# 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 )

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