Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

National Clinical Guideline No. 21

Summary December 2019
This National Clinical Guideline has been developed by a guideline development group convened by the National Dementia Office, to fulfil priority action point 2.3 of the National Dementia Strategy Implementation plan, namely “The Health Service Executive will develop guidance material on the appropriate management of medication for people with dementia, and in particular on psychotropic medication management, and make arrangements for this material to be made available in all relevant settings, including nursing homes”.

Using this summary National Clinical Guideline

This summary should be read in conjunction with the full version NCEC National Clinical Guideline. The full version is available at: https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines/. The complete list of references and appendices can be found in the full version only.

This summary National Clinical Guideline applies to people with dementia of any age, and of any type, and in any setting. However, most evidence is based on common dementia types, particularly Alzheimer’s dementia; this needs to be borne in mind by the user when applying the evidence to other dementia types. Clinicians’ attention is also drawn to the fact that many psychotropic medications are used “off label” for people with dementia, particularly antipsychotic medication. While this is not prohibited by medicine regulations, it does require particular caution by the prescriber.

This National Clinical Guideline is relevant to all doctors, nurses, pharmacists and health and social care professionals working in acute, community or residential care settings in Ireland who provide care to people with dementia.

Disclaimer

NCEC National Clinical Guidelines do not replace professional judgment on particular cases, whereby the clinician or health professional decides that individual guideline recommendations are not appropriate in the circumstances presented by an individual patient, or whereby an individual patient declines a recommendation as a course of action in their care or treatment plan. In these circumstances the decision not to follow a recommendation should be appropriately recorded in the patient’s healthcare record.

Users of NCEC National Clinical Guidelines must ensure they have the current version (hardcopy or softcopy) by checking the relevant section in the National Patient Safety Office on the Department of Health website: https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines/.

Whilst every care has been taken to ensure that all the information contained in this publication is correct, the Department of Health cannot accept responsibility for any errors or omissions which may have occurred.

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Membership of the Guideline Development Group (GDG)

The GDG was co-chaired by Dr. Suzanne Timmons (Clinical Lead, National Dementia Office, Ireland) and Professor Stephen Byrne (Senior Academic Pharmacist, University College Cork). This National Clinical Guideline is supported by the HSE National Dementia Office, the Offices of the National Directors for Acute and Community Operations and the Chief Clinical Officer.

Membership nominations were sought from a variety of clinical and non-clinical backgrounds so as to be representative of all key stakeholders within the acute, community, residential care, and intellectual disability sectors, whilst also being cognisant of geographical spread and urban/rural representation. GDG members included those involved in clinical practice, education, administration, research methodology, and two persons representing patients and family carers, two persons representing dementia advocacy groups, as well as a person representing a representative organisation for nursing homes, pharmacists, and a regulatory body (see overleaf).

Members were recruited and invited to partake in the GDG on the provision that they provided justifiable expertise and/or viewpoints to the group, offering valuable contributions based on their extensive knowledge in the field of dementia, and/or professional experience of working with people with dementia, and/or knowledge of a healthcare sector. Appendix 1 contains the terms of reference for the GDG.

Members were not compensated to be involved or contribute to the GDG and were informed that it was on a voluntary basis. The GDG was divided into a group focusing on the future use of the guidelines in the acute sector, and a group focusing on the community and residential care sector, based on their usual work alignment, experience and expertise. A subgroup with particular expertise in dementia in intellectual disability was also formed, adding new members to the initial GDG to provide this expertise. Several members of the team had experience in performing systematic reviews and in developing guidelines and guidance documents.

