11 - Chapter 6 Prescribing in older people

01 - General principles in prescribing in older ad

General principles in prescribing in older adults

02 - General principles

General principles

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. General principles in prescribing in older adults General principles The pharmacokinetics and pharmacodynamics of most drugs are altered to an important extent in older people. These changes in drug handling and action must be taken into account if treatment is to be effective and adverse effects minimised. Older people often have a number of concurrent illnesses and may require treatment with several drugs. This leads to a greater chance of problems arising because of drug interactions and a higher rate of drug-induced problems in general.1 It is reasonable to assume that all drugs are more likely to cause adverse effects in older patients than in younger patients (Box 6.1). How drugs affect the ageing body (altered pharmacodynamics) As we age, control over reflex actions such as blood pressure and temperature regulation is reduced. Receptors may become more sensitive. This results in an increased incidence and severity of adverse effects. For example, drugs that decrease gut motility are more likely to cause constipation (e.g. anticholinergics and opioids) and drugs that affect blood pressure are more likely to cause falls (e.g. tricyclic antidepressants [TCAs] Chapter 6 Prescribing in older people Box 6.1 Reducing drug-related risk in older people Adherence to the following principles will reduce drug--related morbidity and mortality: ■ ■Use drugs only when absolutely necessary ■ ■Avoid, if possible, drugs that block α1 adrenoceptors, have anticholinergic adverse effects, are very sedative, have a long half-life or are potent inhibitors of hepatic metabolising enzymes ■ ■Start with a low dose and increase slowly but do not undertreat. Some drugs still require the full adult dose ■ ■Try not to treat the adverse effects of one drug with another drug. Find a better-tolerated alternative ■ ■Keep therapy simple; that is, once-daily administration whenever possible

03 - Drug interactions

Drug interactions

628 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 and diuretics). Older people demonstrate an exaggerated response to central nervous system (CNS)-active drugs such as benzodiazepines and opioids. This is partly because of an age-related decline in CNS function and partly due to increased pharmacodynamic sensitivity to these drugs (due to increased blood–brain barrier permeability).2,3 Therapeutic response to medication can also be delayed; for example, older adults may take longer to respond to antidepressants than younger adults.4 Older people may be more prone to developing serious adverse effects such as agranulocytosis5 and neutropenia6 with clozapine, stroke with antipsychotic drugs7 and bleeding with selective serotonin reuptake inhibitors (SSRIs).8 How ageing affects drug therapy (altered pharmacokinetics)9,10 Absorption Gut motility decreases with age, as does secretion of gastric acid. This leads to drugs being absorbed more slowly, resulting in a slower onset of action. In general, the same amount of drug is absorbed as in a younger adult, but the rate of absorption is slower. Distribution Older adults have more body fat, less body water and less albumin than younger adults. This leads to an increased volume of distribution and a longer duration of action for some fat-soluble drugs (e.g. diazepam), higher concentrations of some drugs at the site of action (e.g. digoxin) and a reduction in the amount of drug bound to albumin (increased amounts of active ‘free drug’; e.g. warfarin, phenytoin). Metabolism The majority of drugs are hepatically metabolised. Liver size is reduced in the elderly, but in the absence of hepatic disease or significantly reduced hepatic blood flow, there is no significant reduction in metabolic capacity. The magnitude of pharmacokinetic interactions is unlikely to be altered but the pharmacodynamic consequences of these interactions may be amplified. Excretion Renal function declines with age: 35% of function is lost by the age of 65 years and 50% by the age of 80. More function is lost if there are concurrent medical problems such as heart disease, diabetes or hypertension. Measurement of serum creatinine or urea can be misleading in the elderly because muscle mass is reduced, so less creatinine is produced. It is particularly important that estimated glomerular filtration rate (eGFR)11 is used as a measure of renal function in this age group. It is best to assume that all elderly patients have at most two-thirds of normal renal function. Most drugs are eventually (after metabolism) excreted by the kidney. A few do not undergo biotransformation first. Lithium and sulpiride are important examples. Drugs primarily excreted via the kidney will accumulate in the elderly, leading to toxicity and adverse effects. Dosage reduction is likely to be required (see Chapter 8). Drug interactions Some drugs have a narrow therapeutic index (a small increase in dose can cause toxicity and a small reduction in dose can cause a loss of therapeutic action). The most commonly prescribed ones are digoxin, warfarin, theophylline, phenytoin and lithium.

04 - Administering medicines in foodstuffs1316

Administering medicines in foodstuffs13–16

05 - References

References

Prescribing in older people CHAPTER 6 Changes in the way these drugs are handled in older people and the greater chance of interaction with other drugs mean that toxicity and therapeutic failure are more likely. These drugs can be used safely but extra care must be taken and blood concentrations should be measured where possible. Some drugs inhibit or induce hepatic metabolising enzymes. Important examples include some SSRIs, erythromycin and carbamazepine. This may lead to the metabolism of another drug being altered. Many drug interactions occur through this mechanism. Details of individual interactions and their consequences can be found in the British National Formulary (BNF) online for individual drugs.12 Most can be predicted by a sound knowledge of pharmacology. Administering medicines in foodstuffs13–16 Sometimes patients refuse treatment with medicines, even when such treatment is thought to be in their best interests. In the UK, where the patient has a mental illness or has capacity, the Mental Health Act should be used, but if the patient lacks capacity this option may not be desirable. Medicines should never be administered covertly to older patients with dementia without a full discussion with the multidisciplinary team (MDT) and the patient's relatives. The outcome of this discussion should be clearly documented in the patient's clinical notes. Medicines should be administered covertly only if the clear and express purpose is to reduce suffering for the patient. (For further information, see 'Covert administration of medicines within food and drink' later in this chapter.) For advice on dosing of psychotropics in older people, see 'A guide to medication doses of commonly used psychotropics in older adults' later in this chapter. References

1. Royal College of Physicians. Medication for older people. Summary and recommendations of a report of a working party of The Royal College of Physicians. J R Coll Physicians Lond 1997; 31:254–257.
2. Bowie MW, et al. Pharmacodynamics in older adults: a review. Am J Geriatr Pharmacother 2007; 5:263–303.
3. Cleare A, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015; 29:459–525.
4. Baldwin R, et al. Management of depression in later life. Adv Psychiatr Treat 2004; 10:131–139.
5. Munro J, et al. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry 1999; 175:576–580.
6. O'Connor DW, et al. The safety and tolerability of clozapine in aged patients: a retrospective clinical file review. World J Biol Psychiatry 2010; 11:788–791.
7. Douglas IJ, et al. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 2008; 337:a1227.

8. Paton C, et al. SSRIs and gastrointestinal bleeding. BMJ 2005; 331:529–530.
9. Mayersohn M. Special pharmacokinetic considerations in the elderly. In: Evans W, Schentage J, Jusko J, eds. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. Vancouver, WA: Applied Therapeutics Inc; 1992.
10. Dening T, Thomas A, Stewart R, Taylor JP, eds. Oxford Textbook of Old Age Psychiatry. Oxford: Oxford University Press; 2020.
11. Morriss R, et al. Lithium and eGFR: a new routinely available tool for the prevention of chronic kidney disease. Br J Psychiatry 2008; 193:93–95.
12. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete.com.
13. Royal College of Psychiatrists. College statement on covert administration of medicines. Psychiatric Bull 2004; 28:385–386.
14. Haw C, et al. Administration of medicines in food and drink: a study of older inpatients with severe mental illness. Int Psychogeriatr 2010; 22:409–416.
15. Haw C, et al. Covert administration of medication to older adults: a review of the literature and published studies. J Psychiatr Ment Health Nurs 2010; 17:761–768.
16. Specialist Pharmacy Service. Covert administration of medicines in adults: pharmaceutical issues 2022 (last updated June 2023); https://www.sps. nhs.uk/articles/covert--administration-of-medicines-in-adults-pharmaceutical-issues/.

06 - Dementia

Dementia

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, © 2007 by The Royal College of Psychiatrists.

 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

08 - Vascular dementia (VaD)

Vascular dementia (VaD)

Prescribing in older people CHAPTER 6 24.0% and 31.4% of treated individuals, respectively.113,114 Donanemab is, at the time of writing, undergoing a full evaluation by the FDA and NICE. The development of three monoclonal antibodies, gosuranemab, tilavonemab and zagotenemab, was terminated due to negative results. A phase II study of semorinemab, an anti--tau monoclonal antibody, was negative. While semorinemab had a significant effect on cognition measured by the ADAS-Cog11, this effect did not extend to improved functional or global outcomes.115 Further exploration is required. Clinical trials of anti-tau vaccines are underway. In addition to the above, results of recent trials of solanezumab, crenezumab and gantenerumab were all negative. Vascular dementia (VaD) Vascular dementia comprises 10–50% of dementia cases and is the second most common type of dementia after AD. It is caused by ischaemic damage to the brain and is associated with cognitive impairment and behavioural disturbances. The management options are currently very limited and focus on controlling the underlying risk factors for cerebrovascular disease.116 Note that it is impossible to diagnose with certainty vascular or Alzheimer's dementia and much dementia has mixed causation. This might explain why certain AChE-Is do not always provide consistent results in probable VaD and the data indicating efficacy in cognitive outcomes were derived from older patients, who were therefore likely to have concomitant AD pathology.117 None of the currently available drugs is formally licensed in the UK for VaD. The management of VaD has been summarised.118,119 Unlike the situation with stroke, there is no conclusive evidence that treatment of hyperlipidaemia with statins or treatment of blood clotting abnormalities with acetylsalicylic acid has an effect on VaD incidence or disease progression.120 Similarly, a Cochrane review found that there were no studies supporting the role of statins in the treatment of VaD.121 A Cochrane review of cholinesterase inhibitors for VaD and other vascular cognitive impairments found moderate- to high-certainty evidence that donepezil 5mg, donepezil 10mg and galantamine 16–24mg have a slight beneficial effect on cognition in people with vascular cognitive impairment, although the size of the change is unlikely to be clinically important. Donepezil 10mg and galantamine 16–24mg are probably associated with more adverse events than placebo. The evidence for rivastigmine was less certain. Data suggest that donepezil 10mg has the greatest effect on cognition, but at the cost of adverse effects. The effect is modest, but in the absence of any other treatments, these agents may be considered in people living with vascular cognitive impairments. Further research into rivastigmine is needed, including the use of transdermal patches.122 A meta-analysis of RCTs found that cholinesterase inhibitors and memantine produce small benefits in cognition of uncertain clinical significance and concluded

that data were insufficient to support widespread use of these agents in VaD; the effect is lower than that seen in AD, although no direct comparison has been made.116 A systematic review and Bayesian network meta-analysis comparing the efficacy and safety of cognitive enhancers for treating vascular cognitive impairment found significant efficacy for donepezil, galantamine and memantine on cognition. Memantine was found to provide significant efficacy in global status. They were all safe and well tolerated.123

09 - Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies (DLB)

10 - Mild cognitive impairment (MCI)

Mild cognitive impairment (MCI)

11 - Other dementias

Other dementias

648 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Dementia with Lewy bodies (DLB) DLB may account for 15–25% of cases of dementia. Characteristic symptoms are dementia with fluctuation of cognitive ability, early and persistent visual hallucinations and spontaneous motor features of parkinsonism. Falls, syncope, transient disturbances of consciousness, neuroleptic sensitivity and hallucinations in other modalities are also common.124 There are significant complexities in managing an individual with DLB. Presentation varies between patients and can vary over time within an individual. Treatments can address one symptom but worsen another, which makes disease management difficult. Symptoms are often managed in isolation and by different specialists, which makes high-quality care difficult to accomplish. Clinical trials and meta-analyses now provide an evidence base for the treatment of cognitive, neuropsychiatric and motor symptoms in patients with DLB.125 In summary, robust evidence exists for the efficacy of rivastigmine and donepezil in the treatment of cognitive symptoms in patients with DLB, but high--quality RCTs of galantamine are needed. Memantine could have some benefits, but further studies with larger numbers of patients are also needed to determine whether there is an improvement and, if so, which specific symptoms are improved. Whether memantine should be used as a monotherapy or whether it should be combined with cholinesterase inhibitors is also unclear.125,126 For a helpful guide on the management of specific symptoms in DLB see the management of DLB summary sheets.127 The 2018 update of the NICE guidelines1 recommends the use of AChE-Is and memantine (if AChE-Is are not tolerated) in DLB and Parkinson’s disease dementia (see Box 6.2). Mild cognitive impairment (MCI) Mild cognitive impairment is hypothesised to represent a pre-clinical stage of dementia but forms a heterogeneous group with variable prognosis. A Cochrane review assessing the safety and efficacy of AChE-Is in MCI found there was very little evidence that they affect progression to dementia or cognitive test scores. This weak evidence was countered by the increased risk of adverse effects, particularly gastrointestinal effects, meaning that AChE-Is could not be recommended in MCI.128 A systematic review129 found that there was no replicated evidence that any intervention was effective for MCI including AChE-Is and the NSAID rofecoxib. A further systematic review and meta-analysis found that although AChE-Is have a slight efficacy in the treatment of MCI, there are many safety issues, therefore they are difficult to recommend for MCI.130 Experts from several different countries have reviewed the available evidence for the pharmacological and non-pharmacological treatment for MCI.131,132 Other dementias A systemic review of RCTs for frontotemporal dementias showed that certain drugs may be effective in reducing behavioural symptoms (e.g. SSRIs, trazodone) but none of these had an effect on cognition.133 Due to new techniques in neuroimaging,

12 - Summary of clinical practice guidance for use

Summary of clinical practice guidance for use of anti-dementia drugs

Prescribing in older people CHAPTER 6 genetics and biomarker analysis, much has been discovered about the phenomena underlying frontotemporal lobar degeneration. This has allowed the design of new molecule-based therapies that are still in the early stages of research but may show promise.134 A Cochrane review assessed the efficacy and safety of AChE-Is for rare dementias associated with neurological conditions. The sample sizes of most trials were very small and efficacy on cognitive function was found to be unclear, although AChE-Is were associated with more gastrointestinal adverse effects than placebo.135 Summary of clinical practice guidance for use of anti-dementia drugs AChE-Is and memantine are effective in AD of a broad range of severity. Other drugs including statins, anti-inflammatory drugs, vitamin E, nutritional supplements and Gingko cannot be recommended either for the treatment or prevention of AD. Neither AChE-Is nor memantine are effective in MCI. AChE-Is are not effective in frontotemporal dementia and may cause agitation. AChE-Is may be used for people with Lewy body dementia (both Parkinson's disease dementia and DLB), and memantine may be helpful. No drugs are clearly effective in VaD, though AChE-Is are beneficial in mixed dementia. Early evidence suggests multifactorial interventions may have the potential to prevent or delay the onset of dementia. Many novel pharmacological approaches involving strategies to reduce amyloid and/or tau deposition in those with or at high risk of AD are in progress. Although results of pivotal studies in early (prodromal/ mild) AD are awaited, results to date in more established (mild to moderate) AD have been equivocal and no disease-modifying agents are either licensed or can be currently recommended for clinical use. Table 6.3 summarises the clinical practice guidelines from BAP.23 Table 6.3 Summary of British Association for Psychopharmacology recommendations. First choice Second choice Alzheimer's disease AChE-Is Memantine Vascular dementia None (some benefit with donepezil 10mg – but risk of adverse effects) None Mixed dementia AChE-Is Memantine Dementia with Lewy bodies AChE-Is Memantine Mild cognitive impairment None None Dementia with Parkinson's disease AChE-Is Memantine Frontotemporal dementia None None AChE-Is,

acetylcholinesterase inhibitors.

13 - References

References

1. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. NICE Guideline [NG97]. 2018 (checked September 2023, last accessed December 2023); https://www.nice.org.uk/guidance/ng97.
2. Francis PT, et al. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 1999; 66:137–147.
3. Craig LA, et al. Revisiting the cholinergic hypothesis in the development of Alzheimer's disease. Neurosci Biobehav Rev 2011; 35:1397–1409.
4. Mesulam M, et al. Widely spread butyrylcholinesterase can hydrolyze acetylcholine in the normal and Alzheimer brain. Neurobiol Dis 2002; 9:88–93.
5. Weinstock M. Selectivity of cholinesterase inhibition: clinical implications for the treatment of Alzheimer's disease. CNS Drugs 1999; 12:307–323.
6. Matsunaga S, et al. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PLoS One 2015; 10:e0123289.
7. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete. com.
8. Eisai Ltd. Summary of product characteristics. Aricept 5mg, 10mg tablets (donepezil). 2023; https://www.medicines.org.uk/emc/ product/3776/smpc.
9. Novartis Pharmaceuticals UK Ltd. Summary of product characteristics. Exelon 4.6mg/24h, 9.5mg/24h, 13.3mg/24h transdermal patch. 2023; https://www.medicines.org.uk/emc/product/7764/smpc.
10. Sandoz Ltd. Summary of product characteristics. Rivastigmine Sandoz 1.5mg, 3mg, 4.5mg, 6mg hard capsules. 2021; https://www.medicines. org.uk/emc/product/8407/smpc.
11. Takeda UK Ltd. Summary of product characteristics. Reminyl XL 8mg, 16mg, 24mg prolonged release capsules. 2022; https://www.medicines. org.uk/emc/product/3934/smpc.
12. Takeda UK Ltd. Summary of product characteristics. Reminyl oral solution. 2022; https://www.medicines.org.uk/emc/medicine/10337.
13. Lundbeck Ltd. Summary of product characteristics. Ebixa 5mg/pump actuation oral solution, 20mg and 10 mg tablets and treatment initiation pack. 2021; https://www.medicines.org.uk/emc/product/8222/smpc.
14. NHS Prescription Services. Electronic Drug Tariff. 2020; http://www.drugtariff.nhsbsa.nhs.uk/#/00791628-DD/DD00791615/Home2020.

15. Buckley JS, et al. A risk-benefit assessment of dementia medications: systematic review of the evidence. Drugs Aging 2015; 32:453–467.
16. Lanctot KL, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003; 169:557–564.
17. McShane R, et al. Memantine for dementia. Cochrane Database Syst Rev 2019; 3:CD003154.
18. Vaci N, et al. Real-world effectiveness, its predictors and onset of action of cholinesterase inhibitors and memantine in dementia: retrospective health record study. Br J Psychiatry 2021; 218:261–267.
19. Zuin M, et al. Acetyl-cholinesterase-inhibitors slow cognitive decline and decrease overall mortality in older patients with dementia. Sci Rep 2022; 12:12214.
20. Burns A, et al. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007; 22:806–812.
21. Doody RS, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001; 58:427–433.
22. Farlow MR, et al. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007; 120:388–397.
23. O'Brien JT, et al. Clinical practice with anti-dementia drugs: a revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol 2017; 31:147–168.
24. Singh S, et al. Discontinuation syndrome following donepezil cessation. Int J Geriatr Psychiatry 2003; 18:282–284.
25. Bidzan L, et al. Withdrawal syndrome after donepezil cessation in a patient with dementia. Neurol Sci 2012; 33:1459–1461.
26. Waldemar G, et al. Tolerability of switching from donepezil to memantine treatment in patients with moderate to severe Alzheimer's disease. Int J Geriatr Psychiatry 2008; 23:979–981.
27. Massoud F, et al. Switching cholinesterase inhibitors in older adults with dementia. Int Psychogeriatr 2011; 23:372–378.
28. Winblad B, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease – rivastigmine patch versus capsule. Int J Geriatr Psychiatry 2007; 22:456–467.
29. Zhang ZX, et al. Rivastigmine patch in Chinese patients with probable Alzheimer's disease: a 24-week, randomized, double-blind parallel-group study comparing rivastigmine patch (9.5 mg/24 h) with capsule (6 mg twice daily). CNS Neurosci Ther 2016; 22:488–496.
30. Morgan TM, et al. Absolute bioavailability and safety of a novel rivastigmine nasal spray in healthy elderly individuals. Br J Clin Pharmacol 2017; 83:510–516.
31. Knopman DS. Donepezil 23 mg: an empty suit. Neurol Clin Pract 2012; 2:352–355.
32. Plosker GL. Memantine extended release (28 mg once daily): a review of its use in Alzheimer's disease. Drugs 2015; 75:887–897.
33. Deardorff WJ, et al. A fixed-dose combination of memantine extended-release and donepezil in the treatment of moderate-to-severe Alzheimer's disease. Drug Des Devel Ther 2016; 10:3267–3279.
34. Veroniki AA, et al. Comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia: a systematic review with individual patient data network meta-analysis. BMJ

Open 2022; 12:e053012.
35. Guo J, et al. Memantine, donepezil, or combination therapy – what is the best therapy for Alzheimer's disease? A network meta-analysis. Brain Behav 2020; 10:e01831.
36. Parsons C, et al. Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia. Cochrane Database Syst Rev 2021; 2:CD009081.
37. Periclou AP, et al. Lack of pharmacokinetic or pharmacodynamic interaction between memantine and donepezil. Ann Pharmacother 2004; 38:1389–1394.

