine patch:9 ■ ■The transdermal patch should not be applied to skin that is red, irritated or cut. ■ ■Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation. ■ ■The previous day's patch must be removed before applying a new one every day. ■ ■Only one patch should be worn at a time. ■ ■The patch should not be cut into pieces. The following cautions exist for the use of AChE-Is: asthma, chronic obstructive pulmonary disease (COPD), sick sinus syndrome, supraventricular conduction abnormalities, susceptibility to peptic ulcers, history of seizures, bladder (or gastrointestinal) outflow obstruction, cardiac disease, congestive heart failure, unstable angina, electrolyte disturbances; and for rivastigmine patches: risk of fatal overdose with patch administration errors.7 Memantine appears to be well tolerated51,52 and the only conditions associated with warnings include severe hepatic impairment and epilepsy/seizures.53 (See BNF or equivalent for required dosage adjustments in renal impairment.) Isolated cases of international normalised ratio (INR) increases have been reported when memantine is co-administered with warfarin. Adverse effects of drugs Cholinesterase inhibitors When adverse effects occur with AChE-Is they are largely predictable: excess cholinergic stimulation leads to nausea, vomiting, dizziness, insomnia and diarrhoea.54 Such effects are most likely to occur at the start of therapy or when the dose is increased. They are dose related and tend to be transient. Urinary incontinence has also been reported.55 A network meta-analysis56 compared efficacy and safety with these agents and found the following hierarchy in terms of tolerability: ■ ■Withdrawals from studies due to adverse effects: donepezil > galantamine > rivastigmine patch > rivastigmine (meaning donepezil is best tolerated and so on). ■ ■Nausea: rivastigmine patch > donepezil > galantamine > rivastigmine. ■ ■Vomiting: donepezil > rivastigmine patch > galantamine > rivastigmine. ■ ■Diarrhoea: galantamine > rivastigmine > rivastigmine patch > donepezil. ■ ■Dizziness: rivastigmine patch > galantamine > donepezil > rivastigmine.

 An analysis of 16 years of individual case safety reports from VigiBase found that the most common adverse effects reported with AChE-Is were neuropsychiatric symptoms (31.4%), gastrointestinal disorders (15.9%) and general disorders and administration site conditions (11.9%). Cardiovascular adverse drug reactions (ADRs) accounted for 11.7% of ADRs.57 In view of their pharmacological action, AChE-Is can be expected to have vagotonic effects on the heart rate (i.e. bradycardia). The potential for this action may be of particular importance in patients with sick sinus syndrome or other supraventricular cardiac conduction disturbances, such as sinoatrial or atrioventricular block.7–12 Concerns over the potential cardiac adverse effects associated with AChE-Is were raised following findings from controlled trials of galantamine in mild cognitive impairment (MCI) in which increased mortality was associated with galantamine compared with placebo (1.5% vs 0.5%).58 Although no specific cause of death was dominant, half the deaths reported were due to cardiovascular disorders. As a result, the FDA issued a warning restricting galantamine in patients with MCI. The relevance to AD remains unclear.59 The most prominent cardiovascular adverse effects of AChE-Is are bradycardia and syncope, which can result in serious outcomes such as falls, fractures and other trauma as well as necessitate pacemaker placement. If these adverse effects are experienced, patients should undergo a thorough history/evaluation, including a medication review, rhythm monitoring, consideration of neurological symptoms, lowering the doses of other medications that might contribute to bradycardia, stopping or reducing the AChE-I dose or even pacemaker placement. Many of these factors should be considered before the initiation of these