A core writing group comprising of seven members of the GDG was established. These individuals had significant experience in literature searching and in developing evidence based guidance and/or were highly familiar with the topic area. They were based in the same region to facilitate regular face-to-face meetings and allow for rapid communication between full GDG meetings.
Guideline Development Group membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Job title and affiliation</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td><strong>Community/residential subgroup</strong></td>
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<td>Position, Affiliation</td>
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</tbody>
</table>

*Most writing group members sat on all subgroups.*
3.3.5 Combination therapy (acetylcholinesterase inhibitors with memantine) for noncognitive symptoms
3.3.6 Summary of evidence and recommendations for acetylcholinesterase inhibitors and memantine

3.4 Antidepressant medication
3.4.1 Empirical evidence for the use of antidepressants in a person with dementia
3.4.2 Particular cautions with antidepressants
3.4.3 Cost effectiveness of antidepressants for depression in a person with dementia

3.5 Anticonvulsant medication
3.5.1 Carbamazepine
3.5.2 Gabapentin
3.5.3 Sodium valproate
3.5.4 Lamotrigine
3.5.5 Summary of evidence and recommendations for anticonvulsant medication

3.6 Benzodiazepines
3.7 Z-drugs (hypnotics) and melatonin

3.8 Supporting decision making with regards to psychotropic medication
3.8.1 What information must be discussed?
3.8.2 Capacity of person to make decisions
3.8.3 Making decisions if capacity is absent
3.8.4 Covert administration of medications

Section 4: Appendices
Appendix 3 Evidence tables
Appendix 7 Supporting tools

This National Clinical Guideline draws on NICE guidance
© NICE (2018) Dementia: assessment, management and support for people living with dementia and their carers. Available from www.nice.org.uk/guidance/ng97. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. It is subject to regular review and updating and may be withdrawn. NICE accepts no responsibility for the use of its content in this product/publication.’

This National Clinical Guideline quotes statements from The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia, (Copyright ©2016). American Psychiatric Association. All Rights Reserved.
### 1.1 Summary of recommendations

The following table (1.1) presents the recommendations for appropriate prescribing of psychotropic medications for non-cognitive symptoms in a person with dementia. Section 2.8 (Tables 2.7 and 2.8) explains the GRADE system for determining quality of evidence and the link with recommendation strength.

**Table 1.1:** Summary of recommendations (key recommendations are presented in bold)

<table>
<thead>
<tr>
<th>Section</th>
<th>No.</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General principles of care</td>
<td>1</td>
<td>Prior to considering any psychotropic medication in a person with dementia, a comprehensive assessment¹ should be performed, by an appropriately trained healthcare professional.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Non-pharmacological interventions should be used initially to treat non-cognitive symptoms in a person with dementia, unless there is severe distress, or an identifiable² risk of harm to the person and/or others.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>3</td>
<td>Antipsychotic medication should be used with caution and only in cases where there is aggression, agitation or psychosis that either causes an identifiable risk of harm to the person with dementia and/or others or causes severe distress to the person.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>People with Alzheimer’s disease, vascular dementia or mixed dementias with mild-to-moderate non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of cerebrovascular adverse events and death.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>People with dementia with Lewy bodies³ and Parkinson’s disease dementia with mild to moderate non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of severe adverse reactions.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>People with Alzheimer’s disease, vascular dementia, mixed dementias, dementia with Lewy bodies³, or Parkinson’s disease dementia, with severe non-cognitive symptoms, causing severe distress, or an identifiable² risk of harm to the person and/or others, may be offered antipsychotic medication, where appropriate.</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>A full discussion with the person and/or their relevant Decision Supporter⁴ about the benefits and risks, including the increased risk of stroke, transient ischemic attack and mortality, should occur before antipsychotic medication is commenced.</td>
<td>Low</td>
<td>Conditional</td>
</tr>
</tbody>
</table>

¹ A comprehensive assessment should include: review of medical history and mental health history (including depression) and medication history; physical examination, including consideration of possible delirium, or undetected pain or discomfort (with an appropriate assessment of same); assessment of the severity, type, frequency, pattern, and timing of symptoms, and other potentially contributory or comorbid factors. This assessment should be performed in an appropriate environment that optimises the person’s comfort and ability and includes any support that the person may require. The assessment needs to be performed by a nurse or doctor who is competent in assessing a person with dementia who may be distressed.

² The presence of evident, real or substantial risk or harm.