Prescribing in older people CHAPTER 6 38. Grossberg GT, et al. Rationale for combination therapy with galantamine and memantine in Alzheimer's disease. J Clin Pharmacol 2006; 46:17S–26S. 39. Rogers SL, et al. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998; 158:1021–1031. 40. Rogers SL, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998; 50:136–145. 41. Corey-Bloom J, et al. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998; 1:55–64. 42. Rosler M, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999; 318:633–638. 43. Tariot PN, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000; 54:2269–2276. 44. Raskind MA, et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6--month extension. The Galantamine USA-1 Study Group. Neurology 2000; 54:2261–2268. 45. Wilcock GK, et al. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000; 321:1445–1449. 46. Pariente A, et al. Factors associated with serious adverse reactions to cholinesterase inhibitors: a study of spontaneous reporting. CNS Drugs 2010; 24:55–63. 47. Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. Int J Clin Pract Suppl 2002; 127:45–63. 48. Sadowsky CH, et al. Safety and tolerability of rivastigmine transdermal patch compared with rivastigmine capsules in patients switched from donepezil: data from three clinical trials. Int J Clin Pract 2010; 64:188–193. 49. Sadowsky C, et al. Switching from oral cholinesterase inhibitors to the rivastigmine transdermal patch. CNS Neurosci Ther 2010; 16:51–60. 50. Cummings J, et al. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm2) in Alzheimer's disease. Dement Geriatr Cogn Disord 2012; 33:341–353. 51. Parsons CG, et al. Memantine is a clinically well tolerated N--methyl-D-aspartate (NMDA) receptor antagonist – a review of preclinical data. Neuropharmacology 1999; 38:735–767. 52. Reisberg B, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348:1333–1341. 53. Jones RW. A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. Int J Geriatr Psychiatry 2010; 25:547–553. 54. Dunn NR, et al. Adverse effects associated with the use of donepezil in general practice in England. J Psychopharmacol 2000; 14:406–408. 55. Hashimoto M, et al. Urinary incontinence: an unrecognised adverse effect with donepezil. Lancet 2000; 356:568. 56. Kobayashi H, et al. The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis. Int J Geriatr Psychiatry 2016; 31:892–904. 57. Kroger E, et al. Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. Ann Pharmacother 2015; 49:1197–1206. 58. FDA Alert for Healthcare Professionals. Galantamine hydrobromide (marketed as Razadyne,

formerly Reminyl). 2005; https://www.fda.gov/ Drugs/DrugSafety/ucm109350.htm. 59. Malone DM, et al. Cholinesterase inhibitors and cardiovascular disease: a survey of old age psychiatrists' practice. Age Ageing 2007; 36:331–333. 60. NHS Yorkshire and Humber Clinical Networks. The assessment of cardiac status before prescribing acetyl cholinesterase inhibitors for dementia. Version 1. 2016; http://www.yhscn.nhs.uk/media/PDFs/mhdn/Dementia/ECG%20Documents/ACHEIGuidance%20V1_Final.pdf. 61. Rowland JP, et al. Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol. Adv Psychiatric Treat 2007; 13:178–184. 62. Young S, et al. Cardiovascular complications of acetylcholinesterase inhibitors in patients with Alzheimer's disease: a narrative review. Ann Geriatr Med Res 2021; 25:170–177. 63. Rosenbloom MH, et al. Donepezil-associated bradyarrhythmia in a patient with dementia with Lewy bodies (DLB). Alzheimer Dis Assoc Disord 2010; 24:209–211. 64. Howes LG. Cardiovascular effects of drugs used to treat Alzheimer's disease. Drug Saf 2014; 37:391–395. 65. Farlow MR, et al. Memantine for the treatment of Alzheimer's disease: tolerability and safety data from clinical trials. Drug Saf 2008; 31:577–585. 66. Babai S, et al. Comparison of adverse drug reactions with donepezil versus memantine: analysis of the French pharmacovigilance database. Therapie 2010; 65:255–259. 67. Dooley M, et al. Donepezil: a review of its use in Alzheimer's disease. Drugs Aging 2000; 16:199–226. 68. Scott LJ, et al. Galantamine: a review of its use in Alzheimer's disease. Drugs 2000; 60:1095–1122. 69. Grossberg GT, et al. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. Int J Geriatr Psychiatry 2000; 15:242–247. 70. Tavassoli N, et al. Drug interactions with cholinesterase inhibitors: an analysis of the French pharmacovigilance database and a comparison of two national drug formularies (Vidal, British National Formulary). Drug Saf 2007; 30:1063–1071. 71. Noetzli M, et al. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin Pharmacokinet 2013; 52:225–241. 72. Pasqualetti G, et al. Potential drug-drug interactions in Alzheimer patients with behavioral symptoms. Clin Interv Aging 2015; 10:1457–1466.

73. Medicines Complete. Stockley's drug interactions. 2023; https://www.medicinescomplete.com/. 74. Merative US LP. Micromedex. 2023; https://www.micromedexsolutions.com/home/dispatch/. 75. Howard R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012; 366:893–903. 76. Howard R, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol 2015; 14:1171–1181. 77. Li DQ, et al. Donepezil combined with natural hirudin improves the clinical symptoms of patients with mild-to-moderate Alzheimer's disease: a 20-week open-label pilot study. Int J Med Sci 2012; 9:248–255. 78. Di Santo SG, et al. A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J Alzheimers Dis 2013; 35:349–361. 79. Parsons C. Withdrawal of antidementia drugs in older people: who, when and how? Drugs Aging 2016; 33:545–556. 80. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. NICE Guideline [NG97]. 2018 (checked September 2023, last accessed December 2023); https://www.nice.org.uk/guidance/ ng97. 81. Birks J, et al. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2009; 2:CD003120. 82. Tan MS, et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. J Alzheimers Dis 2015; 43:589–603. 83. National Institute for Health and Clinical Excellence. Donepezil, galantamine, rivastigmine and memantine for the

treatment of Alzheimer’s disease. Technology Appraisal [TA217]. 2011 (last updated June 2018, last accessed December 2023); https://www.nice.org.uk/guidance/ ta217. 84. National Institute for Health and Clinical Excellence. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NICE Guideline [NG5]. 2015 (checked March 2019, last accessed January 2024); https://www.nice.org.uk/guidance/ ng52015. 85. Fan F, et al. The efficacy and safety of Alzheimer’s disease therapies: an updated umbrella review. J Alzheimers Dis 2022; 85:1195–1204. 86. Bent S, et al. Spontaneous bleeding associated with ginkgo biloba: a case report and systematic review of the literature: a case report and systematic review of the literature. J Gen Intern Med 2005; 20:657–661. 87. Gil Martínez V, et al. Vitamin supplementation and dementia: a systematic review. Nutrients 2022; 14:1033. 88. Burckhardt M, et al. Omega-3 fatty acids for the treatment of dementia. Cochrane Database Syst Rev 2016; 4:CD009002. 89. Wang Y, et al. Ginseng for Alzheimer’s disease: a systematic review and meta-analysis of randomized controlled trials. Curr Top Med Chem 2016; 16:529–536. 90. Ghassab-Abdollahi N, et al. The effects of Huperzine A on dementia and mild cognitive impairment: an overview of systematic reviews. Phytother Res 2021; 35:4971–4987. 91. Yue J, et al. Huperzine A for mild cognitive impairment. Cochrane Database Syst Rev 2012; 12:CD008827. 92. Hao Z, et al. Huperzine A for vascular dementia. Cochrane Database Syst Rev 2009; 2:CD007365. 93. Ayati Z, et al. Saffron for mild cognitive impairment and dementia: a systematic review and meta-analysis of randomised clinical trials. BMC Complement Med Ther 2020; 20:333. 94. Gavrilova SI, et al. Cerebrolysin in the therapy of mild cognitive impairment and dementia due to Alzheimer’s disease: 30 years of clinical use. Med Res Rev 2021; 41:2775–2803. 95. Cui S, et al. Cerebrolysin for vascular dementia. Cochrane Database Syst Rev 2019; 11:CD008900. 96. Moreira A, et al. Chocolate consumption is associated with a lower risk of cognitive decline. J Alzheimers Dis 2016; 53:85–93. 97. Burckhardt M, et al. Souvenaid for Alzheimer’s disease. Cochrane Database Syst Rev 2020; 12:CD011679. 98. Galimberti D, et al. Idalopirdine as a treatment for Alzheimer’s disease. Expert Opin Investig Drugs 2015; 24:981–987. 99. Matsunaga S, et al. Efficacy and safety of idalopirdine for Alzheimer’s disease: a systematic review and meta-analysis. Int Psychogeriatr 2019; 31:1627–1633. 100. Jordan F, et al. Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia. Cochrane Database Syst Rev 2020; 4:CD011459. 101. La AL, et al. Long-term trazodone use and cognition: a potential therapeutic role for slow-wave sleep enhancers. J Alzheimers Dis 2019; 67:911–921. 102. Brauer R, et al. Trazodone use and risk of dementia: a population-based cohort study. PLoS Med 2019; 16:e1002728. 103. Sommerlad A, et al. Effect of trazodone on cognitive decline in people with dementia: cohort study using UK routinely collected data. Int J Geriatr Psychiatry 2021; 37:doi: 10.1002/gps.5625. 104. Coupland C, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; 343:d4551. 105. Halliday M, et al. Repurposed drugs targeting eIF2alpha-P-mediated translational repression prevent neurodegeneration in mice. Brain 2017; 140:1768–1783. 106. Sauder C, et al. Effectiveness of KarXT (xanomeline-trospium) for cognitive impairment in schizophrenia: post hoc analyses from a randomised, double-blind, placebo-controlled phase 2 study. Transl Psychiatry 2022; 12:491. 107. Khan H, et al. Neuroprotective effects of quercetin in Alzheimer’s disease. Biomolecules 2019; 10:59. 108. Yu TW, et al. Novel therapeutic approaches for Alzheimer’s disease: an updated review. Int JMol Sci 2021; 22:8208. 109. Schneider L. A resurrection of aducanumab for Alzheimer’s disease. Lancet Neurol 2020; 19:111–112. 110. The Lancet. Lecanemab for Alzheimer’s disease: tempering hype and hope. Lancet 2022; 400:1899. 111. Van Dyck CH, et al. Lecanemab in early Alzheimer’s disease. N Engl J Med 2023; 388:9–21. 112. Jönsson L, et al. The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer’s disease: an

EADC-EC viewpoint. Lancet Reg Health Eur 2023; 29:100657.

Prescribing in older people CHAPTER 6 113. Sims JR, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 2023; 330:512–527. 114. Ramanan VK, et al. Antiamyloid monoclonal antibody therapy for Alzheimer disease: emerging issues in neurology. Neurology 2023; 101:842–852. 115. Monteiro C, et al. Randomized phase II study of the safety and efficacy of semorinemab in participants with mild-to-moderate Alzheimer disease: Lauriet. Neurology 2023; 101:e1391–e1401. 116. Kavirajan H, et al. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol 2007; 6:782–792. 117. Wang J, et al. Cholinergic deficiency involved in vascular dementia: possible mechanism and strategy of treatment. Acta Pharmacol Sin 2009; 30:879–888. 118. Bocti C, et al. Management of dementia with a cerebrovascular component. Alzheimers Dementia 2007; 3:398–403. 119. Demaerschalk BM, et al. Treatment of vascular dementia and vascular cognitive impairment. Neurologist 2007; 13:37–41. 120. Baskys A, et al. Pharmacological prevention and treatment of vascular dementia: approaches and perspectives. Exp Gerontol 2012; 47:887–891. 121. McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev 2016; 1:CD003160. 122. Battle CE, et al. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. Cochrane Database Syst Rev 2021; 2:CD013306. 123. Jin BR, et al. Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis. Neural Regen Res 2019; 14:805–816. 124. Wild R, et al. Cholinesterase inhibitors for dementia with Lewy bodies. Cochrane Database Syst Rev 2003; 3:CD003672. 125. Taylor JP, et al. New evidence on the management of Lewy body dementia. Lancet Neurol 2020; 19:157–169. 126. McKeith IG, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017; 89:88–100. 127. Newcastle University. Management of Lewy body dementia summary sheet. Diamond Lewy. 2019; https://research.ncl.ac.uk/media/sites/ researchwebsites/diamond--lewy/One%20page%20symptom%20LBD%20management%20summaries.pdf. 128. Russ TC, et al. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database Syst Rev 2012; 9:CD009132. 129. Cooper C, et al. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 2013; 203:255–264. 130. Matsunaga S, et al. Efficacy and safety of cholinesterase inhibitors for mild cognitive impairment: a systematic review and meta-analysis. J Alzheimers Dis 2019; 71:513–523. 131. Kasper S, et al. Management of mild cognitive impairment (MCI): the need for national and international guidelines. World J Biol Psychiatry 2020; 21:579–594. 132. Petersen RC, et al. Practice guideline update summary: mild cognitive impairment. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90:126–135. 133. Nardell M, et al. Pharmacological treatments for frontotemporal dementias: a systematic review of randomized controlled trials. Am J Alzheimers Dis Other Demen 2014; 29:123–132. 134. Boeve BF, et al. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. Lancet Neurol 2022; 21:258–272. 135. Li Y, et al. Cholinesterase inhibitors for rarer dementias associated with neurological conditions. Cochrane Database Syst Rev 2015; 3:CD009444.

14 - Safer prescribing for physical conditions in

Safer prescribing for physical conditions in dementia

15 - Anticholinergic drugs

Anticholinergic drugs

654 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Safer prescribing for physical conditions in dementia People with dementia are susceptible to cognitive adverse effects of drugs. Drugs may affect cognition through their action on cholinergic, histaminergic, opioid or other neurotransmitter pathways. Some medications may also interact with cognitive-enhancing medication. Anticholinergic drugs Anticholinergic drugs reduce the efficacy of acetylcholinesterase inhibitors1 and cause sedation, delirium and falls.2 These effects are more severe in older patients with dementia.3 A high anticholinergic burden is associated with cognitive decline4 and increased hospitalisation and mortality.4,5 The Anticholinergic Effect on Cognition (AEC)6 scale can be used to calculate the anticholinergic burden of drugs in patients. Table 6.4 lists the AEC scores of drugs commonly prescribed for older adults in the UK.6 Combining several drugs with anticholinergic activity increases the total anticholinergic burden for an individual. It is good practice to keep the anticholinergic burden to a minimum in older people and those with dementia. Where possible, drugs with no anticholinergic action and an equivalent therapeutic effect should be used. If this is not possible, the prescription of a drug with low anticholinergic activity or high specificity to the site of action (and thus minimal central activity) should be encouraged. Anticholinergic drugs that do not cross the blood–brain barrier (BBB) have less profound effects on cognitive function.7 The AEC takes all of these factors into account. The following are recommendations for using AEC scores:6 ■ ■All individual drugs with an AEC score of 2 or 3 in older people presenting with symptoms of cognitive impairment, dementia or delirium should either be: ■ ■stopped, or ■ ■switched to an alternative drug with a lower AEC score (preferably 0). ■ ■In patients who are not receiving any individual drug with an AEC score of 2 or 3 but who have a total AEC score of 3 or above, a patient–clinician review should take place. ■ ■If withdrawal of the drug is deemed appropriate, this should be gradual (where possible) to avoid rebound (nausea, sweating, urinary frequency, diarrhoea).

Table 6.4 Anticholinergic Effect on Cognition (AEC) scale scores (Adapted from [6]).* Adcal – 0 Clarithromycin – NK Gabapentin – 0 Naproxen – 0 Sitagliptin – 0 Agomelatine – 0 Clemastine – 3 Galantamine – 0 Nifedipine – 0 Solifenacin – 1 Alendronic acid (alendronate) – 0 Clomipramine – 3 Gaviscon – 0 Nimodipine – 0 Sotalol – 0 Alfuzosin – 0 Clonazepam – NK Gliclazide – 0 Nitrofurantoin – NK Spironolactone – NK Alimemazine (trimeprazine) – 3 Clonidine – NK Granisetron – 0 Nortriptyline – 3 Sulphasalazine – 0 Allopurinol – NK Clopidogrel – 0 Haloperidol – 0 Olanzapine – 2 Sulpiride – 0 Alprazolam – 0 Clozapine – 3 Heparin – 0 Omeprazole – 0 Tamoxifen – NK Alverine – 0 Co-beneldopa – 0 Hydrochlorothiazide – 0 Ondansetron – 0 Tamsulosin – 0 Amantadine – 2 Co-careldopa – 0 Hydrocodone – NK Orlistat – 0 Temazepam – 1 Amiloride – 0 Codeine – NK Hydrocortisone – NK Orphenadrine – 3 Tetracycline – 0 Aminophylline – 0 Colchicine – NK Hydroxyzine – 1 Oxcarbazepine – NK Theophylline – 0 Amiodarone – 1 Co-tenidone – 0 Hyoscine

butylbromide (buscopan) – 1 Oxybutynin – 3 Thiamine – 0 Amisulpride – 0 Cyclizine – 1 Hyoscine hydrobromide – 3 Oxycodone – NK Tiotropium bromide (inhalation) – 0 Amitriptyline – 3 Cyproheptadine – 3 Ibuprofen – 0 Paliperidone – 1 Tizanidine – NK Amlodipine – 0 Dabigatran – NK Iloperidone – 1 Pantoprazole – 0 Tolcapone – 0 Amoxicillin – 0 Darifenacin – 0 Imipramine – 3 Paracetamol – 0 Tolterodine – 2 Anastrozole – NK Desipramine – 2 Indapamide – 0 Paroxetine – 2 Topiramate – NK Apixaban – NK Dexamethasone – NK Insulin – 0 Penicillin – 0 Tramadol – 0 Apomorphine – 0 Dexamfetamine – 0 Ipratropium bromide – 0 Peppermint oil – 0 Tranylcypromine – 0 Aripiprazole – 1 Dextropropoxyphene – NK Irbesartan – NK Pergolide – 0 Trazodone – 0 Asenapine – 1 Diazepam – 1 Isocarboxazid – 1 Perindopril – 0 Trifluoperazine – 2 Aspirin – 0 Diclofenac – 0 Isosorbide dinitrate – 0 Perphenazine – 1 Trihexyphenidyl (benzhexol) – 3 (Continued)

Atenolol – 0 Dicycloverine (dicyclomine) – 2 Isosorbide mononitrate – 0 Pethidine – 2 Trimethoprim – 0 Atomoxetine – 0 Digoxin – NK Ketorolac – 0 Phenelzine – 1 Trimipramine – 3 Atorvastatin – 0 Dihydrocodeine – NK Labetalol – 0 Phenytoin – NK Trospium – 0 Atropine – 3 Diltiazem – 0 Lactulose – 0 Pimozide – 2 Valproate – 0 Atropine eye drops – 1 Dimenhydrinate – 2 Lamotrigine – 0 Pirenzepine – 1 Venlafaxine – 0 Azathioprine – 0 Diphenhydramine – 2 Lansoprazole – NK Pravastatin – 0 Verapamil – NK Baclofen – NK Dipyridamole – 0 Lercanidipine – 0 Prazosin – 0 Vitamin B12 – 0 Beclometasone dipropionate (inhaler) – 0 Disopyramide – 2 Levetiracetam – NK Prednisolone – 1 Vitamins – 0 Bendroflumethiazide – 0 Docusate sodium – 0 Levodopa – 0 Pregabalin – NK Vortioxetine – 0 Benztropine – 3 Domperidone – 1 Levomepromazine (methotrimeprazine) – 2 Prochlorperazine – 2 Warfarin – 0 Betahistine – 0 Donepezil – 0 Levothyroxine (thyroxine) – 0 Procyclidine – 3 Ziprasidone – 0 Bezafibrate – 0 Dothiepin (dosulepin) – 3 Liraglutide – 0 Promazine – 2 Zolpidem – 0 Bisacodyl – 0 Doxazosin – 0 Lisinopril – 0 Promethazine – 3 Zopiclone – NK Bisoprolol – NK Doxepin – 3 Lithium – 1 Propantheline – 2 Zotepine – 2 Bromocriptine – 1 Doxycycline – 0 Lofepramine – 3 Propranolol – 0 Zuclopentixol (zuclopenthixol) – 1 Budesonide (inhaler) – 0 Dulaglutide – 0 Loperamide – 0 Quetiapine – 2 Bumetanide – NK Duloxetine – 0 Loratadine – 0 Quinidine – 1 Buprenorphine – 0 Escitalopram – 1 Lorazepam – 0 Quinine – 1 Bupropion – 0 Enalapril – 0 Losartan – 0 Rabeprazole – 0 Buspirone – 1 Enoxaparin – 0 Lovastatin – 0 Ramipril – NK Cabergoline – 0 Entacapone – 0 Lurasidone – 0 Ranitidine – 0 Table 6.4 (Continued)

Calcium – 0 Erythromycin – NK Macrogol – 0 Rasagiline – 0 Calcium and vitamin D – 0 Exanatide – 0 Magnesium – 0 Reboxetine – 0 Candersartan – 0 Ezetimibe – 0 Mebeverine – 0 Risedronate – 0 Captopril – NK Felodipine – 0 Melatonin – 0 Risperidone – 0 Carbachol – 0 Fentanyl – 1 Meloxicam – 0 Rivaroxaban – NK Carbamazepine – 1 Ferrous sulphate – 0 Memantine – 0 Rivastigmine – 0 Carbimazole – NK Fesoterodine – 0 Mesalazine – 0 Ropinirole – 0 Carbocisteine – 0 Fexofenadine – 0 Metformin – NK Rosiglitazone – 0 Cariprazine– 0 Finasteride – 0 Methocarbamol – NK Rosuvastatin – NK Carvedilol – NK Flavoxate – NK Methotrexate – NK Salbutamol – 0 Cefalexin (cephalexin) – 0 Flecainide – 0 Metoclopramide – 0 Salmeterol (inhaler) – 0 Cetirizine – 0 Flucloxacillin – 0 Metoprolol – 0 Selegiline – 0 Chloral hydrate – NK Fludrocortisone – NK Mianserin – 2 Senna – 0 Chlordiazepoxide – 0 Fluoxetine – 1 Midazolam – 1 Sertindole – 1 Chlorphenamine – 2 Flupentixol (flupenthixol) – 1 Minocycline – 0 Sertraline – 1 Chlorpromazine – 3 Fluphenazine – 1 Mirabegron – 0 Sildenafil – 0 Chlortalidone – NK Fluvoxamine – 0 Mirtazapine – 1 Simvastatin – 0 Cimetidine – 0 Folic acid – 0 Moclobemide – 0 Cinnarizine – 1 Furosemide – 0 Morphine – 0 Ciprofloxacin – 0 Citalopram – 1 *The AEC scale is available as a regularly updated web-based app. Please go to

www.medichec.com. This site has been updated to include the identification of medications that are reported to cause dizziness and drowsiness since these adverse effects can add to cognitive impairment and confusion in older people and can increase the risk of falls. Medichec also identifies medications that are reported to cause QTc prolongation, hyponatraemia, bleeding risk and constipation. 1–3, scores 1 to 3; NK, not known.