medications and periodically thereafter to optimise patient care and mitigate possible adverse events60,61 (Figure 6.1). There are also a few reports that they may occasionally be associated with QT prolongation and torsades de pointes.62 It seems that patients with DLB are more susceptible to the bradyarrhythmic adverse effects of these drugs owing to the autonomic insufficiency associated with the disease.63 The manufacturers of all three agents advise that the drugs should be used with caution in patients with cardiovascular disease or in those taking concurrent medicines that reduce heart rate (e.g. digoxin or β blockers). Although a pre-treatment mandatory electrocardiogram (ECG) has been suggested,59 a review of published evidence showed that the incidence of cardiovascular side effects is low and that serious adverse effects are rare. In addition, the value of pre-treatment screening and routine ECGs is questionable and is not currently recommended by NICE. However, in patients with a history of cardiovascular disease or who are prescribed concomitant negative chronotropic drugs with AChE-Is, an ECG is advised.60 Memantine Although little is known about the cardiovascular effects of memantine, there have been reports of bradycardia and reduced cardiovascular survival associated with its use.64 An analysis of pooled prospective data for memantine revealed that the most frequently reported adverse effects in placebo-controlled trials included agitation

Prescribing in older people CHAPTER 6 (7.5% memantine vs 12% placebo), falls (6.8% vs 7.1%), dizziness (6.3% vs 5.7%), accidental injury (6.0% vs 7.2%), influenza-like symptoms (6.0% vs 5.8%), headache (5.2% vs 3.7%) and diarrhoea (5.0% vs 5.6%).65 Given the higher or similar rates seen with placebo, few conclusions can be drawn. The French pharmacovigilance database compared adverse effects reported with donepezil with memantine. The most frequent ADRs with donepezil alone and memantine alone were respectively bradycardia (10% vs 7%), weakness (5% vs 6%) and convulsions (4% vs 3%). Although it is well known that donepezil is often associated with bradycardia and memantine associated with seizures, this analysis suggested that memantine can also induce bradycardia and donepezil seizures, thus highlighting the care required when treating patients with dementia who have a history of bradycardia or epilepsy.66 Drug interactions Potential for interaction may also differentiate currently available cholinesterase inhibitors. Donepezil67 and galantamine68 are metabolised by cytochromes 2D6 and 3A4 so drug levels may be altered by other drugs affecting the function of these enzymes.

- Routine pulse checks should be carried out at baseline, at monthly intervals during titration and at 6-monthly intervals thereafter Symptomatic (e.g. syncope, ‘funny turns’) Asymptomatic Asymptomatic Under 50bpm 50–60bpm Pulse check* Remains asymptomatic • Start/continue drug • Review pulse and symptoms after 1 week • Withhold/stop drug and seek GP or specialist review for underlying cause • If cause is found to be unrelated to drug, or a pacemaker is fitted, consider retrial of drug • Continue drug • Pulse check 1 week after any increase in drug dose • Start/continue drug • Carry out routine pulse checks • Withhold/stop drug and seek GP or specialist review for underlying cause • If cause is found to be unrelated to the drug, or a pacemaker is fitted, consider retrial of drug Over 60bpm Figure 6.1 Suggested guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors (AChE-Is) in Alzheimer’s disease.60,61 bpm, beats per minute. Reproduced with permission from Rowland et al. 2007,