³ Please refer to glossary for definitions of Parkinson’s disease dementia and dementia with Lewy bodies. Extreme caution is required in prescribing antipsychotics to a person with dementia with Lewy bodies, as they can have life-threatening adverse reactions to antipsychotic medications.

⁴ Please refer to glossary for definition of a ‘Decision Supporter’.
Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

### Section 8: Antipsychotic medication

<table>
<thead>
<tr>
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<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
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<tbody>
<tr>
<td>8</td>
<td>Atypical (second generation) antipsychotic medications are associated with fewer extrapyramidal effects and risks than typical (first generation) antipsychotics, and therefore second generation medication should be used if antipsychotic therapy is necessary for the management of non-cognitive symptoms.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>9</td>
<td>If a risk and benefit assessment favours the use of antipsychotic medication, treatment should be initiated at the lowest possible dose and titrated slowly, as tolerated, to the minimum effective dose.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>10</td>
<td>If there is a positive response to treatment with antipsychotic medication, decision making about possible tapering of the medication should occur within 3 months, accompanied by a discussion with the person with dementia and/or their relevant Decision Supporter.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>11</td>
<td>If a person with dementia is taking an adequate therapeutic dose of antipsychotic medication without clear clinical benefit, the medication should be tapered and stopped; where possible after discussion with the person and/or their relevant Decision Supporter.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>12</td>
<td>If antipsychotic treatment is being tapered, assessment of symptoms for re-emergence should occur regularly during tapering, and for a period after discontinuation of antipsychotic medication.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

### Section 13: Acetylcholinesterase inhibitors and memantine

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Acetylcholinesterase inhibitors are indicated for cognitive enhancement in people with mild to moderate Alzheimer’s disease but are NOT recommended solely for the treatment of non-cognitive symptoms in a person with Alzheimer’s disease.</td>
<td>High</td>
<td>Conditional</td>
</tr>
<tr>
<td>14</td>
<td>Due to the particular risks with antipsychotics in people with Parkinson’s disease dementia and dementia with Lewy bodies, rivastigmine or donepezil may be considered for non-cognitive symptoms causing severe distress when non-pharmacological interventions have proved ineffective.</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td>15</td>
<td>People with vascular dementia or frontotemporal dementia who develop non-cognitive symptoms should NOT be prescribed acetylcholinesterase inhibitors.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>16</td>
<td>Memantine is indicated as a cognitive enhancer in people with moderate to severe Alzheimer’s disease, Parkinson’s disease dementia, and dementia with Lewy bodies, but it is NOT recommended to be prescribed solely for the treatment of non-cognitive symptoms in a person with dementia.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

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1. Please refer to glossary for definitions of Parkinson’s disease dementia and dementia with Lewy bodies. Extreme caution is required in prescribing antipsychotics to a person with dementia with Lewy bodies, as they can have life-threatening adverse reactions to antipsychotic medications.
2. Please refer to glossary for definition of a ‘Decision Supporter’.
3. Prescribing an antipsychotic for BPSD, other than risperidone for short-term treatment of persistent aggression in Alzheimer’s dementia, is off-label.
4. This assessment should usually occur at least monthly during tapering, and also for at least 4 months after discontinuation of antipsychotic medication. The exact frequency and duration of monitoring will depend on factors such as the severity and duration of symptoms and also the duration of antipsychotic treatment. The person and their family should be informed of the potential for re-emergence of symptoms, which would necessitate earlier review than might have been planned.
5. As per the NICE 2018 guideline, memantine monotherapy is recommended as an option for managing severe Alzheimer’s disease, and in moderate Alzheimer’s disease when acetylcholinesterase inhibitors are not tolerated or contraindicated. For people with Alzheimer’s disease who are already taking an AChE inhibitor, the recommendation is to consider memantine in addition to an AChE inhibitor in moderate disease and offer memantine in severe disease. At this current time, memantine has a licence for use in Ireland in moderate and severe Alzheimer’s disease.
### Appropriate prescribing of psychotropic medication