16 - Safety of physical health medication prescrib

Safety of physical health medication prescribed in dementia

658 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Safety of physical health medication prescribed in dementia Anticholinergic drugs used in urinary incontinence Oxybutynin penetrates the CNS and is associated with cognitive decline. Although studies of tolterodine found no adverse CNS effects,8 case reports have described memory loss, hallucinations and delirium.9–11 Darifenacin, an M3 selective receptor antagonist, has shown no effects on cognitive function tests compared with placebo,12,13 although studies in dementia are lacking. Solifenacin may cause memory impairment14 although it did not affect cognition in patients with a stroke.15 Trospium16–18 and fesoterodine19 do not seem to cause cognitive changes.17,18,20,21 Tertiary amine drugs (i.e. oxybutynin, tolterodine, solifenacin, fesoterodine, darifenacin) are metabolised by cytochrome P450 (CYP) enzymes. Increasing age or co-administration of drugs that inhibit these enzymes (e.g. erythromycin, fluoxetine) can lead to higher serum levels and increased adverse effects. The metabolism of trospium is unknown, although metabolism via the CYP system does not occur, meaning that pharmacokinetic drug interactions are unlikely with this drug.8 Alpha blockers for urinary retention Alpha blockers such as tamsulosin, alfuzosin and prazosin cause drowsiness, dizziness and depression.22 There is no published literature reporting their effects on cognition, but α blockers are not thought to have any anticholinergic action. Drugs used in gastrointestinal disorders Loperamide Although loperamide may have some anticholinergic activity, there are no data to suggest that it can worsen cognitive function in patients with dementia. It may add to the anticholinergic cognitive burden if used in conjunction with other anticholinergic drugs. Laxatives Laxatives do not have any negative impact on cognitive function. In fact, since constipation can lead to delirium and behavioural and psychological symptoms of dementia, treating it may improve these symptoms. Antiemetics Cyclizine is a first-generation histamine antagonist and can impair cognitive and psychomotor performance (see ‘Antihistamines’ later in this chapter).23 Metoclopramide has little anticholinergic action, but the D2 receptor antagonism of both metoclopramide and prochlorperazine can produce movement disorders and so these drugs must

be used with caution in people with dementia. Domperidone is a dopamine D2 receptor antagonist that does not usually cross the BBB. However, since BBB alterations can occur in dementia, CNS penetration of domperidone and resulting adverse effects can occur.24 There is a small increased risk of serious cardiac adverse effects with domperidone, especially in older people. Domperidone is now contraindicated in those with underlying cardiac conditions or

Prescribing in older people CHAPTER 6 severe hepatic impairment and in patients receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors; treatment should not exceed 1 week.25 Serotonin 5HT3 receptor antagonists, used for treating chemotherapy-induced nausea and vomiting, do not have adverse effects on cognition, and may have some cognitive--enhancing action.26 These drugs should be used cautiously in patients with cardiac comorbidities or taking concomitant arrhythmogenic drugs or drugs known to prolong QT interval. Granisetron can be administered once daily, which is preferable in people with dementia or swallowing difficulties. Granisetron is metabolised exclusively via a single CYP family (CYP3A4), and thus has a lower propensity for drug interactions.27 Antispasmodics Hyoscine hydrobromide (scopolamine) is a centrally acting lipophilic anticholinergic which penetrates the BBB. It impairs memory, speed of processing and attention. Older patients suffer these symptoms at lower doses and are more vulnerable to confusion and hallucinations.28 People with Alzheimer’s disease experience clinically significant cognitive impairment at lower doses compared with healthy, aged-matched controls.3 The effect that hyoscine has on cognition is so significant that it is used in trials to produce memory deficits similar to those seen in dementia (the scopolamine challenge test).29 There is rarely a good reason to use this drug in people with dementia. Hyoscine butylbromide (Buscopan) exerts topical spasmolytic action on smooth muscle of the gastrointestinal tract. Hyoscine butylbromide is not thought to enter the CNS, so central anticholinergic adverse effects are rare.30 Alverine, mebeverine and peppermint oil are relaxants of intestinal smooth muscle with no effect on cognition. Bronchodilators Beta agonists In patients with Parkinson’s disease or essential tremor, tremor induced by β agonists may result in misdiagnosis and over-treatment of Parkinson’s disease.31 Tremor is a common adverse effect of cholinesterase inhibitors so caution should be exercised when used with β agonists. Anticholinergic bronchodilators Inhaled anticholinergic drugs have few systemic side effects.31 A placebo-controlled comparison of ipratropium and theophylline treatment was unable to detect a negative effect with either drug on the cognitive function of older patients. This suggests that treatment with inhaled ipratropium is not associated with significant cognitive impairment in older people.32 Theophylline As with cholinesterase inhibitors, nausea and vomiting are common adverse effects of theophylline. Neurological effects such as headaches, anxiety, behavioural disturbances, depression and seizures can occur in 50% of patients on theophylline. Although seizures are rare, they are much more likely in older people. Theophylline does not cause significant cognitive impairment.32

660 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Hypersalivation Oral anticholinergic agents used for hypersalivation (e.g. hyoscine hydrobromide) should be avoided in older people because of the risk of cognitive impairment, delirium and constipation (see ‘Anticholinergic drugs’ and ‘Antispasmodics’ earlier in this chapter). Pirenzepine is a relatively selective M1 and M4 muscarinic receptor antagonist which is not thought to cross the BBB and therefore has little CNS penetration.33 Atropine solution given sublingually or used as a mouthwash is sometimes used to manage hypersalivation. There are no data available on the extent of penetration through the BBB when atropine is administered by this route. Myasthenia

gravis Unlike acetylcholinesterase inhibitors used in Alzheimer's disease (donepezil, rivastigmine, galantamine), those used in myasthenia gravis (pyridostigmine, neostigmine) act peripherally and do not cross the BBB.34 Combining peripheral and central acetylcholinesterase inhibitors may add to the cholinomimetic adverse effect burden (e.g. nausea, vomiting, diarrhoea, abdominal cramps, increased salivation). Memantine may be an alternative to cholinesterase inhibitors in cases where the combined cholinomimetic effects of drugs used for myasthenia gravis and Alzheimer's disease are not tolerated. Analgesics NSAIDs and paracetamol Paracetamol (acetaminophen) does not cause cognitive impairment other than in overdose, when it may cause delirium.35 There is some evidence that the chronic use of aspirin can cause confusional states.36 Case reports implicate NSAIDs in causing delirium and psychosis37 although clinical trials have not demonstrated significant adverse effects on cognition with naproxen38 or indomethacin.39 NSAIDs are difficult to use in older people due to their cardiovascular risk and risk of gastrointestinal bleeding.40 It is good practice to prescribe gastroprotection with these drugs or consider using topical NSAIDs (if clinically appropriate) to reduce the risk of gastrointestinal bleeding. Opiates Sedation is a potential problem with all opiates.41 Delirium induced by opioids may be associated with agitation, hallucinations or delusions.41 Pethidine is associated with a high risk of cognitive impairment as its metabolites have anticholinergic properties and accumulate rapidly if renal function is impaired.42 Codeine may increase the risk of falls, and both tramadol and codeine have a high risk of drug–drug interactions as well as considerable variation in response and adverse effects.43 Fentanyl patches should not be used to initiate opioid analgesia in frail older people44 because of their long duration of action even after the patch is removed, making the treatment of adverse effects more difficult.43 Morphine is an effective analgesic but is likely to cause cognitive problems and other adverse effects in older patients.45 Oxycodone has a

 short half-life (at least in non-modified-release tablets), few drug–drug interactions and more predictable dose–response relationships than other opiates. It is therefore, theoretically, a good candidate for oral analgesia in dementia.43 Caution, however, should be used owing to its addictive potential. Buprenorphine transdermal patches probably have less severe adverse effects than many other opiates. Antihistamines First-generation H1 antihistamines include chlorpheniramine, hydroxyzine, cyclizine and promethazine. They are non-selective, have anticholinergic activity and readily penetrate the BBB. They can impair cognitive performance and can trigger seizures, dyskinesia, dystonia and hallucinations. The second-generation H1 antihistamines (such as loratadine, cetirizine and fexofenadine) penetrate poorly into the CNS and should be the preferred choice because of their lack of sedative, cognitive and psychomotor impairment and anticholinergic adverse effects. Statins A Cochrane review assessed the clinical efficacy and tolerability of statins in the treatment of dementia46 and showed that there was no significant benefit from statins in terms of cognitive function, but equally no evidence that statins were detrimental to cognition. Earlier case reports had highlighted subjective complaints of memory loss associated with the use of statins.47 These tended to occur within 2 months of starting the drug and were most commonly associated with simvastatin. If cognitive problems occur on simvastatin, it may be worth first stopping the drug, and if the complaint resolves, try atorvastatin or pravastatin instead as these drugs are less likely to cross the BBB. However, in a large prospective cohort study of patients without dementia, baseline statin use was not associated with incident dementia or MCI, nor was statin use associated with decline in cognitive function over time and results did not differ by statin lipophilicity.48 Another Cochrane review49 assessed the efficacy of statins in the prevention of dementia and concluded that there

was no evidence that statins given in late life to people at risk of vascular disease prevented cognitive decline or dementia. A meta-analysis of observational studies found that similar risks were observed for lipophilic and hydrophilic statins for both dementia and Alzheimer's disease, while high- potency statins showed a 20% reduction of dementia risk compared with a 16% risk reduction associated with low-potency statins, suggesting a greater efficacy of the former. While evidence has been mixed, it suggests that statins are unlikely to cause dementia or cognitive decline, but they may not prevent it either. Nevertheless, indications for statin treatment to prevent cardiovascular events remain.50 Antihypertensives Mid-life hypertension has negative effects on cognition and increases the risk of a person developing dementia.51 There is no evidence that antihypertensive treatment worsens cognition; it appears to have a positive effect on global cognition and long-term treatment of hypertension can reduce the risk of dementia.52,53

662 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Anticoagulants Several systematic reviews concluded that oral anticoagulation reduced significantly the incidence of cognitive impairment and dementia in patients with atrial fibrillation, probably due to the reduction of ischaemic cerebrovascular events. It appears that direct oral anticoagulant therapy is associated with a significant decrease in the risk of dementia when compared with vitamin K antagonist therapy, however further studies are needed to confirm these findings.54 Other cardiac drugs Digoxin has been associated with acute confusional states at therapeutic drug concentrations.55 It has also been reported to cause nightmares.56 However, one study showed the treatment of cardiac failure with digoxin improved cognitive performance in 25% of patients treated (and in 23% of patients treated who did not have cardiac failure).57 There are some case reports of amiodarone being associated with delirium.58,59 H2 antagonists and proton pump inhibitors (PPIs) Histamine-2 receptor antagonists (e.g. cimetidine, ranitidine, famotidine) are rarely used nowadays. Cimetidine causes several pharmacokinetic interactions, and ranitidine products have been recalled due to possible contamination with N-nitrosodimethylamine, identified as a potential risk factor in the development of certain cancers. Famotidine remains in use. CNS reactions to these drugs have been reported, especially with cimetidine.60 A study looking at observational data on PPIs found an association between PPI use and incident dementia. This is supported by pharmacoepidemiological analyses on primary data and is in line with animal studies in which the use of PPIs increased the levels of β-amyloid in the brains of mice.61 Randomised prospective clinical trials are needed to confirm this association. Many patients on PPIs have Helicobacter pylori- infected gastric mucosa. As Helicobacter has been reported to be associated with cognitive deterioration, this could be the mechanism behind the apparent link between PPI drugs and dementia. Furthermore, this association was not replicated in other studies.62,63 Despite reports that PPIs are associated with an increased risk of developing dementia,61,64 data collected in a large-scale real-world setting using linked national health data in the UK were unable to confirm this association. This suggests that previously reported links may be associated with confounders of people using PPIs, such as increased risk of cardiovascular disease and/or depression and their associated medications.65 Antibiotics There are reports of many antibiotics being associated with delirium66,67 but there is no consistent pattern of them causing cognitive impairment. Given the importance of treating infection in dementia the most appropriate antibiotic for the infection being treated should be used. Antituberculous therapy, particularly isoniazid, has attracted some case reports of adverse psychiatric reactions.68 Table 6.5 lists drugs that are recommended for use in dementia and those that should be avoided.

Prescribing in older people CHAPTER 6 Table 6.5 Recommended drugs and drugs to avoid in dementia. Adapted with permission.69 Condition Drug class or drug name Drugs to avoid in dementia Recommended drugs in dementia Allergic conditions Antihistamines Chlorphenamine Promethazine Hydroxyzine Cyproheptadine Cyclizine (and other first-generation antihistamines) Cetirizine Loratadine Fexofenadine (and other second- generation antihistamines) Asthma/COPD Bronchodilators Beta agonists Inhaled anticholinergics (have not been reported to affect cognition) Theophylline Constipation Laxatives No evidence to suggest that laxatives have any negative impact on cognitive function. Constipation itself may worsen cognition Diarrhoea Loperamide Low--potency anticholinergic. Not known to have effects on cognitive function, however may add to the anticholinergic cognitive burden if used in combination with other anticholinergics Hyperlipidaemia Statins All are safe but atorvastatin and pravastatin are less likely to cross the BBB. Hypersalivation Anticholinergics Hyoscine hydrobromide Pirenzepine Atropine (sublingually) Hypertension Antihypertensives Beta blockers (avoidance may not always be possible) Calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may all improve cognitive function. Infections Antibiotics Delirium reported mostly with quinolone and macrolide antibiotics. But given the importance of treating infections, the most appropriate antibiotic for the infection should be used. Myasthenia gravis Peripheral acetylcholinesterase inhibitors, e.g. neostigmine and pyridostigmine May add to the cholinergic adverse effects of central acetylcholinesterase inhibitors (e.g. donepezil) in patients with dementia, e.g. increased risk of nausea/vomiting. Nausea/vomiting Antiemetics Cyclizine Metoclopramide Prochlorperazine Domperidone (see main text for restrictions) Serotonin 5HT3 receptor antagonists (Continued)

17 - References

References

1. Sink KM, et al. Dual use of bladder anticholinergics and cholinesterase inhibitors: long--term functional and cognitive outcomes. J Am Geriatr Soc 2008; 56:847–853.
2. Ruxton K, et al. Drugs with anticholinergic effects and cognitive impairment, falls and all--cause mortality in older adults: a systematic review and meta-analysis. Br J Clin Pharmacol 2015; 80:209–220.
3. Sunderland T, et al. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls. A dose-response study. Arch Gen Psychiatry 1987; 44:418–426.
4. Fox C, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. J Am Geriatr Soc 2011; 59:1477–1483.
5. Bishara D, et al. The anticholinergic effect on cognition (AEC) scale – associations with mortality, hospitalisation and cognitive decline following dementia diagnosis. Int J Geriatr Psychiatry 2020; 35:1069–1077.
6. Bishara D, et al. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. Int J Geriatr Psychiatry 2017; 32:650–656.
7. Wagg A. The cognitive burden of anticholinergics in the elderly – implications for the treatment of overactive bladder. Eur Urol Rev 2012; 7:42–49.
8. Pagoria D, et al. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. Curr Urol Rep 2011; 12:351–357.
9. Womack KB, et al. Tolterodine and memory: dry but forgetful. Arch Neurol 2003; 60:771–773.
10. Tsao JW, et al. Transient memory impairment and hallucinations associated with tolterodine use. N Engl J Med 2003; 349:2274–2275. Table 6.5 (Continued) Condition Drug class or drug name Drugs to avoid in dementia Recommended drugs in dementia Other GI conditions Antispasmodics Atropine sulphate Dicycloverine hydrochloride Alverine, mebeverine, peppermint oil Hyoscine-n-butylbromide Propantheline bromide Pain Analgesics Pethidine Pentazocine Dextropropoxyphene Codeine Tramadol Methadone Paracetamol Oxycodone Buprenorphine Topical NSAIDs (where appropriate) Fentanyl patches (caution in opioid-naïve patients) Morphine (may be indicated in treatment--resistant pain or palliative care; use cautiously due to associated cognitive and other adverse effects) Urinary frequency Anticholinergic drugs used in overactive bladder Oxybutynin Tolterodine Fesoterodine Darifenacin Trospium Solifenacin (use if others are not available; some reports of cognitive adverse effects) Data for fesoterodine are still

lacking; it is non-selective, has high central anticholinergic activity but theoretically has very low ability to cross the BBB. Urinary retention Alpha blockers Not known to have effects on cognitive function. BBB, blood–brain barrier; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

Prescribing in older people CHAPTER 6 11. Edwards KR, et al. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. J Am Geriatr Soc 2002; 50:1165–1166. 12. Kay G, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol 2006; 50:317–326. 13. Lipton RB, et al. Assessment of cognitive function of the elderly population: effects of darifenacin. J Urol 2005; 173:493–498. 14. Chancellor MB, et al. Blood-brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. Drugs Aging 2012; 29:259–273. 15. Park JW. The effect of solifenacin on cognitive function following stroke. Dement Geriatr Cogn Dis Extra 2013; 3:143–147. 16. Liabeuf S, et al. Trospium chloride for overactive bladder may induce central nervous system adverse events. Eur Geriatr Med 2014; 5:220–224. 17. Isik AT, et al. Trospium and cognition in patients with late onset Alzheimer disease. J Nutr Health Aging 2009; 13:672–676. 18. Geller EJ, et al. Effect of trospium chloride on cognitive function in women aged 50 and older: a randomized trial. Female Pelvic Med Reconstr Surg 2017; 23:118–123. 19. Heesakkers J, et al. Safety and tolerability of fesoterodine in older adult patients with overactive bladder. Can Geriatr J 2022; 25:72–78. 20. Wagg A. Fesoterodine fumarate for the treatment of overactive bladder in the elderly – a review of the latest clinical data. Clin Investig 2012; 2:825–833. 21. Yonguc T, et al. Randomized, controlled trial of fesoterodine fumarate for overactive bladder in Parkinson’s disease. World J Urol 2020; 38:2013–2019. 22. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete.com. 23. Mahdy AM, et al. Histamine and antihistamines. Anaesth Intens Care Med 2011; 12:324–329. 24. Roy-Desruisseaux J, et al. Domperidone-induced tardive dyskinesia and withdrawal psychosis in an elderly woman with dementia. Ann Pharmacother 2011; 45:e51. 25. Medicines and Healthcare products Regulatory Agency. Domperidone: risks of cardiac side effects – indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use. 2014; http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/ CON418518. 26. Bentley KR, et al. Therapeutic potential of serotonin 5-HT3 antagonists in neuropsychiatric disorders. CNS Drugs 1995; 3:363–392. 27. Gridelli C. Same old story? Do we need to modify our supportive care treatment of elderly cancer patients? Focus on antiemetics. Drugs Aging 2004; 21:825–832. 28. Flicker C, et al. Hypersensitivity to scopolamine in the elderly. Psychopharmacology (Berl) 1992; 107:437–441. 29. Ebert U, et al. Scopolamine model of dementia: electroencephalogram findings and cognitive performance. Eur J Clin Invest 1998; 28:944–949. 30. Sanofi. Summary of product characteristics. Buscopan 10 mg tablets. 2020 (last updated November 2021); https://www.medicines.org.uk/ emc/medicine/30089. 31. Gupta P, et al. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. Drugs Aging 2008; 25:415–443. 32. Ramsdell JW, et al. Effects of theophylline and ipratropium on cognition in elderly patients with chronic obstructive pulmonary disease. Ann Allergy Asthma Immunol 1996; 76:335–340. 33. Fritze J, et al. Pirenzepine for clozapine-induced hypersalivation. Lancet 1995; 346:1034. 34. Pohanka M. Acetylcholinesterase inhibitors: a patent review (2008 – present). Expert Opin Ther Pat 2012; 22:871–886. 35. Gray SL, et al. Drug-induced cognition disorders in the elderly: incidence, prevention and management. Drug Saf 1999; 21:101–122. 36. Bailey RB, et al. Chronic salicylate intoxication. A common cause of morbidity in

the elderly. J Am Geriatr Soc 1989; 37:556–561. 37. Hoppmann RA, et al. Central nervous system side effects of nonsteroidal anti-inflammatory drugs. Aseptic meningitis, psychosis, and cognitive dysfunction. Arch Intern Med 1991; 151:1309–1313. 38. Wysenbeek AJ, et al. Assessment of cognitive function in elderly patients treated with naproxen. A prospective study. Clin Exp Rheumatol 1988; 6:399–400. 39. Bruce-Jones PN, et al. Indomethacin and cognitive function in healthy elderly volunteers. Br J Clin Pharmacol 1994; 38:45–51. 40. Barber JB, et al. Treatment of chronic non-malignant pain in the elderly: safety considerations. Drug Saf 2009; 32:457–474. 41. Ripamonti C, et al. CNS adverse effects of opioids in cancer patients. CNS Drugs 1997; 8:21–37. 42. Alagiakrishnan K, et al. An approach to drug induced delirium in the elderly. Postgrad Med J 2004; 80:388–393. 43. McLachlan AJ, et al. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. Br J Clin Pharmacol 2011; 71:351–364. 44. Dosa DM, et al. Frequency of long-acting opioid analgesic initiation in opioid-naive nursing home residents. J Pain Symptom Manage 2009; 38:515–521. 45. Tannenbaum C, et al. A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. Drugs Aging 2012; 29:639–658. 46. McGuinness B, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev 2014; 7:CD007514. 47. Wagstaff LR, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003; 23:871–880. 48. Zhou Z, et al. Effect of statin therapy on cognitive decline and incident dementia in older adults. J Am Coll Cardiol 2021; 77:3145–3156. 49. McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev 2016; 1:CD003160. 50. Olmastroni E, et al. Statin use and risk of dementia or Alzheimer’s disease: a systematic review and meta-analysis of observational studies. Eur J Prev Cardiol 2022; 29:804–814.