638 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Cholinesterase inhibitors themselves may also interfere with the metabolism of other drugs, although this is perhaps a theoretical consideration. Rivastigmine has almost no potential for interaction since it is metabolised at the site of action and does not affect hepatic cytochromes. A prospective pharmacodynamic analysis of potential drug interactions between rivastigmine and other medications (22 different therapeutic classes) commonly prescribed in the elderly population compared adverse effects odds ratios between rivastigmine and placebo. Rivastigmine was not associated with any significant pattern of increase in adverse effects that would indicate a drug interaction compared with placebo.69 Rivastigmine thus appears to be least likely to cause problematic drug interactions, a factor that may be important in an elderly population subject to polypharmacy (Table 6.2). Analysis of the French pharmacovigilance database found that the majority of reported drug interactions concerning AChE-Is were pharmacodynamic in nature and most frequently involved the combination of AChE-I and bradycardic drugs (β blockers, digoxin, amiodarone, calcium channel antagonists). Almost a third of these interactions resulted in cardiovascular ADRs such as bradycardia, atrioventricular block and arterial hypotension. The second most frequent drug interaction reported was the combination of AChE-I with anticholinergic drugs leading to pharmacological antagonism.70 The pharmacodynamics, pharmacokinetic and pharmacogenetic aspects of drugs used in dementia have been summarised in two comprehensive reviews.71,72 Table 6.2 Drug–drug interactions.8–12,73,74 Drug Metabolism Plasma levels increased by Plasma levels decreased by Pharmacodynamic interactions Donepezil (Aricept®) Substrate at 3A4 and 2D6 Ketoconazole Itraconazole Erythromycin Quinidine Fluoxetine Paroxetine Rifampicin Phenytoin Carbamazepine Alcohol Antagonistic with anticholinergic drugs and competitive neuromuscular blockers (e.g. tubocurarine). Potential for synergistic activity with cholinomimetics such as depolarising neuromuscular blocking agents (e.g. succinylcholine), cholinergic agonists and peripherally acting cholinesterase inhibitors (e.g. neostigmine). Beta blockers, amiodarone or calcium channel blockers may have additive effects on cardiac conduction. Caution with concomitant use of drugs known to induce QT prolongation and/or torsades de pointes. Movement disorders and neuroleptic malignant syndrome have occurred with concomitant use of antipsychotics and cholinesterase inhibitors. Concurrent use with seizure lowering agents may result in reduced seizure threshold.

Prescribing in older people CHAPTER 6 (Continued) Drug Metabolism Plasma levels increased by Plasma levels decreased by Pharmacodynamic interactions Rivastigmine (Exelon®) Non-hepatic metabolism Metabolic interactions appear unlikely Smoking tobacco increases the clearance of rivastigmine Antagonistic effects with anticholinergic and competitive neuromuscular blockers (e.g. tubocurarine). Potential for synergistic activity with cholinomimetics such as depolarising neuromuscular blocking agents (e.g. succinylcholine), cholinergic agonists (e.g. bethanecol) or peripherally acting cholinesterase inhibitors (e.g. neostigmine). Synergistic effects on cardiac conduction with β blockers, amiodarone and calcium channel blockers. Caution with concomitant use of drugs known to induce QT prolongation and/or torsades de pointes. Movement disorders and neuroleptic malignant syndrome have occurred with concomitant use of antipsychotics and cholinesterase inhibitors. Concurrent use with metoclopramide may result in increased risk of EPSEs. Galantamine (Reminyl®) Substrate at 3A4 and 2D6 Ketoconazole Erythromycin Ritonavir Quinidine Paroxetine Fluoxetine Fluvoxamine Amitriptyline None known Antagonistic effects with anticholinergic and competitive neuromuscular blockers (e.g. tubocurarine). Potential for synergistic activity with cholinomimetics such as depolarising neuromuscular blocking agents (e.g.

succinylcholine), cholinergic agonists and peripherally acting cholinesterase inhibitors (e.g. neostigmine). Possible interaction with agents that significantly reduce heart rate such as digoxin, β blockers, certain calcium channel blockers and amiodarone. Caution with concomitant use of drugs known to induce QT prolongation and/or torsades de pointes (manufacturer recommends ECG in such cases). Movement disorders and neuroleptic malignant syndrome have occurred with concomitant use of antipsychotics and cholinesterase inhibitors. Table 6.2 (Continued)