#### for non-cognitive symptoms in people with dementia

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant medication</td>
<td>17</td>
<td>In people with mild to moderate dementia(^8), and mild to moderate depression and/or anxiety, psychological treatments should be considered. Antidepressants may be considered to treat severe comorbid depressive episodes in people with dementia, or moderate depressive episodes that have not responded to psychological treatment.</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td>Anticonvulsant medication</td>
<td>18</td>
<td>Anticonvulsant medication is indicated for the treatment of seizures, bipolar disorder, or as an adjunctive therapy for pain, but is NOT recommended as a treatment for non-cognitive symptoms in a person with dementia.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>Benzodiazepines, z-drugs, and other hypnotics</td>
<td>19</td>
<td>Due to the very limited evidence to support the use of benzodiazepines in the management of non-cognitive symptoms in a person with dementia, and their significant adverse effects, they should be avoided for the treatment of non-cognitive symptoms, and usage strictly limited to the management of short-term severe anxiety episodes(^9).</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>A personalised sleep management regimen(^10) may be considered for sleep disorders in a person with dementia.</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>Melatonin should NOT be used for sleep disorders in people with dementia.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

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\(^8\) There is no evidence as yet to guide the treatment of depression in people with severe dementia, as they were excluded from trials. Thus, the recommendation only applies to people with mild to moderate dementia.


\(^10\) A personalised sleep management regimen may include sleep hygiene practices (e.g. avoiding caffeine before bedtime, having a quiet, comfortable temperature bedroom, avoiding evening naps etc.), exposure to daylight, exercise and personalised activities.

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**A strong recommendation** is one for which the Guideline Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.

**A conditional recommendation** is one for which the Guideline Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the group is not confident about these trade-offs.
### 1.1.2 Summary of good practice points

In addition to evidence-based recommendations, the Guideline Development Group agreed the following good practice points (Table 1.2), based on their collective expertise and consensus opinion.

**Table 1.2: Good practice points**

1. At all times, and throughout the dementia trajectory, an individualised and person-centred approach should be promoted and practiced by all doctors, nurses, pharmacists, and health and social care professionals.

2. The risk and benefits of pharmacological intervention using psychotropic medication should be discussed with the person, and/or their relevant Decision Supporter, in all cases where possible.

3. Psychotropic medication that is commenced for non-cognitive symptoms in a person with dementia should be reviewed regularly to assess efficacy, adverse effects and continued need.

4. If psychotropic medication is necessary for the management of non-cognitive symptoms, oral medication should be used initially. In the exceptional case where parenteral treatment is necessary, the intramuscular route is preferred to intravenous administration, and single agents are preferred to combination therapy.

5. If rapid tranquilisation is needed, the attending doctors and nurses should be adequately trained and have access to adequate monitoring and resuscitation facilities, and should consult their local institutional policy.

6. There is little evidence that antipsychotics are effective in the treatment of certain non-cognitive symptoms such as walking about, hoarding, fidgeting, inappropriate voiding, verbal aggression, screaming, sexual disinhibition and repetitive actions. Therefore, any use in the management of these symptoms needs to be particularly justified.

7. Doctors, nurses, pharmacists and health and social care professionals are strongly advised to contact a specialist team with experience in treating people with Lewy body dementias for direct advice on a person with Parkinson’s disease dementia or dementia with Lewy bodies who has distressing psychosis.

8. Doctors and nurses who prescribe antipsychotics should have written information available for the person with dementia and their family about possible side effects (e.g. falls, confusion, drowsiness), as well as easy to understand information about the risk of serious adverse events (stroke, death).

9. In rare cases where a person with dementia has had two or more failed attempts of antipsychotic withdrawal and requires ongoing maintenance therapy with an antipsychotic, the person should be reviewed at the point of re-prescribing and at least 6 monthly thereafter.