 51. Qiu C, et al. The age--dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 2005; 4:487–499. 52. Wändell P, et al. Antihypertensive drugs and relevant cardiovascular pharmacotherapies and the risk of incident dementia in patients with atrial fibrillation. Int J Cardiol 2018; 272:149–154. 53. Levi MN, et al. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 2013; 31:1073–1082. 54. Branco DR, et al. Direct oral anticoagulants vs vitamin K antagonist on dementia risk in atrial fibrillation: systematic review with meta-analysis. J Thromb Thrombolysis 2023; 56:474–484. 55. Eisendrath SJ, et al. Toxic neuropsychiatric effects of digoxin at therapeutic serum concentrations. Am J Psychiatry 1987; 144:506–507. 56. Brezis M, et al. Nightmares from digoxin. Ann Intern Med 1980; 93:639–640. 57. Laudisio A, et al. Digoxin and cognitive performance in patients with heart failure: a cohort, pharmacoepidemiological survey. Drugs Aging 2009; 26:103–112. 58. Athwal H, et al. Amiodarone--induced delirium. Am J Geriatr Psychiatry 2003; 11:696–697. 59. Foley KT, et al. Separate episodes of delirium associated with levetiracetam and amiodarone treatment in an elderly woman. Am J Geriatr Pharmacother 2010; 8:170–174. 60. Cantu TG, et al. Central nervous system reactions to histamine-2 receptor blockers. Ann Intern Med 1991; 114:1027–1034. 61. Gomm W, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neuroly 2016; 73:410–416. 62. Goldstein FC, et al. Proton pump inhibitors and risk of mild cognitive impairment and dementia. J Am Geriatr Soc 2017; 65:1969–1974. 63. Lochhead P, et al. Association between proton pump inhibitor use and cognitive function in women. Gastroenterology 2017; 153:971–979.e974. 64. Haenisch B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 2015; 265:419–428. 65. Cooksey R, et al. Proton pump inhibitors and dementia risk: evidence from a

cohort study using linked routinely collected national health data in Wales, UK. PLoS One 2020; 15:e0237676. 66. Grahl JJ, et al. Antimicrobial exposure and the risk of delirium in critically ill patients. Crit Care 2018; 22:337. 67. Bhattacharyya S, et al. Antibiotic-associated encephalopathy. Neurology 2016; 86:963–971. 68. Kass JS, et al. Nervous system effects of antituberculosis therapy. CNS Drugs 2010; 24:655–667. 69. Bishara D, et al. Safe prescribing of physical health medication in patients with dementia. Int J Geriatr Psychiatry 2014; 29:1230–1241.

18 - Management of behavioural and psychological s

Management of behavioural and psychological symptoms of dementia (BPSD)

19 - Non drug measures

Non-drug measures

Prescribing in older people CHAPTER 6 Management of behavioural and psychological symptoms of dementia (BPSD) Behavioural and psychological symptoms of dementia (BPSD) cover a range of difficulties including aggression, agitation, vocalisation, distress during care, disinhibition, hallucinations, delusions, apathy, low mood and anxiety.1 Such symptoms occur in over 90% of patients to varying degrees.2 Drug treatment of BPSD is not well supported by evidence3 and many of the drugs used in BPSD have serious adverse effects. Non-drug measures Since the publication in the UK of Time for Action, a report which highlighted the risks of antipsychotic use in dementia,4 there has been a drive to formulate and employ non- pharmacological treatment for BPSD. Systematic reviews have been completed,5 new models of care developed6,7 and guidance documents written.8 The key themes include:

1. An individualised approach rather than the application of more generalised therapies.
2. Ensuring contributory physical factors are addressed as a first step. These factors include pain (see following section), infection, constipation and medication adverse effects (see ‘Safer prescribing for physical conditions in dementia’ earlier in this chapter).
3. The importance of understanding and reframing ‘problem behaviours’ as an expression of distress and unmet need.6,7
4. Use of life history, direct observation of care and data collection (e.g. sleep, pain and ABC charts) to uncover unmet needs and to inform treatment.8
5. Formulation meetings to develop a model of the factors contributing to the behaviour.
6. Clear care plans developed with carers to address unmet needs.
7. Care plans reviewed and adjusted according to effectiveness of the interventions tried. Some structured psychosocial interventions for BPSD9 are supported by research.10 These can be useful to consider within an individualised care plan and are better if implemented by supporting caregivers. Behavioural management techniques and -caregiver psychoeducation centred on an individual patient’s behaviour have been found to be generally successful and the effects can last for months.11 A 2017 systematic review of systematic reviews12 provided a comprehensive summary of the evidence for non-pharmacological interventions in BPSD. Among sensory stimulation interventions, the only convincingly effective intervention (reducing agitation and aggressive behaviour) was music therapy.12,13 Multicomponent interventions that use a comprehensive, integrated multidisciplinary approach combining medical, psychiatric and nursing interventions may be more effective at reducing severe behavioural problems in nursing home patients.12 Animal-assisted therapy has shown a significant reduction in BPSD, especially depression.14 Doll therapy has been shown to reduce agitation, aggressiveness as well as dysphoria, wandering, apathy, professional caregiver burden and delirium.15 Increasing

light exposure and bright light therapy may be beneficial in BPSD and sundowning.16,17 A systematic review suggested that aerobic exercise might be effective in reducing neuropsychiatric symptoms.18 A 2020 Cochrane

20 - Pharmacological measures

Pharmacological measures

668 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 review of aromatherapy (13 studies with 708 participants) found no evidence that it is beneficial for people with dementia although there are many limitations to the existing data.19 Clinicians have limited time to develop non-drug interventions, but in essence they are no more than good clinical practice: taking a clear history to understand factors contributing to behaviours and drawing up a care plan to address these factors. Given drug therapy has such a limited evidence base in this area, there is a duty to do this before even considering prescribing. Pharmacological measures Analgesics Pain in people with dementia may cause agitation and the treatment of pain may reduce agitation.13,20 An RCT investigating the effects of a stepwise protocol of treatment with analgesics noted significant improvement in agitation, overall neuropsychiatric symptoms and pain. Most patients received only paracetamol (acetaminophen). Education of nursing staff on the link between pain and behaviour may be as effective as an algorithm-based pain management intervention.21 A Cochrane review investigated the efficacy and safety of opioids for agitation in people with dementia.22 RCTs of opioids compared with placebo were assessed but there was insufficient evidence to establish any benefit. Antipsychotics Antipsychotic drugs were once widely used in BPSD23 but their use is now discouraged.24,25 Their effect size is small,26–29 tolerability is poor29–31 and they increase mortality.32 Despite this, antipsychotic medications have been the subject of the largest number of studies of any intervention for BPSD. Typical antipsychotics (with the exception of haloperidol) show no efficacy in BPSD, but SGAs do have some efficacy. A comparative effectiveness review found the most effective antipsychotics include risperidone (psychosis, agitation, overall BPSD), olanzapine (agitation) and aripiprazole (overall BPSD). Though commonly used, quetiapine has failed to show effectiveness for BPSD, except at doses (100–200mg/day) that may not be well tolerated.33 A 2006 Cochrane review34 of atypical antipsychotics for aggression and psychosis in AD concluded that risperidone and olanzapine can diminish aggression and that Recommendation: The first-line treatments for BPSD are personalised, multicomponent non-drug measures, which involve working closely with caregivers. Recommendation: The assessment and effective treatment of pain in people with BPSD are important. Even in people without overt pain, a trial of analgesics (usually paracetamol) may be worthwhile.

Prescribing in older people CHAPTER 6 risperidone reduces psychotic symptoms. However, because of modest efficacy and significant increase in adverse effects, neither drug should be used to treat BPSD unless there is severe distress or a serious risk of physical harm to those living or working

with the patient. Brexpiprazole is a relatively newly introduced dopamine D2 receptor partial agonist, like aripiprazole. It has a lower intrinsic activity at D2 and D3 than aripiprazole and so has a lower risk for akathisia and extrapyramidal side effects (EPSEs).35 Brexpiprazole's efficacy and tolerability in the treatment of agitation in AD were investigated in a 12- week RCT. A dose of 2 or 3mg/day showed a statistically significant improvement versus placebo in agitation over 12 weeks and it was generally well tolerated.36 Brexpiprazole is the only drug that is FDA approved for agitation associated with dementia due to AD.37 It is not available in the UK. Increased mortality with antipsychotics in dementia Following analysis of published and unpublished data in 2004, warnings were issued in the UK and USA regarding increased mortality in patients with dementia taking certain atypical antipsychotics.38–40 Warnings now apply to all antipsychotics40,41 and a warning about a possible risk of cerebrovascular events has been added to product labelling for all antipsychotics when used in dementia. Whether mortality risk varies between antipsychotics has been investigated in several studies.42–45 In general, haloperidol led to an increased mortality whereas quetiapine users had a decreased risk. No clinically meaningful differences were observed for olanzapine, aripiprazole and ziprasidone42 (or valproic acid43). The effects were strongest shortly after the start of treatment and remained after adjustment for dose. There was a dose–response relationship for all drugs except quetiapine42 (the higher the dose, the greater the mortality risk). In a 2019 network meta-analysis of 17 studies (5373 patients), no significant differences were found across measures of effectiveness and safety among aripiprazole, olanzapine, quetiapine and risperidone.46,47 Clinical information for antipsychotic use in dementia Antipsychotics should not be used routinely to treat agitation and aggression in people with dementia.48 Risperidone and haloperidol are the only drugs licensed in the UK for the management of BPSD. Owing to the dangers of haloperidol, risperidone is the agent of choice. It is specifically indicated for short-term treatment (up to 6 weeks) of persistent aggression in moderate to severe AD unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.49 Risperidone is licensed up to 1mg twice a day50 although the optimal dose in dementia is 500mcg twice a day (1mg daily).51 Alternative antipsychotic drugs may be used (off--licence) if risperidone is contraindicated or not tolerated (e.g. because of extrapyramidal symptoms or hyperprolactinaemia). Olanzapine has some positive efficacy data for reducing aggression in dementia,34 Recommendation: Risperidone is licensed for persistent aggression in Alzheimer's disease. An alternative agent may be justified if risperidone is contraindicated, not tolerated or not effective. Effect is modest at best. When prescribed, regular review is recommended.

 aripiprazole has shown modest efficacy for BPSD47 and both are less likely to cause Parkinsonian effects. Quetiapine is often considered in patients with Parkinson's disease or DLB (at very small doses) because of its low propensity for causing movement disorders, however it was found to have limited efficacy in dementia so low-dose alternatives (including clozapine) may be required.52 Always consider anticholinergic burden when selecting an antipsychotic drug in dementia (see 'Safer prescribing for physical conditions in dementia' earlier in this chapter). Only prescribe antipsychotics after: ■ ■Treating any physical illness, pain or constipation. ■ ■Addressing sensory deficits (find and clean the person's glasses, get a battery for the hearing aid). ■ ■Trying person-centred non--pharmacological options. ■ ■Only use antipsychotics for psychosis or aggression. Other BPSD need different approaches. ■ ■Assess if the antipsychotic drug is safe to use. Assess fall risk and risk factors for stroke. ■ ■Discussing possible risks and benefits with carer (and patient if they have capacity). ■ ■Clear documentation of the above points.48 ■ ■Review appropriateness of

treatment regularly so that an ineffective drug is not continued unnecessarily. ■ ■Monitor for adverse effects. Guidance on the monitoring of antipsychotic use in dementia is limited. See Appropriate Prescribing of Antipsychotic Medication in Dementia Toolkit (https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2022/10/ Antipsychotic--Prescribing-Toolkit-for-Dementia.pdf). Ideally, patients prescribed antipsychotics for longer than a few weeks (and who are not terminally ill) should have the following tests at baseline, at 3 months and annually (or as appropriate), if possible, and if it does not lead to unnecessary distress.

1. Blood pressure and pulse.
2. Weight (ideally also monitor monthly for the first 3 months).
3. Blood tests: a. fasting glucose or HbA1c b. urea and electrolytes (U&Es) including eGFR c. full blood count (FBC) d. lipids (if possible fasting) e. liver function tests (LFTs) f. prolactin levels.
4. ECG (repeat at between 4 weeks and 3 months or when clinically indicated). ■ ■In--patients or physically frail patients may need more frequent physical health monitoring. ■ ■Review of the antipsychotic drug needs to be done at 4–6 weeks (maybe earlier for in-patients), then at 3 months and then every 6 months if physically stable and there are no adverse effects. Consider stopping the antipsychotic at each review, where appropriate.

Prescribing in older people CHAPTER 6 ■ ■Several deprescribing studies have shown that antipsychotics53–55 (and other psychotropics)55,56 can be deprescribed successfully (Table 6.6) as the reductions in psychotropic drug use did not negatively affect BPSD, while ADL improved.55 Other pharmacological agents in BPSD Cognitive enhancers Acetylcholinesterase inhibitors and memantine have a modest effect on BPSD.13 According to a meta-analysis59 and systematic review,60 the effect of AChE-Is on BPSD is at least statistically significant. Overall, cholinesterase inhibitors are more effective for depression, dysphoria, apathy and anxiety than for agitation or aggression. Memantine can help to improve agitation, aggression and delusions. Benzodiazepines Benzodiazepines61,62 are widely used but their use is poorly supported. Benzodiazepines increase the rate of cognitive decline,61 risk of dementia,63 risk of pneumonia64 and increase all-cause mortality.65 They may contribute to the increased frequency of falls and hip fractures62,66 in older people. Table 6.6 Reduction or discontinuation regimen for antipsychotic drugs in BPSD – a guide.57,58 Antipsychotic Usual dose range in dementia Suggested regimen for reduction/discontinuation (generally over 4 weeks if possible)* Amisulpride 25–50mg/day Reduce by 12.5–25mg every 1–2 weeks (depending on dose) then stop Aripiprazole 5–15mg/day Reduce by 5mg every 1–2 weeks (depending on dose) then stop (if patient is on 5mg daily, reduce to 2.5mg for 2 weeks) Haloperidol Not recommended in older people with dementia (except in delirium) Reduce by 0.25–0.5mg every 1–2 weeks (depending on dose) then stop Olanzapine 2.5–10mg/day Reduce by 2.5mg every 1–2 weeks (depending on dose) then stop Quetiapine 12.5–300mg/day For doses 12.5–100mg/day – reduce by 12.5–25mg every 1–2 weeks (depending on dose) then stop For doses >100–300mg/day – reduce by 25–50mg every 1–2 weeks (depending on dose) then stop If dose is 300mg/day – reduce to 150–200mg/day for 1 week then by 50mg/week then stop Risperidone 0.25–2mg/day Reduce by 0.25–0.5mg every 1–2 weeks (depending on dose) then stop *Duration of taper should not normally exceed the duration of treatment. NB If serious adverse effects occur, stop the antipsychotic drug immediately. BPSD, behavioural and psychological symptoms of dementia. Recommendation: AChE-Is or memantine can help with mild BPSD and are worth considering if a patient is not already on one of these drugs.

672 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Antidepressants Depression is a risk factor and consequence of AD. The prevalence of depression and AD comorbidity is estimated to be 30–50%.67 As with other BPSD, non-pharmacological approaches such as reminiscence, cognitive stimulation/rehabilitation, therapeutic approaches, music-based approaches and education/training have the potential to reduce symptoms of depression in dementia.68 If you can, try simple measures to improve quality of life as the first-line intervention in mild to moderate depression in dementia. The evidence for efficacy of antidepressants in BPSD is mixed and limited, showing that antidepressants are most helpful for treating agitation and less useful for depression, apathy, anxiety or psychosis in dementia.33 Citalopram has the strongest evidence for efficacy in agitation, with the CitAD trial69 showing that a high dose (30mg) of citalopram daily had a positive effect on agitation in dementia; unfortunately this study also confirmed a risk of QT prolongation with citalopram. The maximum dose of citalopram in older people is limited to 20mg a day because of the drug's effect on cardiac QT interval. Although there is less evidence, escitalopram may also be effective in BPSD. The evidence for efficacy of sertraline is mixed, though its cardiac safety is compelling.33 One Cochrane review of trazodone for agitation in dementia70 found insufficient evidence from RCTs to support its use in dementia, but another Cochrane review found trazodone 50mg at bedtime was well tolerated and improved sleep for people with dementia and insomnia.71 Additionally, trazodone 150–300mg/day was found effective in reducing BPSD in frontotemporal dementia.72 Although mirtazapine is frequently used to treat older adults with depression, a pilot study showed no significant therapeutic effect of 15mg mirtazapine on Alzheimer's patients with sleep disorders and in fact found worsening of daytime sleep patterns.73 A study of mirtazapine for agitation in dementia randomly assigned patients to receive either mirtazapine (titrated to 45mg) or placebo, and found no benefit of mirtazapine and a potentially higher mortality in patients who received it.74 Bupropion has not been studied in controlled trials in dementia.33 Vortioxetine has multimodal activity and potential effects on cognitive function through its mechanisms on glutamate neurotransmission and neuroplasticity in the prefrontal cortex, which may be useful in dementia. In a 12-month open-label observational study of 108 patients with mild AD and depressive symptoms, vortioxetine had a beneficial effect on cognition and mood and was well tolerated.75 However, a 12-week placebo-controlled RCT of 100 patients with AD and depression found no statistically significant difference between the two groups in terms of depressive symptoms, cognitive functions and ADL. The percentage of adverse events and drug discontinuation was similar between groups.76 A possible explanation for the divergent results is that the second study included patients with more severe cognitive impairment and depressive symptoms. An open-label prospective study in patients with Parkinson's disease and major depression showed that vortioxetine was well tolerated and improved depressive symptoms as well as cognitive function, apathy, fatigue and quality of life 3 months after starting the drug.77 Recommendation: Avoid benzodiazepines other than as a single use for emergency sedation.

Prescribing in older people CHAPTER 6 Tricyclic antidepressants are best avoided in patients with dementia. They can cause falls, via orthostatic hypotension, and worsen cognition owing to their anticholinergic adverse effect.78 While some studies have found that antidepressant use in older people may be associated with an increased risk of dementia,79 it is important to keep in mind that previous studies have shown that late-life depression is associated with an increased risk for dementia. Hence any comparisons of antidepressant users with non-depressed non- users are subject to indication bias as the increased dementia risk could be due to depression, not the

medication. Mood stabilisers/antiseizure medications Randomised controlled trials of mood stabilisers in BPSD have been completed for oxcarbazepine,80 carbamazepine81 and valproate.82 Gabapentin, lamotrigine and topiramate have also been used.83 Of the mood stabilisers, carbamazepine has the most robust evidence of efficacy in non-cognitive symptoms.84 However, its serious adverse effects (especially Stevens-Johnson syndrome, ataxia and hyponatraemia) and its potential for drug interactions limit its use. One RCT of valproate found it to be ineffective in controlling BPSD symptoms.85 A Cochrane review of valproate for the treatment of agitation in dementia concluded that it was ineffective and associated with a higher rate of adverse effects, and possibly of serious ones.86 Valproate does not delay emergence of agitation in dementia.87 Literature reviews of anticonvulsants in non-cognitive symptoms of dementia found that valproate, oxcarbazepine and lithium showed low or no evidence of efficacy and that more RCTs are needed to strengthen the evidence for gabapentin, topiramate and lamotrigine.84 Preliminary low-grade evidence based on case series and case reviews suggests a possible benefit of gabapentin and pregabalin in patients with BPSD in AD. Evidence in frontotemporal dementia is lacking.88 In a small case series, gabapentin reduced aggression among seven patients with vascular dementia or mixed vascular/AD, using daily doses ranging from 200 to 600mg daily. Three of the seven patients were able to discontinue antipsychotics after gabapentin initiation; thus, it may be useful in patients with cardiac conditions where antipsychotics are inappropriate. Caution should be noted about the use of gabapentin in DLB. Dramatic worsening of neuropsychiatric symptoms has been reported after its use to treat behavioural symptoms.89 There is inadequate evidence to support the use of levetiracetam for BPSD, with concerns regarding tolerability.90 Although clearly beneficial in some patients, anticonvulsants/mood stabilisers cannot be recommended for routine use in the treatment of the neuropsychiatric symptoms in dementia at present.83 Recommendation: Although evidence is weak, use of antidepressants is justified in people with dementia who have clear symptoms of moderate or severe depression, especially if non--pharmacological approaches have been ineffective. Recommendation: Limited evidence to support use; use may be justified where other treatments are contraindicated or ineffective. Valproate is best avoided.