640 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 When to stop treatment A large multicentre study75 of community-dwelling patients with moderate or severe AD investigated the long-term effects of donepezil over 12 months compared with stopping donepezil after 3 months, switching to memantine or combining donepezil with memantine. Continued treatment with donepezil was associated with continued cognitive benefits, and patients with an MMSE score as low as 3 also benefitted from treatment. This suggests that patients should continue treatment with AChE-Is for as long as possible and there should not be a cut-off MMSE score where treatment is stopped automatically. Moreover, secondary and post-hoc analyses of this study found that withdrawal of donepezil in patients with moderate to severe AD increased the risk of nursing home placement during 12 months of treatment but made no difference during the following 3 years of follow-up. This highlights the point that decisions to stop or Table 6.2 (Continued) Drug Metabolism Plasma levels increased by Plasma levels decreased by Pharmacodynamic interactions Memantine (Exiba®) Primarily non-hepatic metabolism Renally eliminated Cimetidine Ranitidine Procainamide Quinidine Quinine Nicotine Trimethoprim Isolated cases of INR increases reported with concomitant warfarin (close monitoring of prothrombin time or INR advisable) Drugs that alkalinise urine (pH ~8) may reduce renal elimination of memantine, e.g. carbonic anhydrase inhibitors, sodium bicarbonate None known (Possibility of reduced serum level of hydrochlorothiazide when co-administered with memantine) Effects of L-dopa, dopaminergic agonists, selegiline and anticholinergics may be enhanced. Effects of barbiturates and antipsychotics may be reduced. Avoid concomitant use with amantadine, ketamine and dextromethorphan – increased risk of CNS toxicity. One published case report on possible risk for phenytoin and memantine combination. Dosage adjustment may be necessary for antispasmodic agents, dantrolene or baclofen when administered with memantine. A single case report of myoclonus and confusion when co-administered with co-trimoxazole or trimethoprim NB This list is not exhaustive. Take caution with other drugs that are also inhibitors or enhancers of CYP3A4 and CYP2D6 enzymes. EPSEs, extrapyramidal side effects; INR, international normalised ratio.

Prescribing in older people CHAPTER 6 continue treatment should be informed by potential risks of withdrawal, even if the perceived benefits of continued treatment are not clear.76 A 2021 Cochrane review came to similar conclusions.36 The consensus opinion is that if the drug is well tolerated and the patient’s physical health is stable, then it is probably best to continue the drug. The risks of discontinuation of dementia medication should be balanced against the adverse effects.77 In addition to this, a meta-analysis evaluating the efficacy of the three AChE-Is and memantine in relation to the severity of AD found that the efficacy of all drugs except memantine was independent of dementia severity in all domains. The effect of memantine on functional impairment was actually better in patients with more severe AD. This suggests that the severity of a patient’s illness should not preclude treatment with these drugs.78 Guidance for discontinuation of dementia medication in clinical practice is summarised here.79 Reasons for stopping treatment

■ ■When the patient/caregiver decides to stop (after being advised on the risks and benefits of stopping treatment). ■ ■When the patient refuses to take the medication (but see ‘Covert administration of medicines within food and drink’ later in this chapter). ■ ■When there are problems with patient compliance which cannot be reasonably resolved. ■ ■When the patient’s cognitive, functional or behavioural decline is worsened by treatment. ■ ■When there are intolerable adverse effects. ■ ■When comorbidities make treatment risky or futile (e.g. terminal illness). ■ ■Where there is no clinically meaningful benefit to continuing therapy (clinical judgement should be used here rather than ceasing treatment when a patient reaches a certain score on a cognitive outcome or when they are institutionalised). ■ ■When dementia has progressed to a severely impaired stage (Global Deterioration Scale stage 7: development of swallowing difficulties). When a decision is made to stop therapy (for reasons other than lack of tolerability), tapering of the dose and monitoring the patient for evidence of significant decline during the next 1–3 months are advised. If such decline occurs, reinstatement of therapy should be considered. NICE recommendations NICE guidance on dementia80 was last updated in June 2018 (Box 6.2). Other treatments (where the evidence remains less certain) A 2009 Cochrane review81 concluded that Ginkgo biloba appears to be safe in use with no excess adverse effects compared with placebo, but the evidence that it has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable. In contrast, a 2015 systematic review and meta-analysis82