10. Apart from their role in the treatment of depression, antidepressants may have a role in the treatment of other severe non-cognitive symptoms in a person with dementia (such as agitation), where pharmacological treatment has been deemed necessary. If trialled for other non-cognitive symptoms, antidepressants should be used with caution, with close monitoring for side effects.

11. There are no studies of z-drugs for sleep disorders in people with dementia. Due to their significant side effects, if z-drugs are considered, it should be for the shortest period possible (or as specified by medication license).
The development of the National Clinical Guideline

2.1 Background

Dementia is a syndrome in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. The cognitive impairment is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation (WHO, 2018). Dementia is a progressive condition, with symptoms gradually worsening over time. This progression varies from person to person; most individuals experience the same general symptoms, but the degree of symptoms can differ (National Institute for Health and Care Excellence (NICE), 2018). In addition, the lived experience of dementia is not a linear decline, but a varying experience of good weeks and bad weeks, good hours and bad hours. It is important to note that the lived experience of dementia is just as much influenced by social and environmental factors as by the disease status (Sabat, 1994).

2.1.2 Symptoms of dementia

While the precise mechanism associated with the development of dementia is dependent on the type of dementia, it is predominantly recognised as a set of characteristic symptoms (International Psychogeriatric Association (IPA), 2012). These symptoms can be broadly classified as cognitive symptoms or non-cognitive symptoms (IPA, 2012).

Cognitive symptoms

Cognitive symptoms refer to problems incurred with memory, cognition, perceptual or language skills. These symptoms continue to exacerbate over time and can be distressing for the person with dementia and/or their families. Cognitive symptoms can begin gradually with forgetfulness or an inability to recall or remember. They continue to increase in severity as the disease progresses.

Non-cognitive symptoms

Non-cognitive symptoms such as psychosis, agitation or restlessness, aggression, apathy, anxiety and depression are common in people with dementia (Dyer et al., 2017; Alzheimer’s Society, 2017). These are also referred to as neuropsychiatric symptoms. In some instances, people with non-cognitive symptoms of dementia may exhibit behaviours such as: walking about; pacing; hoarding; repetitive vocalisations (calling out); inappropriate sexual behaviour etc.

These are frequently expressions of unmet needs. In addition, a person with dementia may find certain situations or events stressful and may respond through their behaviour. This is generally called ‘responsive behaviours’. It is important to note that the trigger for a responsive behaviour may appear to another person as quite innocuous (such as showering, or personal care). It is important to attempt to see the situation through the eyes of the person with dementia, who is distressed by the situation, even if another person would not be distressed in that situation. Together, non-cognitive symptoms and responsive behaviours are often termed Behavioural and Psychological Symptoms of Dementia, or BPSD (Finkel et al., 1997; Lawlor, 2002).

The term BPSD describes a broad, heterogeneous group of symptoms and signs of disturbed perception, thought content, mood or behaviour (IPA, 2012) (Figure 2.1).
Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

In this guideline, we will often use the term non-cognitive symptoms in preference to BPSD, as the term BPSD is less acceptable to people with dementia, and it may promote a focus on ‘behaviours’ and the perception of a behaviour by other people, rather than focussing primarily on symptoms and needs of the person with dementia that may, in part, be manifested in their behaviour. At times it will be necessary to use the term BPSD to keep the meaning of a reference to existing literature.

Nearly all people with dementia will develop one or more non-cognitive symptoms as the dementia progresses (Lyketsos et al., 2002; Kales et al., 2015). These are often associated with a worsening cognition and progression to more severe stages of dementia. Non-cognitive symptoms can increase the risk of physical complications, such as falls and fractures. In addition, they are often associated with distress (in both the person with dementia and/or their family). It has been reported that non-cognitive symptoms are associated with higher costs of care and therapy (Beeri et al., 2002). Non-cognitive symptoms are also associated with lower quality of life for the person with dementia (Banerjee et al., 2006; Hurt et al., 2008). Thus, the appropriate management of non-cognitive symptoms is an important aspect of dementia care.