 Non-pharmacological management of sleep disturbances using established sleep hygiene methods should be the first-line treatment for insomnia in dementia.91,92 A 2020 Cochrane review93 of pharmacotherapies for sleep disturbances in dementia found a distinct lack of evidence to guide decisions about drug treatment of sleep problems in dementia. There were no RCTs for the many widely prescribed drugs (including benzodiazepine and non-benzodiazepine hypnotics), despite considerable uncertainty about the balance of benefits and risks for these common treatments. The authors found no evidence for beneficial effects of melatonin (up to 10mg) or a melatonin receptor agonist. There was evidence of some beneficial effects on sleep outcomes from trazodone and orexin antagonists (suvorexant and lemborexant; two studies, n = 323) and no evidence of harmful effects in these small trials, although larger trials are needed. Of note, melatonin (at 2mg and occasionally up to 10mg/day modified release) is used in patients with dementia with good effects. In one study, melatonin 9mg resulted in improvement in subjective sleep, reduction of sundowning behaviour and lack of decline in cognitive function testing over a period of 22–35 months. Several other case reports and small open-label trials described benefits on subjective sleep characteristics and cognitive function, but data quality is limiting.94 An expert review92 also deduced that non-pharmacological interventions

are generally preferred as the first-line approach to improve sleep-related symptoms in AD; however, when non-pharmacological interventions alone are insufficient, a range of pharmacological agents can be considered. Trazodone and melatonin are commonly used as adjunctive therapies, while Z-drugs including zopiclone and zolpidem are specifically employed to treat insomnia in patients with late-onset AD. Furthermore, dual orexin receptor antagonists have emerged and gained approval for improving sleep onset and maintenance in AD patients. The review proposed a stepwise algorithm for the management of sleep disturbances in AD.92 Sedating antihistamines Promethazine is frequently used in BPSD for its sedative effects. It has strong anticholinergic effects and readily penetrates the BBB, potentially causing significant cognitive impairment.95 Miscellaneous agents96,97 A meta-analysis of RCTs for Gingko biloba (240mg daily, 22–24-week treatment) showed improvement in BPSD (except psychotic-like features) and in caregiver distress caused by such symptoms.98 Recommendation: Despite limited evidence for the efficacy of melatonin, it is safe to use and may be justified in cases where benefits are seen. Non--pharmacological management of sleep disturbances should be tried first. Recommendation: Promethazine should be avoided.

21 - Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT)

22 - Summary

Summary

Prescribing in older people CHAPTER 6 Pimavanserin (inverse agonist and antagonist at 5HT2A receptors) is approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis. One RCT evaluated its use for the treatment of psychosis in AD and showed improved psychotic symptoms when compared with placebo and a lower risk of relapse with continuation. Headache, constipation, urinary tract infection and asymptomatic QT prolongation occurred with pimavanserin.99 It has also shown improvement of depressive symptoms in patients with Parkinson’s disease.100 A recent phase III, randomised double-blind placebo-controlled multicentre study investigating the efficacy of lumateperone (a potent antagonist at 5HT2A receptors, and a serotonin reuptake inhibitor) in reducing dementia-related agitation failed to show any benefit.101 Other agents being investigated for BPSD include dextromethorphan/quinidine (one RCT found it decreased agitation and was well tolerated),102 bupropion/dextromethorphan103 and methylphenidate (one RCT found it to be effective for apathy in AD in individuals who were not anxious or agitated).103,104 Prazosin (a centrally acting α1 adrenoceptor antagonist) appears to benefit individuals with dementia and agitation and aggression. When compared with other treatments for BPSD, the data for its use in BPSD are limited to just one good-quality RCT. Given these limitations, its routine use for the management of BPSD cannot be recommended at this time; however, it may be used when other medications (e.g. acetylcholinesterase inhibitors, memantine, antidepressants and/or atypical antipsychotics) have been ineffective or not tolerated.47,105 A Cochrane review (4 small studies, 110 participants) found low-certainty evidence suggesting there may be little or no clinically important effect of cannabinoids on overall BPSD assessed with the Neuropsychiatric Inventory.106 Electroconvulsive therapy (ECT) Electroconvulsive therapy may have a place in the treatment of severe and refractory BPSD. A review (20 published reports, 172 individuals with dementia; 40% AD) found that over 90% of the individuals responded to ECT treatment. Adverse effects were infrequent, mild and transient. The most common adverse event noted was postictal confusion/ memory impairment that was seen in approximately 15% of the individuals.47 However, ECT would not be recommended as a common intervention given limited evidence, and the considerable practical aspects of transporting patients to the ECT clinic and difficulty with obtaining consent. Summary The evidence base available to guide treatment in this area is insufficient to allow specific recommendations on appropriate management and drug choice. The basic approach is to exclude physical illness and try non-drug measures before resorting to the use of psychotropics. When using pharmacological treatments, there should be clearly documented treatment aims and prescribing should cease if these aims are not met within a specified timeframe. Recommendation: There is insufficient evidence to recommend ECT use in BPSD. Caution: It can cause significant cognitive adverse effects.

23 - References

References

1. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. NICE Guidance [NG97]. 2018 (last checked September 2023, last accessed December 2023); https://www.nice.org.uk/guidance/ng97.
2. Steinberg M, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 2008; 23:170–177.
3. Salzman C, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. J Clin Psychiatry 2008; 69:889–898.
4. Department of Health. The use of antipsychotic medication for people with dementia: time for action. A report for the Minister of State for Care Services by Professor Sube Banerjee. 2009; https://psychrights.org/research/digest/nlps/banerjeereportongeriatricneurolepticuse.pdf.
5. Livingston G, et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. Health Technol Assess 2014; 18:1–226, v–vi.
6. Kales HC, et al. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015; 350:h369.
7. James IA. Understanding Behaviour in Dementia That Challenges: A Guide to Assessment and Treatment. London: Jessica Kingsley Publishers; 2011.
8. Brechin D, et al. British Psychological Society. Briefing paper. Alternatives to antipsychotic medication: psychological approaches in managing psychological and behavioural distress in people with dementia. 2013; https://explore.bps.org.uk/content/report--guideline/bpsrep.2013. inf207.
9. Douglas S, et al. Non-pharmacological interventions in dementia. Adv Psychiatric Treat 2004; 10:171–177.
10. Ayalon L, et al. Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. Arch Intern Med 2006; 166:2182–2188.
11. Livingston G, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 2005; 162:1996–2021.
12. Abraha I, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open 2017; 7:e012759.

13. Dyer SM, et al. An overview of systematic reviews of pharmacological and non--pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr 2018; 30:295–309.
14. Chen H, et al. Effects of animal-assisted therapy on patients with dementia: a systematic review and meta-analysis of randomized controlled trials. Psychiatry Res 2022; 314:114619.
15. Santagata F, et al. The doll therapy as a first line treatment for behavioral and psychologic symptoms of dementia in nursing homes residents: a randomized, controlled study. BMC Geriatr 2021; 21:545.
16. Guu TW, et al. Light, sleep-wake rhythm, and behavioural and psychological symptoms of dementia in care home patients: revisiting the sundowning syndrome. Int J Geriatr Psychiatry 2022; 37:10.
17. Kolberg E, et al. The effects of bright light treatment on affective symptoms in people with dementia: a 24-week cluster randomized controlled trial. BMC Psychiatry 2021; 21:377.
18. Steichele K, et al. The effects of exercise programs on cognition, activities of daily living, and neuropsychiatric symptoms in community- dwelling people with dementia – a systematic review. Alzheimers Res Ther 2022; 14:97.
19. Ball EL, et al. Aromatherapy for dementia. Cochrane Database Syst Rev 2020; 8:CD003150.
20. Husebo BS, et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ 2011; 343:d4065.
21. Manietta C, et al. Algorithm-based pain management for people with dementia in nursing homes. Cochrane Database Syst Rev 2022; 4:CD013339.
22. Brown R, et al. Opioids for agitation in dementia. Cochrane Database Syst Rev 2015; 5:CD009705.
23. Lee PE, et al. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. BMJ 2004; 329:75.
24. Jeste DV, et al. Atypical antipsychotics in elderly patients with dementia or schizophrenia: review of recent literature. Harv Rev Psychiatry 2005; 13:340–351.
25. Jeste DV, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 2008; 33:957–970.
26. Aupperle P. Management of aggression, agitation, and psychosis in dementia: focus on atypical antipsychotics. Am J Alzheimers Dis Other Demen 2006; 21:101–108.
27. Yury CA, et al. Meta-analysis of the effectiveness of atypical antipsychotics for the treatment of behavioural problems in persons with dementia. Psychother Psychosom 2007; 76:213–218.
28. Deberdt WG, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry 2005; 13:722–730.
29. Schneider LS, et al. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006; 14:191–210.
30. Anon. How safe are antipsychotics in dementia? Drug Ther Bull 2007; 45:81–86.
31. Rosack J. Side-effect risk often tempers antipsychotic use for dementia. Psychiatr News 2006; 41:1–38.

32. Schneider LS, et al. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294:1934–1943.

 33. Bessey LJ, et al. Management of behavioral and psychological symptoms of dementia. Curr Psychiatry Rep 2019; 21:66. 34. Ballard C, et al. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease (review). Cochrane Database Syst Rev 2006; 1:CD003476. 35. Stahl SM. Mechanism of action of brexpiprazole: comparison with aripiprazole. CNS Spectr 2016; 21:1–6. 36. Lee D, et al. Brexpiprazole for the treatment of agitation in Alzheimer dementia: a randomized clinical trial. JAMA Neurol 2023; 80:1307–1316. 37. US Food and Drug Administration. FDA approves first drug to treat agitation symptoms associated with dementia due to Alzheimer's disease. 2023 (last accessed January 2024); https://www.fda.gov/news-events/press-announcements/fda--approves-first-drug-treat-agitation-symptoms- associated-dementia-due-alzheimers-disease. 38. Gov.UK. PhVWP assessment report: antipsychotics and cerebrovascular accident. 2005; https://www.gov.uk/government/publications/ antipsychotic-medicines-licensed-products-uses-and-side-effects. 39. Duff G. Atypical antipsychotic drugs and stroke – Committee on Safety of Medicines. 2004; https://webarchive.nationalarchives.gov.uk/20141206131857/http://www.mhra.gov.uk/home/groups/pl--p/documents/websiteresources/con019488.pdf. 40. US Food and Drug Administration. Information on conventional antipsychotics – FDA alert [6/16/2008]. 2008; http://www.fda.gov/. 41. European Medicines Agency. CHMP assessment report on conventional antipsychotics. 2008; http://www.emea.europa.eu. 42. Huybrechts KF, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ 2012; 344:e977. 43. Kales HC, et al. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry 2012; 169:71–79. 44. Schmedt N, et al. Comparative risk of death in older adults treated with antipsychotics: a population-based cohort study. Eur Neuropsychopharmacol 2016; 26:1390–1400. 45. Maust DT, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry 2015; 72:438–445. 46. Yunusa I, et al. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis. JAMA Network Open 2019; 2:e190828. 47. Tampi RR, et al. Prazosin for the management of behavioural and psychological symptoms of dementia. Drugs Context 2022; 11;2022-3-3. 48. Corbett A, et al. Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. BMJ 2014; 349:g6420. 49. Janssen-Cilag Ltd. Summary of product characteristics. RISPERDAL CONSTA 25mg, 37.5mg, 50mg powder and solvent for prolonged- release suspension for injection. 2022 (last accessed December 2023); https://www.medicines.org.uk/emc/product/1690/smpc#gref. 50. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete.com. 51. Katz IR, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999; 60:107–115. 52. Kyle K, et al. Treatment of psychosis in Parkinson's disease and dementia with Lewy bodies: a review. Parkinsonism Relat Disord 2020; 75:55–62. 53. Brodaty H, et al. Antipsychotic deprescription for older adults in long--term care: the HALT Study. J Am Med Dir Assoc 2018; 19:592–600.e597. 54. Ballard C, et al. The Dementia Antipsychotic Withdrawal Trial (DART-AD): long-term follow-up of a randomised placebo--controlled trial. Lancet Neurol 2009; 8:151–157. 55. Gedde MH, et al. Less is more: the impact of

deprescribing psychotropic drugs on behavioral and psychological symptoms and daily functioning in nursing home patients. results from the cluster-randomized controlled COSMOS Trial. Am J Geriatr Psychiatry 2021; 29:304–315. 56. Cossette B, et al. Optimizing practices, use, care, and services-antipsychotics (OPUS-AP) in long-term care centers in Quebec, Canada: a successful scale-up. J Am Med Dir Assoc 2022; 23:1084–1089. 57. NHS PrescQIPP. T7: reducing antipsychotic prescribing in dementia. 2014; https://www.prescqipp.info/our-resources/bulletins/t7-reducing-antipsychotic-prescribing-in-dementia/. 58. Bjerre LM, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: evidence-based clinical practice guideline. Can Fam Physician 2018; 64:17–27. 59. Campbell N, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: a meta-analysis. Clin Interv Aging 2008; 3:719–728. 60. Seibert M, et al. Efficacy and safety of pharmacotherapy for Alzheimer's disease and for behavioural and psychological symptoms of dementia in older patients with moderate and severe functional impairments: a systematic review of controlled trials. Alzheimers Res Ther 2021; 13:131. 61. Verdoux H, et al. Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med 2005; 35:307–315. 62. Lagnaoui R, et al. Benzodiazepine utilization patterns in Alzheimer's disease patients. Pharmacoepidemiol Drug Saf 2003; 12:511–515. 63. Billioti de Gage S, et al. Benzodiazepine use and risk of dementia: prospective population based study. BMJ 2012; 345:e6231. 64. Taipale H, et al. Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. CMAJ 2017; 189:e519–e529. 65. Palmaro A, et al. Benzodiazepines and risk of death: results from two large cohort studies in France and UK. Eur Neuropsychopharmacol 2015; 25:1566–1577. 66. Chang CM, et al. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 2008; 16:686–692.

 67. Aboukhatwa M, et al. Antidepressants are a rational complementary therapy for the treatment of Alzheimer's disease. Mol Neurodegener 2010; 5:10. 68. Burley CV, et al. Nonpharmacological approaches reduce symptoms of depression in dementia: a systematic review and meta-analysis. Ageing Res Rev 2022; 79:101669. 69. Porsteinsson AP, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA 2014; 311:682–691. 70. Martinon-Torres G, et al. Trazodone for agitation in dementia. Cochrane Database Syst Rev 2004; 4:CD004990. 71. McCleery J, et al. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database Syst Rev 2016; 11:CD009178. 72. Trieu C, et al. Effectiveness of pharmacological interventions for symptoms of behavioral variant frontotemporal dementia: a systematic review. Cogn Behav Neurol 2020; 33:1–15. 73. Scoralick FM, et al. Mirtazapine does not improve sleep disorders in Alzheimer's disease: results from a double-blind, placebo-controlled pilot study. Psychogeriatrics 2017; 17:89–96. 74. Banerjee S, et al. Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial. Lancet 2021; 398:1487–1497. 75. Cumbo E, et al. Treatment effects of vortioxetine on cognitive functions in mild Alzheimer's disease patients with depressive symptoms: a 12 month, open-label, observational study. J Prev Alzheimers Dis 2019; 6:192–197. 76. Jeong HW, et al. Vortioxetine treatment for depression in Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Clin Psychopharmacol Neurosci 2022; 20:311–319. 77. Santos García D, et al. Vortioxetine improves depressive symptoms and cognition in Parkinson's disease patients with major depression: an open-label prospective study. Brain Sci 2022; 12:1466. 78. Ballard C, et al. Management of neuropsychiatric symptoms in people

with dementia. CNS Drugs 2010; 24:729–739. 79. Wang YC, et al. Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. Behav Neurol 2018; 2018:5315098. 80. Sommer OH, et al. Effect of oxcarbazepine in the treatment of agitation and aggression in severe dementia. Dement Geriatr Cogn Disord 2009; 27:155–163. 81. Tariot PN, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998; 155:54–61. 82. Lonergan E, et al. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev 2009; 3:CD003945. 83. Konovalov S, et al. Anticonvulsants for the treatment of behavioral and psychological symptoms of dementia: a literature review. Int Psychogeriatr 2008; 20:293–308. 84. Yeh YC, et al. Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: an update review. Kaohsiung J Med Sci 2012; 28:185–193. 85. Sival RC, et al. Sodium valproate in aggressive behaviour in dementia: a twelve--week open label follow-up study. Int J Geriatr Psychiatry 2004; 19:305–312. 86. Baillon SF, et al. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev 2018; 10:CD003945. 87. Tariot PN, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Arch Gen Psychiatry 2011; 68:853–861. 88. Supasitthumrong T, et al. Gabapentin and pregabalin to treat aggressivity in dementia: a systematic review and illustrative case report. Br J Clin Pharmacol 2019; 85:690–703. 89. Cooney C, et al. Use of low-dose gabapentin for aggressive behavior in vascular and mixed vascular/Alzheimer dementia. J Neuropsychiatry Clin Neurosci 2013; 25:120–125. 90. Gallagher D, et al. Antiepileptic drugs for the treatment of agitation and aggression in dementia: do they have a place in therapy? Drugs 2014; 74:1747–1755. 91. David R, et al. Non-pharmacologic management of sleep disturbance in Alzheimer’s disease. J Nutr Health Aging 2010; 14:203–206. 92. Javed B, et al. Pharmacological and non-pharmacological treatment options for sleep disturbances in Alzheimer’s disease. Expert Rev Neurother 2023; 23:501–514. 93. McCleery J, et al. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database Syst Rev 2020; 11:CD009178. 94. Roland JP, et al. Impact of pharmacotherapy on insomnia in patients with Alzheimer’s disease. Drugs Aging 2021; 38:951–966. 95. Bishara D, et al. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. Int J Geriatr Psychiatry 2017; 32:650–656. 96. Porsteinsson AP, et al. An update on the advancements in the treatment of agitation in Alzheimer’s disease. Expert Opin Pharmacother 2017; 18:611–620. 97. Carrarini C, et al. Agitation and dementia: prevention and treatment strategies in acute and chronic conditions. Front Neurol 2021; 12:644317. 98. Savaskan E, et al. Treatment effects of Ginkgo biloba extract EGb 761® on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials. Int Psychogeriatr 2018; 30:285–293. 99. Tariot PN, et al. Trial of pimavanserin in dementia-related psychosis. N Engl J Med 2021; 385:309–319. 100. DeKarske D, et al. An open-label, 8-week study of safety and efficacy of pimavanserin treatment in adults with Parkinson’s disease and depression. J Parkinsons Dis 2020; 10:1751–1761. 101. ClinicalTrials.gov. ITI-007 for the treatment of agitation in patients with dementia, including Alzheimer’s disease [NCT02817906]. 2021; https://clinicaltrials.gov/study/NCT02817906.

 102. Tampi RR, et al. Evidence for using dextromethorphan--quinidine for the treatment of agitation in dementia. World J Psychiatry 2020; 10:29–33. 103. Ahmed M, et al. Current agents in development for treating behavioral and psychological symptoms associated with dementia. Drugs Aging 2019; 36:589–605. 104. Lanctôt KL, et al. Heterogeneity of response to methylphenidate in apathetic patients in the ADMET 2 Trial. Am J Geriatr Psychiatry 2023; 31:1077–1087. 105. Chen A, et al. The Psychopharmacology Algorithm

Project at the Harvard South Shore Program: an update on management of behavioral and psychological symptoms in dementia. Psychiatry Res 2021; 295:113641. 106. Bosnjak Kuharic D, et al. Cannabinoids for the treatment of dementia. Cochrane Database Syst Rev 2021; 9:CD012820.

24 - Management of inappropriate sexual behaviour

Management of inappropriate sexual behaviour in older adults

680 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Management of inappropriate sexual behaviour in older adults This section deals with sexual behaviours that are causing distress either to the person with dementia or to other people. Sexually inappropriate behaviours have been reported in between 1.8% and 25.9% of patients with neurocognitive disorders,1 and in people with dementia the prevalence rate is 2–17%, occurring with about equal frequency in men and women.2 Sexual symptoms are more prevalent in frontal lobe disorders (most commonly stroke and behavioural variant frontotemporal dementia) and in Parkinson's (adverse effects of dopaminergic drugs), but can occur in any dementia subtype.1 These symptoms present a challenge for patients, carers and healthcare workers. Assessment of the behaviours, the contexts in which they arise and their risks is essential. It is important to manage the environment and to educate and discuss the behaviour with carers and families. Behavioural measures are probably helpful, although no specific intervention has been shown to be effective in this area. Several classes of drug may help to control aberrant sexual behaviours, but owing to the lack of large-scale studies there is no gold standard treatment. No treatments are licensed for hypersexuality in this population and the medications used are all potentially harmful.2 A thorough history should be taken before starting any drug therapy to obtain the relevant medical, psychiatric, medication and sexual history. Changes in sexual behaviour can be caused by urinary or genital conditions, delirium or a medication side effect. Benzodiazepines, dopamine-receptor agonists (e.g. apomorphine, pramipexole, rotigotine) and L-dopa can cause hypersexuality.2 Non--pharmacological treatment, such as distraction/diversion of the patient when inappropriate sexual behaviours occur,1 is recommended as first-line therapy (Box 6.3). Antidepressants Box 6.3 Non--pharmacological measures1 ■ ■Identify and treat medical causes for behaviour, e.g. urinary

retention and genital disorders causing the patient to touch their genitals due to discomfort. Delirium can cause sexual disinhibition ■ ■Identify and treat any psychiatric disorder that may cause inappropriate sexual behaviour, e.g. mania or depression ■ ■If possible, stop or reduce dose of medication that may be causing the behaviour, e.g. benzodiazepines, dopamine agonists and high-dose L-dopa ■ ■Prevention: fulfil the need for intimacy/connection in other ways such as having meals in groups, conversation among peers and activities such as walking or exercise ■ ■Discussion with patient, caregivers and relatives to better understand the behaviour and explore attitudes to sexuality, which may inform therapy ■ ■Distraction or diversion, redirect behaviour, engage patients in activities that involve the hands and reduce sexual stimulation (e.g. iPads, magazines, TV) ■ ■Provide sensory and environmental stimulation (e.g. aromatherapy, music therapy, multisensory therapy, pet therapy). ■ ■Behavioural/cognitive behavioural therapy if available (though evidence is limited)

25 - Management

Management

Prescribing in older people CHAPTER 6 have been recommended as the first line of pharmacological treatment after attempting non-pharmacological interventions. Several other categories of pharmacological interventions are listed in Table 6.7. Management To inform the management of inappropriate sexual behaviour, evaluation should include a medical history, physical examination, sexual history and medication review. The history should cover specifics of the demonstrated behaviour, such as potential precipitants and consequences including the frequencies of episodes, when and where they occur and with whom.3 Sometimes normal sexual behaviour, such as a patient masturbating in their bedroom, can be labelled as ‘disinhibition’, particularly in care home settings. In these cases, a discussion with staff and relatives about simple measures (e.g. a care plan to allow the resident periods of privacy in their room at set times each day) can avoid normal behaviours being pathologised. Non- pharmacological treatments should be tried first to prevent unnecessary prescription of psychotropics. Because of the complex nature of sexual disinhibition and varying origins of this behaviour, treatment will be most successful when tailored to the patient’s specific presentation.1 Studies on the pharmacological treatment of sexual disinhibition are limited and larger studies are necessary to establish a preferred medication regimen. In addition, there are few data available on treating these symptoms in women.1 A systematic review4 concluded that when treating patients with Alzheimer’s disease, vascular dementia or unspecified dementia, serotonergic agents including SSRIs and TCAs are recommended as a first--line treatment, followed by antiandrogens as a second line, and luteinising hormone-releasing hormone agonists and oestrogens as a third line. A literature review5 determined SSRIs to be the first line of treatment, antipsychotics to be the second line and hormonal modulators to be the third line (owing to cost and adverse effects).