CHAPTER 6 Box 6.2 Summary of NICE guidance for the treatment of AD80,83 ■ ■The three AChE--Is donepezil, galantamine and rivastigmine are recommended for managing mild to moderate AD ■ ■Memantine is recommended for managing moderate AD for people who are intolerant of or have a contraindication to AChE-Is or for managing severe AD ■ ■For people with an established diagnosis of AD who are already taking an AChE-I: ■ ■consider memantine in addition to an AChE-I if they have moderate disease ■ ■offer memantine in addition to an AChE-I if they have severe disease ■ ■For people who are not taking an AChE-I or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include: ■ ■secondary care medical specialists such as psychiatrists, geriatricians and neurologists ■ ■other healthcare professionals (such as GPs, nurse consultants and advanced nurse practitioners) if they have specialist expertise in diagnosing and treating AD ■ ■Once a decision has been made to start an AChE-I or memantine, the first prescription may be made in primary care ■ ■For people with an established diagnosis of AD who are already taking an AChE-I, primary care prescribers may start treatment with memantine without taking advice from a specialist clinician ■ ■Ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation84 ■ ■Do not stop AChE-Is in people with AD because of disease severity alone ■ ■Therapy with an AChE-I should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). An alternative may be considered on the basis of adverse effects profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles Summary of NICE guidance for the treatment of non-AD dementia80,83 ■ ■Offer donepezil or rivastigmine to people with mild to moderate DLB ■ ■Only consider galantamine for people with mild to moderate DLB if donepezil and rivastigmine are not tolerated ■ ■Consider donepezil or rivastigmine for people with severe DLB ■ ■Consider memantine for people with DLB if AChE-Is are not tolerated or are contraindicated ■ ■Only consider AChE-Is or memantine for people with VaD if they have suspected comorbid AD, Parkinson’s disease dementia or DLB ■ ■Do not offer

AChE-Is or memantine to people with frontotemporal dementia ■ ■Do not offer AChE-Is or memantine to people with cognitive impairment caused by multiple sclerosis ■ ■For guidance on pharmacological management of Parkinson's disease dementia, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease Medicines that may cause cognitive impairment1 ■ ■Be aware that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment ■ ■Consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives: ■ ■when assessing whether to refer a person with suspected dementia for diagnosis ■ ■during medication reviews with people living with dementia ■ ■Be aware that there are validated tools for assessing anticholinergic burden but there is insufficient evidence to recommend one over the others (see 'Safer prescribing for physical conditions in dementia' later in this chapter). ■ ■For guidance on carrying out medication reviews, see the medication review in the NICE guideline on medicines optimisation84 NB The Anticholinergic Effect on Cognition (AEC) scale can be accessed at www.medichec.com. AChE-I, acetylcholinesterase inhibitors; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; VaD, vascular dementia.

Prescribing in older people CHAPTER 6 found that Ginkgo biloba 240mg/day was able to stabilise or slow decline in cognition, function, behaviour and global change at 22–26 weeks in patients with cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms. A 2022 umbrella review confirmed the efficacy of Ginkgo.85 Several reports have noted that Ginkgo may increase the risk of bleeding.86 The findings of a systematic review87 suggest that supplementation of B complex vitamins, especially folic acid, may have a positive effect on delaying and preventing the risk of cognitive decline. Ascorbic acid and a high dose of vitamin E, when given separately, also showed positive effects on cognitive performance, but there is not sufficient evidence to support their use. The results of vitamin D supplementation trials are not conclusive in assessing the potential benefits that vitamin D might have on cognition. A Cochrane review of omega-3 fatty acids for the treatment of dementia (632 people with mild to moderate AD) found that taking omega-3 polyunsaturated fatty acid supplements for 6 months had no effect on cognition (learning and understanding), everyday functioning, quality of life or mental health. The trials did not report side effects very well, but none of the studies described significant harmful effects on health.88 A systematic review and meta-analysis including four RCTs involving 259 participants suggested that the effects of ginseng on AD remain unproven.89 Natural hirudin, isolated from the salivary gland of the medicinal leech, is a direct thrombin inhibitor and has been used for many years in China. A small 20-week open- label RCT of 84 patients receiving donepezil or donepezil plus hirudin (3g/day) found that patients on the combination showed significant decrease in ADAS-cog scores and significant increase in ADL scores compared with donepezil alone. However, haemorrhage and hypersensitivity reactions were more common in the combination group than in the donepezil group (11.9% and 7.1% vs 2.4% and 2.4%, respectively).77 The potential haemorrhagic effects of hirudin need further exploration before it can be considered for clinical use. Huperzine A, an alkaloid isolated from the Chinese herb Huperzia serrata, is a potent, highly selective, reversible AChE-I used for treating AD since 1994 in China and available as a nutraceutical in the USA. Despite its promising effects on cognition and ADLs, there is insufficient evidence to support its use in dementia90 or MCI90,91 due to the high heterogeneity of reviews and low quality of primary studies. High-quality, large, multicentre RCTs with long-term follow-up in different settings are warranted but no studies have been published since 2020. A Cochrane review of huperzine A in VaD found no convincing evidence for its value in VaD.92 There

