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.

670 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 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.

674 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 6 Management of sleep disturbances in dementia 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.

Revision #1
Created 2026-01-04 20:17:01 UTC by Omar Ayman
Updated 2026-01-04 20:17:01 UTC by Omar Ayman