Table 6.7 Pharmacological options in inappropriate sexual behaviour in older adults.1,6–8 Medication Drug Dose Mechanism of action Adverse effects Cautions/additional information Antiandrogens Cyproterone acetate Low dose 10mg/day9 High dose 50–100mg/day10 Cyproterone is licensed in the UK for hypersexuality in males: 50mg bd11 Reduction in serum testosterone level by inhibiting LH and FSH1 Gynaecomastia, galactorrhoea, elevated blood glucose, depression, osteoporosis1 Cyproterone acetate has been associated with risk of meningioma. Monitor patients for meningiomas and discontinue treatment if diagnosed. Surgical implantation of hormonal therapy to reduce male sex drive is subject to the conditions of Section 57 of the UK MHA and requires patient consent and a second medical opinion.12 Medroxyprogesterone acetate (MPA) Oral 5mg/day7 Oral 100–400mg/ day13 IM 100–300mg/week every 2 weeks14 Reduction in testosterone1 Sedation, weight gain, hot flushes, depression, elevated blood glucose1 Finasteride (for men who have benign prostatic hyperplasia) 5mg/day7 Reduction in testosterone1 Gynaecomastia, testicular pain, depression1 Antidepressants SSRIs

usually first-line treatment Citalopram 20mg/day15 Decreased libido and antiobsessive effects Insomnia, somnolence, nausea, diarrhoea, headache, anorexia1 SSRIs cited as best first-line treatment Escitalopram 10–20mg/day Paroxetine 20mg/day16 Clomipramine 150–175mg/day16 Decreased libido1 Postural hypotension, anticholinergic effects including constipation, dry mouth, urinary retention and memory impairment1 Anticholinergic activity less than ideal in this group of patients Trazodone 100–500mg/day16 Decreased libido1 Day-time sedation, orthostatic hypotension, priapism, falls and fractures, delirium1 Mirtazapine 30mg/day16 Unknown Appetite increase, arthralgia, confusion, constipation, diarrhoea, dizziness, drowsiness, dry mouth, fatigue

Anticonvulsants Gabapentin 300–1800mg/day17 Increased GABA1 GI upset, skin reactions, confusion, nystagmus, dizziness, drowsiness6 Carbamazepine 200–800mg/day16 May help lower testosterone levels leading to decreased libido1 Dizziness, ataxia, drowsiness, diplopia, hyponatraemia, blood dyscrasias, severe skin reaction6 Potent enzyme inducer with many interactions Oxcarbazepine Starting dose 150mg/ day, titrated by 150mg/day in two divided doses. Average effective dose 600–750mg/ day in two divided doses18 May help lower testosterone levels leading to decreased libido1 Abdominal pain, alopecia, asthenia, ataxia, concentration impaired, depression, dizziness, drowsiness, hyponatraemia, nausea, nystagmus, skin reactions, vertigo, vision disorders, leucopenia Valproate Dose not specified but 50–200mg/day has been used Unknown Abdominal pain, tremor, agitation, alopecia (regrowth may be curly), anaemia, confusion, deafness, diarrhoea, drowsiness, haemorrhage, hallucination, headache, hepatic disorders Valproate causes serious harm in pregnancy and in children of men taking valproate (see Chapter 7). (Continued)

Antipsychotics Haloperidol 1.5–3mg/day16 Blocks dopamine receptors to decrease libido1 Cognitive decline, extrapyramidal symptoms, sedation, gait disturbances, falls, tardive dyskinesia, delirium, QT prolongation, increases in UTI and respiratory infections1 Increased risk of stroke and mortality in dementia. Extrapyramidal symptoms First-line treatment in cases where patients present with pathological irritability or unstable mood1 Olanzapine 2.5–15mg/day7 Arrhythmias, constipation, dizziness, drowsiness, dry mouth, erectile dysfunction, fatigue, galactorrhoea, gynaecomastia, hyperglycaemia, weight increase11 Quetiapine 25–75mg/day16 Appetite increased, asthenia, dysarthria, dyspepsia, dyspnoea, fever, headache, irritability, palpitations, peripheral oedema11 Zuclopenthixol 50mg IM monthly6 Tardive dyskinesia, delirium, QT prolongation, increases in UTI and respiratory infections, peripheral oedema, extrapyramidal effects1 Beta blockers Pindolol 5–40mg/day6,16 Decreased adrenergic drive1 Dizziness, sleep disturbance, headache, weakness, fatigue, GI upset Buspirone 10–60mg/day16,19 Unknown Abdominal pain, cold sweat, confusion, depression, dizziness, drowsiness, dry mouth, laryngeal pain, movement disorders, musculoskeletal pain, paraesthesia, skin reactions, tachycardia Table 6.7 (Continued) Medication Drug Dose Mechanism of action Adverse effects Cautions/additional information

Cimetidine 600–1600mg/day14 Antiandrogen actions1 Worsening cognition, dizziness, nausea, arthralgia, headache1 A small study (n = 20) on elderly patients exhibiting hypersexual behaviours with dementia. This study found that 14 patients improved with cimetidine alone while six patients improved with a combination of cimetidine with ketoconazole or spironolactone.1 Ketoconazole 100–200mg/day20 Antiandrogen actions1 Sedation, headache, rash, photosensitivity, pruritus, hepatotoxicity, GI upset1 Gonadotropin and luteinising hormone- releasing hormone (GnRH and

LHRH) agonists Leuprolide 7.5mg IM monthly6 Triptorelin is licensed in the UK for male hypersexuality: 11.25 mg IM every 12 weeks Decrease testosterone and decrease libido1 Hot flushes, decreased erectile dysfunction1 Caution: risk factors for osteoporosis L-tryptophan supplementation Dose not specified Increases 5HT synthesis in brain, stimulating 5HT release and function1 High blood glucose, increased risk of bladder cancer, eosinophilia-myalgia syndrome1 Naltrexone 100–150mg/day21 Unknown Abdominal pain, anxiety, appetite abnormal, arthralgia, asthenia, chest pain, dizziness, eye disorders, headache, hyperhidrosis, myalgia, nausea, palpitations, sexual dysfunction, skin reactions, sleep disorders, tachycardia, thirst Naltrexone is used after establishing normal liver and kidney function tests. (Continued)

Oestrogens Conjugated oestrogens Diethylstilbestrol 0.625mg once daily 0.05–0.1mg/day transdermal patch8 1mg once to twice daily7 Decreased testosterone and decreased libido Weight gain, gynaecomastia, venous thromboembolism, risk of cardiovascular adverse effects, fluid retention, GI effects1 Rivastigmine Up to 4.5mg bd (oral)22 4.6–9.5mg/day (patch) Reduces behavioural symptoms by improving cognitive functioning1 Nausea, diarrhoea, urinary incontinence, syncope1 Conflicting evidence. Rivastigmine has been shown to help many patients with sexual disinhibition while donepezil may exacerbate these symptoms.1 Spironolactone 12.58–75mg/day20 Antiandrogen actions1 Hyperkalaemia, gynaecomastia, GI ulcers1 bd, twice a day; FSH, follicle-stimulating hormone; GABA, gamma-aminobutyric acid; GI, gastrointestinal; LH, luteinising hormone; MHA, Mental Health Act; UTI, urinary tract infection. Table 6.7 (Continued) Medication Drug Dose Mechanism of action Adverse effects Cautions/additional information

26 - References

References

Prescribing in older people CHAPTER 6 References

1. Sarangi A, et al. Treatment and management of sexual disinhibition in elderly patients with neurocognitive disorders. Cureus 2021; 13:e18463.
2. Dégano P, et al. Hypersexuality in dementia. Adv Psychiatr Treat 2005; 11:424–431.
3. Cipriani G, et al. Sexual disinhibition and dementia. Psychogeriatrics 2016; 16:145–153.
4. Guay DRP. Inappropriate sexual behaviors in cognitively impaired older individuals. Am J Geriatr Pharmacother 2008; 6:269–288.
5. Ibrahim C, et al. Hypersexuality in neurocognitive disorders in elderly people – a comprehensive review of the literature and case study. Psychiatr Danub 2014; 26 Suppl 1:36–40.
6. Tucker I. Management of inappropriate sexual behaviors in dementia: a literature review. Int Psychogeriatr 2010; 22:683–692.
7. Kindrat A, et al. Pharmacologic management of inappropriate sexual behaviour in long--term care residents. Can Fam Physician 2023; 69:687–689.
8. Joller P, et al. Approach to inappropriate sexual behaviour in people with dementia. Can Fam Physician 2013; 59:255–260.
9. Haussermann P, et al. Low-dose cyproterone acetate treatment of sexual acting out in men with dementia. Int Psychogeriatr 2003; 15:181–186.
10. Tavares A, et al. Cyproterone for treatment of hypersexuality in an elderly Huntington’s disease patient. Progr Neuropsychopharmacol Biol Psychiatry 2008; 32:1994–1995.
11. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete.com.
12. Department of Health. Code of practice: Mental Health Act 1983 (last updated October 2017); https://www.gov.uk/government/publications/ code-of-practice-mental-health-act--1983#history.
13. Cross BS, et al. High-dose oral medroxyprogesterone for inappropriate hypersexuality in elderly men with dementia: a case series. Ann Pharmacother 2013; 47:e1.
14. Ozkan B, et al. Pharmacotherapy for inappropriate sexual behaviors in dementia: a systematic review of literature. Am J Alzheimers Dis Other Demen 2008; 23:344–354.
15. Mania I, et al. Citalopram treatment for inappropriate sexual behavior in a cognitively impaired patient. Prim Care Companion J Clin Psychiatry 2006; 8:106.
16. De Giorgi R, et al. Treatment of inappropriate sexual behavior in dementia. Curr Treat Options Neurol 2016; 18:41.
17. Alkhalil C, et al. Can gabapentin be a safe alternative to hormonal therapy in the treatment of inappropriate sexual behavior in demented patients? Int Urol Nephrol 2003;

35:299–302.
18. Shua-Haim JR, et al. P1–446: safety and efficacy of oxcarbazepine in the treatment of hypersexuality in Alzheimer’s disease patients residing in a special care unit in an assisted living facility. Alzheimers Dement 2006; 2:S228–S229.
19. Plantier D, et al. Drugs for behavior disorders after traumatic brain injury: systematic review and expert consensus leading to French recommendations for good practice. Ann Phys Rehabil Med 2016; 59:42–57.
20. Wiseman SV, et al. Hypersexuality in patients with dementia: possible response to cimetidine. Neurology 2000; 54:2024.
21. Sultana T, et al. Compulsive sexual behavior and alcohol use disorder treated with naltrexone: a case report and literature review. Cureus 2022; 14:e25804.
22. Canevelli M, et al. Rivastigmine in the treatment of hypersexuality in Alzheimer disease. Alzheimer Dis Assoc Disord 2013; 27:287–288.

27 - Depression in older adults

Depression in older adults

688 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Depression in older adults The prevalence of most physical illnesses increases with age and physical problems such as cardiovascular disease, chronic pain, diabetes and Parkinson’s disease are associated with a high risk of depressive illness.1,2 The morbidity and mortality associated with depression are increased in older adults3 as older people are more likely to be physically frail and therefore vulnerable to serious consequences from self-neglect (e.g. life- threatening dehydration or hypothermia) and immobility (e.g. venous stasis). Suicide is relatively more common in older people.4 Mortality is reduced by effective treatment of depression.5 A meta-analysis of placebo-controlled and antidepressant-controlled studies found a response rate of 51% in older patients,6 similar to that for the adult population.7 There is a common perception that older patients do not respond as well or as quickly to antidepressants as their younger counterparts,8 perhaps because of structural brain changes or higher rates of physical comorbidity.9 It may be that biological age is more relevant than chronological age.10 The presence of physical illness, as well as baseline anxiety and reduced executive functioning, is also associated with poorer treatment outcomes.11 Nonetheless, even in older people, it may still be possible to identify non- responders as early as 4 weeks into treatment.12,13 A Cochrane review examined the efficacy and associated withdrawal rates of different classes of antidepressants in older people and found that SSRIs and tricyclics have similar efficacy, but TCAs are associated with higher withdrawal rates.14 A 2022 population study found non-TCA antidepressants to have broadly similar effectiveness.15 In the UK, NICE guidance for depression in adults recommends starting with an SSRI in the first instance (sertraline is commonly used first line in older people). When switching to another antidepressant, NICE recommends switching initially to a different SSRI or a better tolerated newer-generation antidepressant (this effectively indicates mirtazapine). Subsequently, an antidepressant of a different pharmacological class that may be less well tolerated is recommended, for example venlafaxine or lofepramine.16 The OTIMUM trial17 found that augmenting with aripiprazole or bupropion was better than switching to bupropion in ‘treatment- resistant geriatric depression’. Network meta-analysis suggests that quetiapine, duloxetine, agomelatine, imipramine and vortioxetine have the highest efficacy in major depressive disorder in older people, although individual data are somewhat inconsistent.18 Two studies have found that, in older people who had recovered from an episode of depression and had received antidepressants for 2 years, over 60% relapsed within 2 years if antidepressant treatment was withdrawn.19,20 Some of this relapse may have been a result of the speed and method of antidepressant discontinuation.21 Deprescribing antidepressants in older

people presents a particular conundrum. Effective treatment should usually be continued, especially if depression was severe or recurrent. Ineffective treatment (i.e. was never effective or has become ineffective) should usually be withdrawn owing to the risk of adverse effects and interaction with polypharmacy regimens.22

Prescribing in older people CHAPTER 6 There is no ideal antidepressant in older people; all are associated with problems. TCAs are broadly considered to be agents of last resort owing to the increased risk of cardiac conduction abnormalities and because of anticholinergic effects. Although SSRIs are generally better tolerated than TCAs14 they do, however, increase the risk of gastrointestinal bleeds, particularly in the very old and those with established risk factors such as a history of bleeds or who are on treatment with an NSAID, steroid or warfarin. The risk of other types of bleed such as haemorrhagic stroke may also be increased23,24 (see Chapter 3). In older people, this increase in risk of stroke may persist after cessation of antidepressants.25 Older people are also particularly prone to develop hyponatraemia26 when starting SSRIs and most other antidepressants (see Chapter 3), as well as postural hypotension and falls27 (the clinical consequences of which may be increased by SSRI-induced osteopenia28). TCAs may also increase fracture risk.29 Table 6.8 summarises the use of antidepressants in older adults. Trazodone was once widely used in elderly populations30 but sedation and postural hypotension may be dose limiting. It retains some utility in depression occurring in dementia.31 Agomelatine is effective in older patients, is well tolerated and has not been linked to hyponatraemia.32,33 Its use is limited by the need for frequent blood sampling to check LFTs. Vortioxetine and duloxetine have also been shown to be effective and reasonably well tolerated in the older person34 but the caveats related to SSRIs are relevant here. A general practice database study found that, compared with SSRIs, ‘other antidepressants’ (venlafaxine, mirtazapine, etc.) were associated with a greater risk of a number of potentially serious adverse effects in the old (stroke/transient ischaemic attack [TIA], fracture, seizures, attempted suicide/self-harm) as well as increased all- cause mortality.26 However, SSRIs showed the highest risk for falls and hyponatraemia. All classes of antidepressant were associated with an increased risk of a range of adverse outcomes compared with no use. The study was observational and so could not separate the effect of antidepressants from any increased risk inherent in the group of patients treated with these antidepressants. Polysaturated fatty acids (fish oils) may be helpful in mild to moderate depression (compared with placebo),35 as may memantine.36 Methylphenidate seems effective in older people37 and may be useful where a rapid onset of action is required. There is some evidence that esketamine and ketamine are rapidly effective in people over 65 (without worsening cognition).38,39 The effect of antidepressants on cognition in later life is still debated – some studies find antidepressants to worsen cognitive outcomes,40–42 others find no effect.43 The choice of antidepressant may affect the risk – highly anticholinergic medicines undoubtedly worsen cognition and are known to increase the likelihood of developing dementia.44 Depression in dementia is probably best treated by cognitive or physical therapies rather than antidepressants.45 Antidepressants are of doubtful benefit.45–48 The same might be said for their use in the treatment of MCI in older people.49 Ultimately, choice is determined by the individual clinical circumstances of each patient, particularly physical comorbidity and concomitant medication (both prescribed and ‘over the counter’).

Table 6.8 Antidepressants and older people. Anticholinergic side effects (urinary retention, dry mouth, blurred vision, constipation) Postural hypotension Sedation Weight gain Safety in overdose Other side effects Drug interactions Older tricyclics50 Moderate to severe with all TCAs All can

also cause central anticholinergic effects (confusion, impaired cognition) All can cause postural hypotension Dosage titration is required Variable: from moderate with imipramine to profound with amitriptyline All tricyclics can cause weight gain All are toxic in overdose (seizures, cardiac arrhythmia) Seizures, anticholinergic-induced cognitive impairment Increased risk of bleeds with serotonergic drugs Mainly pharmacodynamic: increased sedation with benzodiazepines, increased hypotension with diuretics, increased constipation with other anticholinergic drugs, etc. Lofepramine Moderate, although constipation/sweating can be severe Can be a problem but generally better tolerated than older tricyclics Minimal Few data, but lack of spontaneous reports may indicate less potential than older tricyclics Relatively safe Raised LFTs Less likely to cause hyponatraemia than other TCAs and SSRIs SSRIs50,51 Dry mouth with paroxetine – probably best avoided in older people Unlikely, but an increased risk of falls is documented with SSRIs Sometimes seen with paroxetine and fluvoxamine Unlikely with the other SSRIs Paroxetine and possibly citalopram may cause weight gain Others are weight neutral Safe with the possible exceptions of citalopram and escitalopram which have the greatest effect on QT. Still much less toxic than TCAs GI effects and headaches, hyponatraemia, increased risk of bleeds in the older person (add gastroprotection if also on an NSAID or aspirin), orofacial dyskinesia with paroxetine, cognitive impairment,41 interstitial lung disease52,53 Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of several hepatic cytochrome enzymes (see Chapter 3). Sertraline is safer and citalopram, escitalopram and vortioxetine are safest.