is increasing evidence to suggest possible efficacy of Crocus sativus (saffron) in the management of AD. A systematic review and meta-analysis of RCTs revealed that saffron significantly improves cognitive function measured by ADAS-cog and the Clinical Dementia Rating Scale – Sums of Boxes (CDR-SB) compared with placebo groups. In addition, there was no difference between saffron and conventional medicines (donepezil, memantine). No serious adverse events were reported in the included studies. Saffron may be beneficial in improving cognitive function in patients with MCI and AD, however no evidence was found to support its effects on other types of dementia. More high--quality randomised placebo-controlled trials are needed to further confirm the efficacy and safety of saffron for MCI and dementia.93 Cerebrolysin is a parenterally administered, porcine brain--derived peptide preparation that has pharmacodynamic properties similar to those of endogenous neurotrophic

644 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 factors. A meta-analysis included six RCTs comparing cerebrolysin 30mg/day with placebo in mild to moderate AD. Cerebrolysin was more effective than placebo at 4 weeks regarding cognitive function and at 4 weeks and 6 months regarding global clinical change and 'global benefit'. Its safety was comparable with placebo. In addition, a large 28-week RCT comparing cerebrolysin, donepezil or combination therapy showed (i) higher improvements in global outcome for cerebrolysin and the combination therapy than for donepezil alone at study endpoint; (ii) a lack of significant group differences in cognitive, functional and behavioural domains at the endpoint; and (iii) best scores of cognitive improvement in the combination therapy group at all study visits.94 This therapeutic option requires further investigation in large trials. A Cochrane review assessing cerebrolysin in VaD found that intravenous courses improved cognition and general function in people living with VaD, with no suggestion of adverse effects. However, these data are not definitive. The analyses were limited by heterogeneity, and studies had high risk of bias. If there are benefits, the effects may be too small to be clinically meaningful. Cerebrolysin continues to be used and promoted as a treatment for VaD, but the supporting evidence base is weak. The most commonly reported non--serious adverse events were headache, aesthenia, dizziness, hypertension and hypotension.95 For information on statins see 'Safer prescribing for physical conditions in dementia' later in this chapter. A longitudinal prospective study examined the relationship between chocolate consumption and cognitive decline in an elderly cognitively healthy population. A total of 531 participants aged ≥65 years with normal MMSE scores were followed for a median of 48 months. Dietary habits were evaluated at baseline and the MMSE was used to assess global cognitive function at baseline and at follow-up. After adjustment for confounders, chocolate intake was associated with a 41% lower risk of cognitive decline. This protective effect was observed only among subjects with an average daily consumption of caffeine lower than 75mg.96 Souvenaid is a medical food for the dietary management of early AD. A Cochrane review97 concluded that it probably does not reduce the risk of progression to dementia, there is no convincing evidence that it affects other outcomes important to people with AD (in the prodromal stage or mild to moderate stages) and its effects in more severe AD remain unclear. Idalopirdine is a 5HT6 receptor antagonist. The 5HT6 receptor is expressed in areas of the CNS involved with memory and there is evidence suggesting that blocking of these receptors induces acetylcholine release and could restore ACh levels in a deteriorated cholinergic system.98 A systematic review and meta-analysis analysed four RCTs with 2803 patients with AD. Idalopirdine was not shown to be effective for AD patients and is associated with a risk of elevated liver enzymes and vomiting. Although idalopirdine might be more effective at high doses and in moderate AD subgroups, the effect size is small.99 A