Mirtazapine, mianserin and trazodone are sedative with significant hangover in older people Venlafaxine, duloxetine have neutral effects Agomelatine aids sleep Venlafaxine and duloxetine can cause hypotension at lower doses, but usually increase BP at higher doses Occasional postural hypotension with trazodone Dizziness common with agomelatine Others54,55 Minimal with mirtazapine, trazodone and venlafaxine* Can be observed with reboxetine* Duloxetine* – few effects Agomelatine has no anticholinergic potential *Noradrenergic drugs may produce ‘anticholinergic’ effects via norepinephrine reuptake inhibition. GI, gastrointestinal; TCA, tricyclic antidepressant. Insomnia and hypokalaemia with reboxetine Nausea with venlafaxine and duloxetine Weight loss and nausea with duloxetine Possibly hepatotoxicity with agomelatine – monitor LFTs Cognitive impairment reported with trazodone41 but may be no worse than other antidepressants56 Venlafaxine is more toxic in overdose than SSRIs, but safer than TCAs Others are relatively safe Highest risk with mirtazapine, although older people are not particularly prone to weight gain Low incidence with agomelatine Duloxetine inhibits CYP2D6 Moclobemide and venlafaxine inhibit CYP450 enzymes. Check for potential interactions. Reboxetine has a low interaction potential. Agomelatine should be avoided in patients who take potent CYP1A2 inhibitors. Interstitial lung disease with SNRIs53

28 - References

References

1. Katona C, et al. Impact of screening old people with physical illness for depression? Lancet 2000; 356:91–92.
2. Lyketsos CG. Depression and diabetes: more on what the relationship might be. Am J Psychiatry 2010; 167:496–497.
3. Gallo JJ, et al. Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. BMJ 2013; 346:f2570.
4. Naghavi M. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. BMJ 2019; 364:l94.
5. Ryan J, et al. Late-life depression and mortality: influence of gender and antidepressant use. Br J Psychiatry 2008; 192:12–18.
6. Gutsmiedl K, et al. How well do elderly patients with major depressive disorder respond to antidepressants: a systematic review and single- group meta-analysis. BMC Psychiatry 2020; 20:102.
7. Cipriani A, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357–1366.
8. Paykel ES, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995; 25:1171–1180.
9. Iosifescu DV, et al. Brain white-matter hyperintensities and treatment outcome in major depressive disorder. Br J Psychiatry 2006; 188:180–185.
10. Brown PJ, et al. Biological age, not chronological age, is associated with late-life depression. J Gerontol A Biol Sci Med Sci 2018; 73:1370–1376.
11. Tunvirachaisakul C, et al. Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis. J Affect Disord 2018; 227:164–182.
12. Zilcha-Mano S, et al. Early symptom trajectories as predictors of treatment outcome for citalopram versus placebo. Am J Geriatr Psychiatry 2017; 25:654–661.
13. Mulsant BH, et al. What is the optimal duration of a short-term antidepressant trial when treating geriatric depression? J Clin Psychopharmacol 2006; 26:113–120.
14. Mottram P, et al. Antidepressants for depressed elderly. Cochrane Database Syst Rev 2006; 1:CD003491.
15. Hsu CW, et al. Comparative effectiveness of antidepressants on geriatric depression: real--world evidence from a population-based study. J Affect Disord 2022; 296:609–615.
16. National Institute for Health and Care Excellence. Depression in adults: treatment and management. NICE Guideline [NG222]. 2022 (last accessed December 2023);

https://www.nice.org.uk/guidance/ng222.
17. Lenze EJ, et al. Antidepressant augmentation versus switch in treatment-resistant geriatric depression. N Engl J Med 2023; 388:1067–1079.
18. Krause M, et al. Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: a systematic review, pairwise and network meta-analysis. Eur Neuropsychopharmacol 2019; 29:1003–1022.
19. Flint AJ, et al. Recurrence of first-episode geriatric depression after discontinuation of maintenance antidepressants. Am J Psychiatry 1999; 156:943–945.
20. Reynolds CF, III, et al. Maintenance treatment of major depression in old age. N Engl J Med 2006; 354:1130–1138.
21. Horowitz MA, et al. Distinguishing relapse from antidepressant withdrawal: clinical practice and antidepressant discontinuation studies. BJPsych Advances 2022; 28:297–311.
22. Romdhani A, et al. Discontinuation of antidepressants in older adults: a literature review. Ther Clin Risk Manag 2023; 19:291–299.
23. Smoller JW, et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med 2009; 169:2128–2139.
24. Laporte S, et al. Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: a meta-analysis of observational studies. Pharmacol Res 2017; 118:19–32.
25. Ön BI, et al. Antidepressant use and stroke or mortality risk in the elderly. Eur J Neurol 2022; 29:469–477.
26. Coupland C, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; 343:d4551.
27. Haddad YK, et al. A comparative analysis of selective serotonin reuptake inhibitors and fall risk in older adults. J Am Geriatr Soc 2022; 70:1450–1460.
28. Williams LJ, et al. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. Int Clin Psychopharmacol 2008; 23:84–87.
29. Power C, et al. Bones of contention: a comprehensive literature review of non-SSRI antidepressant use and bone health. J Geriatr Psychiatry Neurol 2019; 33:340–352.
30. Fagiolini A, et al. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs 2012; 26:1033–1049.
31. Fagiolini A, et al. Trazodone in the management of major depression among elderly patients with dementia: a narrative review and clinical insights. Neuropsychiatr Dis Treat 2023; 19:2817–2831.
32. Heun R, et al. The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo-controlled study. J Clin Psychiatry 2013; 74:587–594.
33. Laux G. The antidepressant efficacy of agomelatine in daily practice: Results of the non--interventional study VIVALDI. Eur Psychiatry 2011; 26 Suppl 1:647.
34. Katona C, et al. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol 2012; 27:215–223.
35. Bae JH, et al. Systematic review and meta-analysis of omega-3-fatty acids in elderly patients with depression. Nutr Res 2018; 50:1–9.
36. Hsu TW, et al. The efficacy and tolerability of memantine for depressive symptoms in major mental diseases: a systematic review and updated meta-analysis of double-blind

randomized controlled trials. J Affect Disord 2022; 306:182–189.

Prescribing in older people CHAPTER 6 37. Smith KR, et al. Methylphenidate use in geriatric depression: a systematic review. Int J Geriatr Psychiatry 2021; 36:1304–1312. 38. Ochs-Ross R, et al. Comparison of long-term efficacy and safety of esketamine nasal spray plus oral antidepressant in younger versus older patients with treatment-resistant depression: post-hoc analysis of SUSTAIN-2, a long-term open-label phase 3 safety and efficacy study. Am J Geriatr Psychiatry 2022; 30:541–556. 39. Subramanian S, et al. Ketamine for depression in older adults. Am J Geriatr Psychiatry 2021; 29:914–916. 40. Moraros J, et al. The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: a systematic review and meta-analysis. Depress Anxiety 2017; 34:217–226. 41. Leng Y, et al. Antidepressant use and cognitive outcomes in very old women. J Gerontol A Biol Sci Med Sci 2018; 73:1390–1395. 42. Chan JYC, et al. Depression and antidepressants as potential risk factors in dementia: a systematic review and meta-analysis of 18 longitudinal studies. J Am Med Dir Assoc 2019; 20:279–286.e271. 43. Carriere I, et al. Antidepressant use and cognitive decline in community-dwelling elderly people – the Three-City Cohort. BMC Med 2017; 15:81. 44. Wang YC, et al. Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. Behav Neurol 2018; 2018:5315098. 45. Watt JA, et al. Comparative efficacy of interventions for reducing symptoms of depression in people with dementia: systematic review and network meta-analysis. BMJ 2021; 372:n532. 46. Jeong HW, et al. Vortioxetine treatment for depression in Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Clin Psychopharmacol Neurosci 2022; 20:311–319. 47. Leong C. Antidepressants for depression in patients with dementia: a review of the literature. Consult Pharm 2014; 29:254–263. 48. Costello H, et al. Antidepressant medications in dementia: evidence and potential mechanisms of treatment-resistance. Psychol Med 2023; 53:654–667. 49. Jin B, et al. Comparative efficacy and acceptability of treatments for depressive symptoms in cognitive impairment: a systematic review and Bayesian network meta--analysis. Front Aging Neurosci 2022; 14:1037414. 50. Draper B, et al. Tolerability of selective serotonin reuptake inhibitors: issues relevant to the elderly. Drugs Aging 2008; 25:501–519. 51. Bose A, et al. Escitalopram in the acute treatment of depressed patients aged 60 years or older. Am J Geriatr Psychiatry 2008; 16:14–20. 52. Deidda A, et al. Interstitial lung disease induced by fluoxetine: systematic review of literature and analysis of Vigiaccess, Eudravigilance and a national pharmacovigilance database. Pharmacol Res 2017; 120:294–301. 53. Rosenberg T, et al. The relationship of SSRI and SNRI usage with interstitial lung disease and bronchiectasis in an elderly population: a case- control study. Clin Interv Aging 2017; 12:1977–1984. 54. Raskin J, et al. Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. J Clin Psychopharmacol 2008; 28:32–38. 55. Johnson EM, et al. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. Am J Geriatr Psychiatry 2006; 14:796–802. 56. Gonçalo AMG, et al. The effects of trazodone on human cognition: a systematic review. Eur J Clin Pharmacol 2021; 77:1623–1637.

29 - Covert administration of medicines within foo

Covert administration of medicines within food and drink

30 - Assessment of mental capacity[4,6,7]

Assessment of mental capacity[4,6,7]

31 - Guidance on covert administration

Guidance on covert administration

694 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Covert administration of medicines within food and drink This section deals with covert medication administration within UK law only. Other countries may have different laws pertaining to this area, or indeed no laws or official guidance.1 In mental health settings it is common for patients to refuse medication. People with psychiatric disorders may lack capacity to make an informed choice about whether medication will be beneficial to them or not. In these cases, the clinical team may consider whether it would be in the patient's best interests to administer medication covertly. This practice is known as covert administration of medicines. Guidance from the Royal Pharmaceutical Society and Royal College of Nursing2 and the Royal College of Psychiatrists3 has been published in order to protect patients from the unlawful and inappropriate administration of medication in this way. In the UK, the legal framework for such interventions is either the Mental Capacity Act (MCA)4 or, more rarely, the Mental Health Act (MHA).5 Assessment of mental capacity4,6,7 The assessment of capacity regarding medication is primarily a matter for the prescriber, usually a doctor treating the patient,4,6 or less commonly a pharmacist or nurse. Nurses and allied health professionals who are not prescribers will also have to be mindful of their own codes of professional practice and should be satisfied that the doctor's assessment is reasonable. The assessment must be made in relation to the particular treatment proposed as part of a covert medication care plan. Capacity can vary over time and the assessment should be made at the time of the proposed treatment. The assessment should be documented in the patient's notes and recorded in the care plan. Assessment of capacity should be conducted in line with the MCA code of practice. Guidance on covert administration If a patient has the capacity to give a valid refusal to medication and is not detainable under the MHA, their refusal should be respected. If a patient has the capacity to give a valid refusal and is either being treated under the MHA or is legally detainable under the Act, the provisions of the MHA with regard to treatment will apply (which are outside the scope of this chapter). The administration of medicines to patients who lack the capacity to consent and who are unable to appreciate that they are taking medication (e.g. unconscious patients) should not need to be carried out covertly. However, some patients who lack the capacity to consent would be aware of receiving medication if they were not deceived into thinking otherwise,7 for example a patient with moderate dementia who has no insight and does not believe they need to take

medication but will take liquid medication if this is mixed with their tea without being aware of this. It is this group to whom this guidance applies. Treatment may be given to people who lack capacity if the treatment is in the patient's best interests (Section 5, MCA4) and is proportionate to the harm to be avoided (Chapter 6.41, MCA Code of Practice7). So, there should be a clear expectation that the

Prescribing in older people CHAPTER 6 patient will benefit from covert administration, and that this will avoid significant harm (either mental or physical) to the patient or others. The treatment must be necessary to save the patient's life, to prevent deterioration in health or to ensure an improvement in physical or mental health.4,7 Covert administration must be the least restrictive option after trying all other options. An assessment should be carried out to understand why the person is refusing to take their medicines. Alternative methods of administration (e.g. liquid formulation) and trial of different approaches in nursing care (e.g. explaining to the patient about the medicines at the time they are administered or changing the time of administration to a time of day when the patient is more alert or less distressed) should be considered.8 The decision to administer medication covertly should not be made by a single individual but through discussion with the multidisciplinary team caring for the patient and the patient's relatives or informal carers. A Best Interests meeting should be held, except in urgent situations if the decision cannot wait, in which case a less formal decision can take place with a view to arranging a Best Interests meeting as soon as practicably possible. If it were determined at this meeting that the provision of covert medication would amount to a deprivation of liberty (where previously there was none), then an application for Deprivation of Liberty Safeguards (DoLS) authorisation should be made. Decisions regarding covert administration of medication should be carefully documented in the patient's medical records with a clear management plan, including details of how the covert medication plan will be reviewed. This documentation must be easily accessible on viewing the person's records and the decision should be subject to regular review. It is not necessary to have a new Best Interests meeting each time there is a change in medication. However, when covert medication is first considered, healthcare professionals should consider what types of changes in medication may be anticipated in future and should agree on the thresholds of what changes may require a new Best Interests meeting. This management plan should be recorded in the patient's notes. If significant changes that could cause adverse effects are envisaged, then a new meeting should be held before changes are made. In deciding how often capacity assessments should be repeated, clinicians should follow the guidance within the practical guide to the MCA.6 If there is any evidence that the patient has regained capacity with regard to administration of their medication, an immediate capacity assessment must be done. Decisions in the patient's best interest can no longer be made if they are under a DoLS authorisation for reasons including the administration of medication covertly; this part of the DoLS authorisation will no longer be valid and covert administration of medication must cease immediately. Case law9,10 has dealt with the relationship between the use of covert medication and the need for a DoLS authorisation. A person is deprived of their liberty when they are under continuous supervision and control and are not free to leave. The administration of covert medication will only in itself lead to a deprivation of liberty where that covert medication affects the person's behaviour, mental health or it acts as a sedative to such an extent that it will deprive the person of their liberty. The use of covert medication within a care plan must be clearly identified within the DoLS assessment and authorisation.

32 - Summary of process

Summary of process

696 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 When considering covert use of psychiatric medication the following must be considered:11

1. If the patient meets the criteria for the MHA, this must be used in preference to the MCA.
2. The MCA might be used to provide authority for covert medication for physical health whether or not the patient is detained under the MHA. The MCA can be used as authority for covert use of psychiatric medication in patients not under the MHA if the medication is necessary to prevent deterioration or ensure an improvement in the patient's mental health and it is in the person's best interest to receive the drug. The usual procedures for covert medication, including documentation of capacity assessment, Best Interests meeting and pharmacist's review, should be followed.
3. Caution is needed in the use of medication that may sedate or reduce a patient's physical mobility, as use of such drugs may constitute a deprivation of liberty and require the patient to be under the DoLS framework. Documentation of whether the proposed use of a covert psychiatric drug constitutes a deprivation of liberty is important. Note that if a patient is found to lack capacity to consent to the admission and does not meet the criteria for detention under the MHA, DoLS should be used, so most in-patients who lack capacity to consent to medication will already be under the MHA or DoLS, although there may be some who can consent to admission but not to medication. However, even if the patient is already under the MHA or MCA as part of their admission, there still needs to be the same approach and considerations as documented here with regard to medication being given covertly. Summary of process The process for covert administration of medicines should include: ■ ■The assurance that all efforts have been made to give medication openly in its normal form before considering covert administration. ■ ■Assessment of capacity of the patient to make a decision regarding their treatment with medication. If the patient has capacity their wishes should be respected and covert medication not administered. ■ ■A record of the examination of the patient's capacity must be made in the clinical notes, and evidence for incapacity documented. ■ ■If the patient lacks capacity there should be a Best Interests meeting which should be attended by relevant health professionals and a person who can communicate the views and interests of the patient (family member, friend or independent mental capacity advocate). These meetings can be held virtually. If the patient has an attorney appointed under the MCA for health and welfare decisions then this person should be present at the meeting. ■ ■Those attending the meeting should ascertain whether the patient has made an 'advance decision' refusing a particular medication or treatment which can be used to guide decision-making.

Prescribing in older people CHAPTER 6 ■ ■The Best Interests meeting should consider whether a formal legal procedure such as the MHA or DoLS is appropriate. Discussion of the indications and use of this legislation in the context of covert medication is outside the scope of this guidance but specialist psychiatric and/or legal opinion should be sought in individual circumstances if necessary. However, the other considerations given here – including the involvement of pharmacy, the recording of medication being given covertly on the drug chart, the dispensing nurse ensuring the covert medication is taken by the patient and regular reviews – apply for all patients, whichever legal framework is being used to give medication covertly. ■ ■Medication should not be administered covertly until a Best Interests meeting has been held. If the situation is urgent, it is acceptable for a less formal discussion to occur between carer/nursing staff, prescriber and family/advocate in order to make an urgent decision, but a formal meeting should be arranged as soon as possible. ■ ■After the meeting, there should be clear documentation of the outcome of the meeting. If the decision is to use covert administration of medication, a check should be made with the pharmacy to determine whether the properties of the medications are likely to be affected by crushing and/or being mixed with food or drink.12 The medication chart and electronic prescribing and medicines administration record should be amended to describe how the medication is to be administered. ■ ■When the medication is administered in foodstuffs, it is the responsibility of the dispensing nurse to ensure that the medication is taken. This can be facilitated by direct observation or by nominating another member of the clinical team to observe the patient taking the medication. ■ ■A plan should be made to review on a regular basis the need for continued covert administration of medicines. Additional information ■ ■For patients in care homes, the NICE guideline ‘Managing medicines in care homes’ should be referred to.13,14 The basic principles of this NICE guidance are the same as the policy discussed in this section. Mental health practitioners have a duty to inform the care home manager if they suspect the correct procedures are not being followed as regards covert medication, and to discuss with their team leader possible safeguarding referral if the home manager does not act on their advice. The role of mental health teams supporting care homes is to support the care homes and prescriber (usually GP) in carrying out this guidance. For patients with complex mental health needs, it may be appropriate that they attend or contribute to the Best Interests meeting. However, it should be the prescriber (usually the GP), care home staff and care home pharmacist who manage the process. ■ ■There are no specific restrictions to state that relatives or other informal carers cannot give medication covertly and in certain cases it may be acceptable as long as they have been advised to do so by a health professional (e.g. GP) and all standards of the policy have been met. Figure 6.2 provides an algorithm for determining whether or not to administer medicines covertly.

698 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Consider second opinion or ethics forum or legal advice Is there agreement at ‘Best Interest’ discussion? Reason established and resolved Give medication as normal DO NOT GIVE: Seek alternative preparation Unable to resolve USE ALTERNATIVE No No No No No No Yes Yes Yes Yes Yes Yes Establish why the patient does not want to take medication Is medication essential? Is there a viable alternative? Does the patient have mental capacity? Yes Is there a Lasting Power of Attorney (LPA)* or Advance Decision to Refuse Treatment (ADRT)? DO NOT GIVE DO NOT GIVE DO NOT GIVE Does attorney or ADRT prevent or conflict with treatment plan medication? Have pharmacy confirmed how to give covertly? Give medication covertly (ensure covert medication care plan is in place) Document and review regularly *LPA covering health and welfare decisions. NB Any deprivation of liberty would need to be authorised by a legal framework, e.g. Mental Health Act, Deprivation of Liberty

Safeguards or Court of Protection, as appropriate. No Figure 6.2 Flow chart for the use of covert medication.

33 - References

References

Prescribing in older people CHAPTER 6 References

1. Wikipedia. Covert medication. 2023; https://en.wikipedia.org/wiki/covert_medication.
2. Royal Pharmaceutical Society and Royal College of Nursing. Professional guidance on the administration of medicines in healthcare settings. 2019; https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/SSHM%20and%20 Admin/Admin%20of%20Meds%20prof%20guidance.pdf?ver=2019-01-23-145026-567.
3. Royal College of Psychiatrists. College statement on covert administration of medicines. Psychiatric Bull 2004; 28:385–386.
4. Office of Public Sector Information. Mental Capacity Act 2005 – Chapter 9. 2005; http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ ukpga_20050009_en.pdf.
5. The National Archives. Mental Health Act 2007. 2007; http://www.legislation.gov.uk/ukpga/2007/12/contents.
6. British Medical Association and the Law Society. Assessment of Mental Capacity. A Practical Guide for Doctors and Lawyers, 4th edn. London: Law Society Publishing; 2015.
7. Gov.uk. Office of the Public Guardian. Mental Capacity Act Code of Practice. 2013 (last updated October 2020); https://www.gov.uk/ government/publications/mental-capacity--act-code-of-practice.
8. Care Quality Commission. Covert administration of medicines. 2020; https://www.cqc.org.uk/guidance-providers/adult-social-care/ covert-administration--medicines.
9. Medication Training Company. Covert administration of medicines. Recent Court of Protection ruling on covert medication – 6th July 2016. 2016; https://medicationtraining.co.uk/covert-administration-medicines/.
10. Doughty Street Chambers. Covert medication of persons lacking capacity. What guidance is there? 2023; https://insights.doughtystreet.co.uk/ post/102i743/covert-medication-of--persons-lacking-capacity-what-guidance-is-there.
11. Care Quality Commission. Brief guide: covert medication in mental health services. 2018 (reviewed 2019); https://www.cqc.org.uk/sites/ default/files/20180406_9001398_briefguide-covert_medication_mental_health_v2.pdf.
12. Specialist Pharmacy Service. Covert administration of medicines in adults: pharmaceutical issues. 2022 (last updated June 2023); https:// www.sps.nhs.uk/articles/covert--administration-of-medicines-in-adults-pharmaceutical-issues/.
13. National Institute for Health and Care Excellence. Managing medicines in care homes. Social Care Guideline [SC1]. 2014 (last updated 2020);

https://www.nice.org.uk/guidance/sc1.
14. PrescQIPP. Bulletin 101. Best practice guidance in covert administration of medication. 2015; https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f1174%2fb101-covert-administration--21.pdf.

34 - A guide to medication doses of commonly used

A guide to medication doses of commonly used psychotropics in older adults, [1] / National Institute for Health and Care Excellence (NICE).