large number of RCTs of anti-inflammatory drugs in AD have failed to reach primary outcomes. Large-scale studies of non-steroidal anti-inflammatory drugs (NSAIDs) including indomethacin, naproxen and rofecoxib in AD have been unsuccessful. RCTs with a range of other anti--inflammatory drugs including prednisolone, hydroxychloroquine, simvastatin, atorvastatin, aspirin and rosiglitazone have also shown no clinically significant changes in primary cognitive outcomes in patients with AD.23 A 2020 Cochrane review evaluated aspirin and other NSAIDs for the prevention of dementia

Prescribing in older people CHAPTER 6 and found no evidence to support the use of low-dose aspirin or other NSAIDs of any class (celecoxib, rofecoxib, naproxen) for the prevention of dementia. There was, however, evidence of harm including higher rates of death and major bleeding compared with placebo with aspirin, and in one of the studies more people developed dementia in the NSAID group. More stomach bleeding and other stomach problems, such as pain, nausea and gastritis, were also reported with NSAIDs.100 Two existing compounds, trazodone and dibenzoylmethane, were found to be markedly neuroprotective in mouse models of neurodegeneration, using clinically relevant doses over a prolonged period of time, without systemic toxicity. Trazodone, a serotonin antagonist and reuptake antidepressant with additional anxiolytic and hypnotic effects, was associated with delayed cognitive decline in a small retrospective study examining its long-term use. Trazodone non-users had a 2.6-fold faster decline in MMSE (primary outcome) assessment than trazodone users.101 However, a study of UK population- based electronic health records found no association between trazodone use and a reduced risk of dementia compared with other antidepressants. These results suggest that the clinical use of trazodone is not associated with a reduced risk of dementia.102 Similarly, three identical naturalistic cohort studies using UK clinical registers found no evidence of cognitive benefit from trazodone compared with other antidepressants in people with dementia.104 Despite pre-clinical evidence, trazodone should not be prescribed for cognition in dementia.103 There are no observational data suggesting trazodone reduces risk of dementia but some data that suggest important adverse outcomes in older people.104 Dibenzoylmethane (DBM) is a minor constituent of liquorice that has been found to have antineoplastic effects, with efficacy against prostate and mammary tumours. In prion-diseased mice, both trazodone and DBM treatment restored memory deficits, abrogated the development of neurological signs, prevented neurodegeneration and significantly prolonged survival. In tauopathy-frontotemporal dementia mice, both drugs were neuroprotective, rescued memory deficits and reduced hippocampal atrophy. Further, trazodone reduced p-tau burden.105 KarXT (xanomeline plus trospium (Cobenfy)) is an investigational treatment that has shown early promise in the treatment of positive and negative symptoms of schizophrenia. Unlike all currently approved treatments for schizophrenia, KarXT does not directly bind to dopamine receptors; instead, the therapeutic effects of KarXT appear to be mediated through direct agonism of muscarinic acetylcholine receptors. To mitigate the cholinomimetic effects of xanomeline (e.g. vomiting), trospium is combined with xanomeline. Findings suggest that KarXT may have a separable and meaningful impact on cognition, particularly among patients with cognitive impairment.106 Quercetin is a flavonoid widely distributed among plants and found commonly in our daily diet (fruits and vegetables). It has beneficial properties against general mechanisms of AD aetiology; it protects neuronal cells by attenuating oxidative stress and neuro inflammation. Quercetin inhibits β-amyloid (Aβ) aggregation and tau phosphorylation and restores acetylcholine levels through the inhibition of hydrolysis of acetylcholine by AChE enzyme. Although showing neuroprotective efficacy in several in vitro and animal models, in vivo studies have