700 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 A guide to medication doses of commonly used psychotropics in older adults, [1] / National Institute for Health and Care Excellence (NICE). Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Antidepressants Agomelatine Depression Monitor LFTs Data suggest agomelatine is not effective in patients

> 75 years 25mg nocte 25–50mg daily 50mg nocte Bupropion2 Depression Immediate release tablets: 100mg bd2 Sustained release tablets (SR): 150mg once daily2 Extended-release tablets (XL): 150mg once daily2 May increase to 100mg tds after 3 days2 May increase dose to 150mg SR twice daily after 3 days2 May increase dose to 300mg XL once daily after at least 4 days2 300mg/day* Consider reduced dosage and/or dosage frequency in patients with a CrCl <90mL/min2 Bupropion and dextromethorphan3 Depression Each

> tablet contains 45mg dextromethorphan hydrobromide (equivalent to 32.98mg dextromethorphan base) in an immediate-release formulation and 105mg bupropion hydrochloride (equivalent to 91.14mg bupropion base) in an XL formulation.3 1 tablet mane3 1 tablet bd (at least 8 hours apart; dose can be increased to bd after 3 days)3 Reduced dosage of 1 tablet mane is recommended for patients with moderate kidney impairment (eGFR 30–59mL/ min/1.73m2), those known to be poor CYP2D6 metabolisers and when co-- administered with strong CYP2D6 inhibitors. Concomitant use with strong CYP2B6 inducers should be avoided. 1 tablet bd3 Citalopram Depression/anxiety disorder 10mg mane 10–20mg mane 20mg mane Clomipramine Depression/phobic and obsessional states 10mg nocte (dose increases should be cautious) 30–75mg daily4 should be reached after about 10 days. 75mg daily4

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Desvenlafaxine5 Major depression No formal recommendations are available for dosing in older adults.5 However, possible reduced renal clearance of desvenlafaxine should be considered when determining an appropriate dose. 50mg daily Dosage in renal impairment: CrCl 50–80mL/ min: no dosage adjustment needed CrCl 30–50mL/ min: 50mg daily is recommended daily and max. dose CrCl <30mL/min or ESRD: 50mg every other day is recommended daily and max. dose 50mg daily Usual dose 50mg/ day Max. dose 400mg daily5 however no additional benefit was demonstrated at doses >50mg/ day and adverse reactions and discontinuations were more frequent at higher doses. Duloxetine Depression/anxiety disorder 30mg daily* 60mg daily 120mg daily6 (caution as limited data in elderly for this dose) Escitalopram Depression/anxiety disorder 5mg mane 5–10mg mane 10mg mane Fluoxetine Depression/anxiety disorder Caution as long half-life and inhibitor of several CYP enzymes 20mg mane 20mg mane 40mg mane usually (but 60mg can be used) Lofepramine Depression 35mg nocte* 70mg nocte* 140mg nocte or in divided doses* (occasionally 210mg nocte required) Mirtazapine Depression 7.5mg nocte or usually 15mg nocte* 15–30mg nocte 45mg nocte Sertraline Depression/anxiety disorder 25–50mg mane (25mg can be increased to 50mg mane after 1 week) 50–100mg mane* 100mg (occasionally up to 150mg mane)* Trazodone Depression 100mg daily in divided doses or as a single night time dose7 100–200mg daily* 300mg daily7 (Continued)

 Agitation in dementia Avoid single doses

> 100mg 25mg bd* 25–100mg daily* 200mg daily* (in divided doses) Venlafaxine Depression/anxiety disorder Monitor BP on initiation 37.5mg mane (increased to 75mg XL mane after 1 week)* 75–150mg (XL) mane* 150mg daily (occasionally 225mg daily is necessary)* Vortioxetine8 Major depressive disorder Vortioxetine is extensively metabolised in the liver, primarily by

> CYP2D6 and to a minor extent by CYP3A4/5 and CYP2C9. Co-administration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. 5mg daily 5–10mg daily 10mg daily Caution advised in ≥65 years with doses >10mg daily for which data are limited8 Antipsychotics† Amisulpride Chronic schizophrenia 50mg daily* 100–200mg daily* 400mg daily9 (caution >200mg daily)* Late life psychosis 25–50mg daily* 50–100mg daily* (increase in 25mg steps) 200mg daily10 (caution >100mg daily)* Agitation/psychosis in dementia Caution QTc prolongation 25mg nocte11 25–50mg daily11 50mg daily11 Aripiprazole Schizophrenia, mania (oral) 5mg mane* 5-15mg daily* 20mg mane* Control of agitation (IM injection) 5.25mg* 5.25–9.75mg* 15mg daily* (combined oral + IM) Brexpiprazole12 Schizophrenia12 Metabolism is primarily mediated by CYP3A4 and CYP2D6. Co-administration of certain drugs may need to be avoided or dosage adjustments may be necessary. 0.5mg once daily On day 5 may increase to 1mg once daily On day 8 may further increase to 2mg daily 4mg daily Max. 3mg/day if CrCl <60mL/min, including ESRD12

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Further titration may be made weekly in 1mg increments based on response and tolerability. Recommended range: 2–4mg once daily12 Depression (adjunctive treatment) 0.5 once daily12 Target dose 2mg once daily. Titrate dosage at weekly intervals based on response and tolerability.12 3mg/day12 Max. 2mg/day if CrCl <60mL/min, including ESRD12 Agitation in Alzheimer’s disease 0.5mg once daily12 On day 8 increase dose to 1mg once daily for an additional 7 days. On day 15 increase to 2mg po once daily, the recommended target dose. May increase to 3mg once daily after at least 14 more days based on clinical response and tolerability.12 3mg/day12 Max. 2mg/day if CrCl <60mL/min, including ESRD12 Cariprazine13 Schizophrenia Cariprazine and its major active metabolites are highly protein bound and extensively metabolised by CYP3A4 and, to a lesser extent, by CYP2D6. Co-administration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. 1.5mg once daily13 May increase to 3mg once daily on day 2 Make further dose adjustments in 1.5mg increments based on response and tolerability.13 Effective range: 1.5–6mg po once daily14 6mg/day14 (Continued)

704 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Mania or mixed episodes of bipolar disorder 1.5mg once daily14 May increase to 3mg once daily on day 2 Adjust dose by 1.5–3mg/day based on clinical response and tolerability Usual dose: 3–6mg/day14 6mg/day for acute mania14 Bipolar depression and adjunctive treatment of major depressive disorder 1.5mg once daily14 May increase dose to 3mg/day after 2 weeks based on clinical response and tolerability14 3mg/day14 BPSD Dose not yet established14 Clozapine Schizophrenia 6.25–12.5mg daily,15,16 increased by no more than 6.25–12.5mg once or twice a week15 50–100mg daily15,16 100mg daily15,16 Parkinson’s related psychosis 6.25mg daily17 25–37.5mg daily17 50mg daily17 IM injection The oral bioavailability of clozapine is about half that of the IM injection (e.g. 50mg daily of the IM injection is roughly equivalent to 100mg daily of the tablets/oral

solution). After each injection has been given the patient must be observed every 15 minutes for the first 2 hours to check for excess sedation. NB If IM lorazepam is required, leave at least 1 HOUR between administration of IM clozapine and IM lorazepam. Iloperidone No formal recommendations are available for dosing in older adults18 Lumateperone19 Schizophrenia 42mg daily (equivalent to 60mg lumateperone tosylate) Dose titration not required 42mg daily 42mg daily Lurasidone Schizophrenia 37mg once daily (or 18.5mg daily when given with concomitant moderate CYP3A4 inhibitors, max. dose 74mg once daily) 18.5–111mg daily20 Limited data on higher doses used in older adults. No data are available in elderly people treated with 148mg. Caution should be exercised when treating patients ≥65 years of age with higher doses.20

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Dosing for elderly with normal renal function (CrCl ≥80mL/min) is the same as for adults with normal renal function. In diminished renal function, dose adjustments may be required according to their renal function status.20 Olanzapine Schizophrenia 2.5mg nocte* 5–10mg daily* 15mg nocte16 Agitation/psychosis in dementia 2.5mg nocte* 2.5–10mg daily* 10mg nocte* (optimal dose is 5mg daily)16 Olanzapine and samidorphan No formal recommendations are available for dosing in older adults.21 Pimavanserin22,23 Treatment of hallucinations and delusions associated with Parkinson's disease psychosis 34mg daily (or 10mg daily if co-administered with strong CYP3A4 inhibitors) Dose titration not required 34mg daily (or 10mg daily if co- administered with strong CYP3A4 inhibitors) 34mg daily (or 10mg daily if co-administered with strong CYP3A4 inhibitors) Monitor patients for reduced efficacy if used concomitantly with strong CYP3A4 inducers. Quetiapine Schizophrenia 12.5–25mg daily16 75–125mg daily15 200–300mg daily16 Agitation/psychosis in dementia 12.5–25mg daily* 50–100mg daily* 100–300mg daily16 Risperidone Psychosis 0.5mg bd (0.25–0.5mg daily in some cases)16 1–2.5mg daily15 4mg daily Late-onset psychosis 0.5mg daily* 1mg daily* 2mg daily* (optimal dose is 1mg daily) Agitation/psychosis in dementia 0.25mg daily* or bd 0.5mg bd 2mg daily (optimal dose is 1mg daily)16 (Continued)

706 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Haloperidol Psychosis/mania associated with bipolar disorder/delirium 0.25–0.5mg daily15 1–3.5mg daily15 Caution >3.5mg – assess tolerability and ECG Max. 5mg/day (oral) Max. 5mg/day (IM) Doses >5mg/day should only be considered in patients who have tolerated higher doses and after reassessment of the patient's individual benefit–risk profile Agitation Avoid in older adults (except in delirium) owing to risk of QTc prolongation. 0.25–0.5mg daily* 0.5–1.5mg daily or bd Long-acting conventional antipsychotic drugs† Flupentixol decanoate Test dose: 5–10mg After at least 7 days of test dose: 10–20mg every 2–4 weeks* Dose increased gradually according to response and tolerability in steps of 5–10mg every 2 weeks* 40mg every 2 weeks* (extend frequency to every 3-–4 weeks if EPSE develop) Occasionally up to 50 or 60mg every 2 weeks* may be used if tolerated Fluphenazine decanoate Caution – high risk of EPSE Test dose: 6.25mg After 4–7 days of test dose: 12.5–25mg every 2-4 weeks Dose increased gradually according to response and tolerability in steps of 12.5mg every 2–4 weeks* 50mg every 4 weeks* Haloperidol decanoate Risk of EPSE and QTc prolongation No test dose 12.5–25mg every 4 weeks 12.5–25mg every 4 weeks 50mg every 4 weeks* Pipotiazine palmitate Test dose: 5–10mg 25–100mg every 4 weeks 100mg every 4 weeks* Zuclopenthixol decanoate Test dose: 25–50mg After at least 7 days of test dose: 50–200mg every 2–4 weeks* 200mg every 2 weeks*

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Long-acting atypical antipsychotic drugs† Aripiprazole (long-acting injection24) One injection start No detectable effect of age on pharmacokinetics24 One injection of 400mg and continue treatment with oral dose 10–20mg/day for 14 days One injection of 300mg in frail individuals or poor metabolisers of CYP2D6 (and continue with prescribed oral dose for 14 days) One injection of 200mg used for patients known to be CYP2D6 poor metabolisers or concomitantly use a strong CYP3A4 inhibitor (and continue with prescribed oral dose for 14 days) 400mg monthly (reduce to 300mg/ month if adverse effects) 300mg monthly in frail individuals or poor metabolisers of CYP2D6 400mg monthly (reduce to 300mg/ month if adverse effects) 300mg monthly in frail individuals or poor metabolisers of CYP2D6 Two injection start (two injection start not to be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor) Two separate injections of 400mg at separate injection sites along with one 10–20mg dose of oral aripiprazole Two injections of 300mg in frail individuals or poor metabolisers of CYP2D6 (along with one single dose of the previous prescribed dose of oral aripiprazole) 400mg monthly (reduce to 300mg/ month if adverse effects) 300mg monthly in frail individuals or poor metabolisers of CYP2D6 400mg monthly (reduce to 300mg/ month if adverse effects) 300mg monthly in frail individuals or poor metabolisers of CYP2D6 (Continued)

708 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Olanzapine pamoate25 Has not been systematically studied in elderly patients (>65 years). Not recommended for treatment in the elderly population unless a well-tolerated and effective dose regimen using oral olanzapine has been established. A lower starting dose (150mg/4 weeks) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant. Not recommended to be started in patients >75 years. Paliperidone palmitate Dose based on renal function Because elderly patients may have diminished renal function, they are dosed as in mild renal impairment even if tests show normal renal function.* Loading doses: day 1: 100mg day 8: 75mg (lower loading doses may be appropriate in some)* 25–100mg monthly* 100mg monthly* Paliperidone palmitate 3-monthly injection Dose based on renal function Because elderly patients may have diminished renal function, they are dosed as in mild renal impairment even if tests show normal renal function.* If the last dose of 1-monthly paliperidone palmitate injectable is: 50mg 75mg 100mg Initiate the 3-monthly injection at the following doses: 175mg 263mg 350mg (There is no equivalent dose for the 25mg dose of 1-monthly paliperidone palmitate injection).26 350mg 3-monthly* Paliperidone palmitate 6-monthly injection27 Dose based on renal function Because elderly patients may have diminished renal function, they are dosed as in mild renal impairment even if tests show normal renal function.* Patients adequately treated with 1-monthly paliperidone palmitate injection 100mg (preferably for 4 months or more) or 3-monthly paliperidone palmitate injection at 350mg (for at least one injection cycle) may be transitioned to 6-monthly paliperidone palmitate injection 700mg 700mg every 6 months* There are no equivalent doses of 6-monthly paliperidone palmitate for the 25, 50 or 75mg doses of 1-monthly injection, nor for the 175 or 263 mg 3-monthly injection. 700mg every 6 months*

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Risperidone long-acting injection Monitor renal function 25mg every 2 weeks 25mg every 2 weeks 25mg every 2 weeks Consider 37.5mg every

2 weeks in patients treated with oral risperidone doses

> 4mg/day28 Mood stabilisers Carbamazepine Bipolar disorder Caution – drug interactions Check LFTs, FBC and U Es; consider checking plasma levels. 50mg bd or 100mg bd* 200–400mg/day* 600–800mg/day* Lamotrigine Bipolar disorder (titration as in young adults) Check for interactions and make appropriate dose alterations (see BNF). 25mg daily (monotherapy) Increase by 25mg steps every 14 days 200mg/day* 25mg on alternate days (if with valproate) Increase by 25mg steps every 14 days 100mg/day* 50mg daily (if with carbamazepine) Increase by 50mg steps every 14 days 100mg bd* Lithium carbonate modified release Bipolar disorder Mania/depression Caution – drug interactions Check renal and thyroid function and regularly monitor plasma levels. 100–200mg nocte* 200–600mg daily* 600–1200mg daily (aim for plasma levels 0.4–0.7mmol/L in elderly)29 Sodium valproate Bipolar disorder Check LFTs and consider checking plasma levels. Sodium valproate: 100–200mg bd* Semi-sodium valproate: 250mg daily or bd* Sodium valproate: 200–400mg bd* Semi-sodium valproate: 500mg to 1g daily* Sodium valproate: 400mg bd* Semi-sodium valproate: 1g daily* Agitation in dementia (not licensed and not recommended) Check response, tolerability and plasma levels for guide. Sodium valproate: 50mg bd (liquid) or 100mg bd* Sodium valproate: 100–200mg bd* Sodium valproate: 200mg bd* (Continued)

Anxiolytics/hypnotics Clonazepam Agitation 0.5mg daily 1–2mg/day* 4mg/day* Daridorexant30 Insomnia Taken within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening 25mg nocte 25–50mg nocte 50mg nocte Diazepam Agitation 1mg tds 1mg tds* 7.5–15mg/day in divided doses (for anxiety) Lemborexant31 Insomnia 5mg nocte (take no more than once per night, immediately before bed) 5–10mg nocte 10mg nocte Elderly are at a higher risk of falls. Caution when using doses >5mg in patients ≥65 years old The maximum recommended dose is 5mg nocte when co-administered with weak CYP3A inhibitors or in moderate hepatic impairment (avoid in severe hepatic impairment). Lorazepam PRN only – avoid regular use due to short half-life and risk of dependence 0.5mg daily 0.5–2mg daily* 2mg/day Melatonin Insomnia – short-term use (up to 13 weeks) 2mg (modified release) once daily (1–2 hours before bedtime) 2mg once daily Occasionally 10mg/day (modified release) has been used successfully in dementia Pregabalin Generalised anxiety disorder Dose adjustment based on renal function (see product information)32 Usually 25mg bd (increase by 25mg bd weekly) Up to 75mg bd (if healthy and normal renal function) Usually 150mg daily* Up to 150mg bd (if healthy and normal renal function) 150–300mg/day*

35 - References

References

Prescribing in older people CHAPTER 6 Drug Specific indication/ additional notes Starting dose Usual maintenance dose Maximum dose in elderly Zolpidem Insomnia (short-term use – up to 4 weeks) 5mg nocte 5mg nocte 5mg nocte Zopiclone Insomnia (short-term use – up to 4 weeks) 3.75mg nocte 3.75–7.5mg nocte 7.5mg nocte Where no references were given the British National Formulary (BNF) October 20231 was used. *There is no specific information available in the literature for these drug doses in elderly patients. The doses stated are a guide only. Where there are no data, the maximum doses are conservative and may be exceeded if the drug is well tolerated and following clinician's assessment. †NB All antipsychotic drugs contain warnings for increased mortality in elderly patients with dementia. bd, twice a day; BPSD, behavioural and psychological symptoms of dementia; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; EPSE, extrapyramidal side effects; ESRD, end-stage renal disease; mane, in the morning; nocte, at night; po, by mouth; prn, as required; tds, three times a day. References

1. Joint Formulary Committee. British National Formulary (online). London: BMJ and Pharmaceutical Press; http://www.medicinescomplete.com.
2. Prescribers' Digital Reference (PDR) by Connective Rx®. Bupropion – drug summary. 2023 (last assessed October 2023); https://www.pdr.net/ drug-summary/?drugLabelId=237.
3. Keam SJ. Dextromethorphan/bupropion: first approval. CNS Drugs 2022; 36:1229–1238.
4. Mylan. Summary of product characteristics. Clomipramine 25mg capsules, hard. 2021 (last checked December 2023); https://www.medicines. org.uk/emc/medicine/33260.
5. Prescribers' Digital Reference (PDR) by Connective Rx®. Desvenlafaxine – drug summary. 2023 (last accessed October 2023); https://www. pdr.net/drug--summary/?drugLabelId=3333.
6. Eli Lilly and Company Ltd. Summary of product characteristics. Cymbalta 30mg, 60mg hard gastro-resistant capsules. 2023; https://www. medicines.org.uk/emc/medicine/15694.
7. Zentiva. Summary of product characteristics. Molipaxin 100mg/trazodone 100mg capsules. 2021 (last checked December 2023); https://www.medicines.org.uk/emc/medicine/26734.
8. Lundbeck Ltd. Summary of product characteristics. Brintellix 10mg film-coated tablets (vortioxetine). 2023; https://www.medicines.org.uk/ emc/product/10441/smpc;%202022.
9. Muller MJ, et al. Amisulpride doses and plasma levels in different age groups of patients with schizophrenia or schizoaffective disorder. J Psychopharmacol 2009; 23:278–286.
10. Psarros C, et al. Amisulpride for the treatment of very-late-onset schizophrenia-like psychosis. Int J Geriatr Psychiatry 2009; 24:518–522.
11. Clark-Papasavas C, et al. Towards a therapeutic window of D2/3 occupancy for treatment of psychosis in Alzheimer's disease, with [18F] fallypride positron emission tomography.

Int J Geriatr Psychiatry 2014; 29:1001–1009.
12. Prescribers' Digital Reference (PDR) by Connective Rx®. Brexpiprazole – drug summary. 2023 (last accessed October 2023); https://www. pdr.net/drug--summary/?drugLabelId=3759.
13. Prescribers' Digital Reference (PDR) by Connective Rx®. Cariprazine – drug summary. 2023 (last accessed October 2023); https://www.pdr. net/drug--summary/?drugLabelId=3792.
14. Szatmári B, et al. Cariprazine safety in adolescents and the elderly: analyses of clinical study data. Front Psychiatry 2020; 11:61.
15. Jeste DV, et al. Conventional vs. newer antipsychotics in elderly patients. Am J Geriatr Psychiatry 1999; 7:70–76.
16. Karim S, et al. Treatment of psychosis in elderly people. Adv Psychiatr Treat 2005; 11:286–296.
17. Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 1999; 340:757–763.
18. Caccia S, et al. New atypical antipsychotics for schizophrenia: iloperidone. Drug Des Devel Ther 2010; 4:33–48.
19. Intra-Cellular Therapies, Inc. Highlights of prescribing information. CAPLYTA (lumateperone) capsules, for oral use. 2019; https://www. accessdata.fda.gov/drugsatfda_docs/label/2019/209500s000lbl.pdf.
20. CNX Therapeutics Ltd (formerly Sunovion Pharmaceuticals Europe). Summary of product characteristics. Latuda 18.5mg, 37mg and 74mg film-coated tablets. 2022 (last checked December 2023); https://www.medicines.org.uk/emc/product/3299/smpc.
21. Alkermes, Inc. Highlights of prescribing information. LYBALVI® (olanzapine and samidorphan) tablets, for oral use. 2023; https://www. lybalvi.com/lybalvi-prescribing--information.pdf.
22. ACADIA Pharmaceuticals, Inc. Highlights of prescribing information. Nuplazid (pimavanserin) tablets for oral use. 2016; https://www. accessdata.fda.gov/drugsatfda_docs/label/2016/207318lbl.pdf.
23. Prescribers' Digital Reference (PDR) by Connective Rx®. Pimavanserin – drug summary. 2023 (last accessed October 2023); https://www. pdr.net/drug--summary/?drugLabelId=3909#dosing-considerations.

 24. Otsuka Pharmaceuticals (UK) Ltd. Summary of product characteristics. Abilify Maintena 300mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe (aripiprazole). 2022 (last checked December 2023); https://www.medicines.org.uk/emc/ product/12955/smpc%202022. 25. Eli Lily and Company Ltd. Summary of product characteristics. Zypadhera 210mg powder and solvent for prolonged release suspension for injection (olanzapine). 2023; https://www.medicines.org.uk/emc/product/6429/smpc. 26. Janssen-Cilag Ltd. Summary of product characteristics. TREVICTA 175mg, 263mg, 350mg, 525mg prolonged release suspension for injection (paliperidone). 2023; https://www.medicines.org.uk/emc/medicine/32050. 27. Janssen--Cilag Ltd. Summary of product characteristics. Byannli 700mg prolonged-release suspension for injection in pre-filled syringe (paliperidone). 2023; https://www.medicines.org.uk/emc/product/13307/smpc. 28. Janssen-Cilag Ltd. Summary of product characteristics. RISPERDAL CONSTA 25mg powder and solvent for prolonged-release suspension for intramuscular injection (risperidone). 2022 (last checked December 2023);

https://www.medicines.org.uk/emc/medicine/9939. 29. Essential Pharma Ltd. Summary of product characteristics. Camcolit 400mg controlled release lithium carbonate. 2023; https://www.medicines. org.uk/emc/product/10829/smpc. 30. Idorsia Pharmaceuticals US, Inc. Highlights of prescribing information. QUVIVIQ (daridorexant) tablets, for oral use (controlled substance schedule pending). 2022 (last checked December 2023); https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214985s000lbl.pdf. 31. Eisai, Inc. Medication guide. DAYVIGO™ (lemborexant) tablets, for oral use (controlled substance schedule pending). 2019; https://www. accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf#page=21. 32. Upjohn UK Ltd. Summary of product characteristics. Lyrica (pregabalin) 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg capsules. 2023; https://www.medicines.org.uk/emc/product/10303/smpc.