reported that it is extensively metabolised upon absorption from the gut, affecting its bioavailability, and has low blood–brain barrier penetrability, thus limiting its efficacy in combating neurodegenerative disorders. Therefore, future clinical trials must improve its bioavailability, developing related molecules with greater gut and brain penetrability, which will likely improve clinical efficacy.107

646 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Novel treatments Amyloid plaques are composed of β-amyloid (Aβ) in the extracellular space. Aβ is derived from the amyloid precursor protein (APP), a transmembrane protein. B secretase and γ secretase cleave the APP and generate pathological Aβ, and accumulation of Aβ results in neurotoxicity. Reducing the accumulation of Aβ has become a therapeutic purpose of AD. Antiamyloid therapy consists of three strategies: secretase inhibitors, Aβ aggregation inhibitors and Aβ immunotherapy.108 Aducanumab is an antibody that works by targeting Aβ and preferentially binds to the aggregated Aβ. Through this interaction, aducanumab could reduce the build-up of Aβ and therefore the number of amyloid plaques present in the brain, thus potentially slowing neurodegeneration and disease progression. Although in early 2019 the manufacturers (Biogen) announced that aducanumab failed futility analyses in two identically designed phase III AD trials and discontinued its development, later in the year they made the announcement that they were applying for US FDA marketing approval. They explained they had reanalysed data from the trials to include patients who had continued in the studies after the cut-off date for the futility analyses and stated that one trial showed significant findings and a subset from the second trial supports these positive findings.109 One concern with aducanumab was the frequency of adverse effects, particularly amyloid-related imaging abnormalities (ARIAs). In June 2021, the FDA made the decision to grant conditional accelerated approval for aducanumab to treat AD patients. Aducanumab was not approved in Europe. The phase III trial of lecanemab (Clarity-AD trial) was more encouraging. Lecanemab lowers brain Aβ plaque burden through binding to soluble Aβ protofibrils as well as (to a variable extent) other forms of Aβ. The study included 1795 participants with MCI or early AD plus evidence of amyloid on a positron emission tomography (PET) scan or by cerebrospinal fluid testing. They were randomly assigned to receive 10mg/kg body weight of lecanemab via intravenous infusion every 2 weeks or matched placebo. After 18 months, lecanemab reduced cognitive decline, as measured by CDR-SB, which quantifies symptom severity across a range of cognitive and functional domains, by 27% compared with placebo; an absolute difference of 0.45 points (change from baseline 1.21 for lecanemab vs 1.66 with placebo, $p < 0.001$). All key secondary endpoints were also met. The incidence of ARIAs, which manifest as oedema or microhaemorrhages, was 21% of the lecanemab group. Most cases were asymptomatic and detected incidentally. However, reports of deaths in the open-label extension phase of the study (possibly linked to co--administration of the thrombolytic drug alteplase) have heightened concerns about lecanemab's safety in patients taking thrombolytic drugs.110,111 Lecanemab has been approved by the FDA and was undergoing a full evaluation by the European Medicines Agency at the time of writing.112 Donanemab is another high-potency antiamyloid drug infused intravenously every 4 weeks. In 2022, results were announced for the phase III trial (TRAILBLAZER-ALZ 2 trial) which included 1736 participants with early symptomatic AD (MCI/mild dementia) with amyloid and low/medium or high tau pathology based on PET imaging. Compared with placebo, donanemab treatment over 18 months resulted in slowing of cognitive and functional decline by approximately 35% in the primary target population studied. In addition, 52% of treated participants converted to amyloid PET-negative status by 12 months. ARIA-E (with oedema) and ARIA-H (with microhaemorrhage/haemosiderosis) occurred in

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