Non-cognitive symptoms can be rated for presence and severity using validated tools, such as the Neuropsychiatric Inventory (Cummings et al., 1994) or the Cohen-Mansfield Agitation Index (which focuses only on behaviours rather than symptoms) (Cohen-Mansfield et al., 1989), or the Behavioural Pathologic Rating Scale for Alzheimer’s disease (BEHAVE-AD) (Reisberg et al., 1987).

For the purpose of this guideline, non-cognitive symptom severity is defined as per the scoring recommendation of the Neuropsychiatric Inventory (Table 2.1).

**Figure 2.1: Examples of BPSD**

- **Behavioural symptoms may include:** Aggression, Hoarding, Loud vocalisation, Pacing, Walking about
- **Psychological symptoms may include:** Anxiety, Depressive symptoms, Delusions, Hallucinations, Apathy
### Table 2.1: Non-cognitive symptom severity

<table>
<thead>
<tr>
<th>Mild symptoms</th>
<th>Present but not distressing to the person</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate symptoms</td>
<td>Stressful and upsetting; may require specific management</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>Very stressful and upsetting; typically requires specific management</td>
</tr>
</tbody>
</table>

#### 2.1.3 Delirium

It is very important to differentiate between non-cognitive symptoms and delirium. Delirium is a disturbance in attention and awareness, typically developing over hours to days, often fluctuating in severity during the course of a day, and representing a change from usual status.

Delirium is caused by a variety of insults, typically acute infection, metabolic derangement, medication side effect, or acute brain injury. Due to the different treatments required in the management of non-cognitive symptoms of dementia and delirium, it is important that these conditions are appropriately diagnosed. Diagnostic criteria for delirium emphasise that it is different from dementia, with delirium being of acute onset and fluctuating, versus chronic and progressive in the case of dementia; and with attention predominantly affected in delirium versus memory in dementia. However, people with dementia are at significant risk of developing and/or experiencing delirium (NICE, 2018).

Within clinical practice, it can be challenging to differentiate between dementia alone and dementia with delirium, and this is probably more difficult in acute settings where staff are not familiar with the person’s usual cognitive function. Acute onset or fluctuating non-cognitive symptoms, especially if associated with illness or if incongruent to the person’s stage of dementia, should always trigger the suspicion of delirium superimposed on dementia. Table 2.2 lists some of the key features of delirium (sources include Burns et al, 2004; Martins and Fernandes, 2012).

Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

National Clinical Guideline No. 21 - Summary

Onset The key feature of delirium, unlike dementia, is that changes develop over a very short period of time (usually hours to a few days, but sometimes it can be over a few weeks).

Attention A disturbance in attention is a key symptom in delirium. People with delirium have reduced ability to focus or sustain their attention on a task, or to shift their attention to a second task. This is often tested by asking the person to say the months of the year backwards, or count backwards. It can be also observed from the person doing activity of daily living tasks, where they might leave one task half done and move to another, or struggle with a task that they normally can do easily. It is important for staff caring for a person with dementia to know the person’s usual abilities, so that they can spot a change.

Awareness This is the person’s awareness or orientation to their environment. So for example, a person may suddenly start to get lost in a familiar environment; or not recognise a close family member or staff member, or get mixed up in the day of the week.

Sleep-wake Another typical feature of delirium is altered sleep-wake patterns - so dozing more during the day, and being more awake at night. Particularly in an acute hospital, where staff do not know a person’s usual abilities, daytime drowsiness is an important clue to delirium. Delirium can cause both hyper-alertness and reduced alertness. (The terms alertness and arousal are often used interchangeably in delirium terminology).

Psychosis New onset of delusions (false beliefs) or hallucinations (seeing or hearing things that others do not see or hear) are slightly less common but very important features of delirium. Some people with dementia have chronic hallucinations, but any new onset in a person who hasn’t previously had hallucinations should raise the question of delirium.

Other cognitive and functional changes Delirium can also affect language abilities, mood, visuospatial ability, and perception. An older person with delirium may begin to fall, or become incontinent of urine. Again, the key thing is to recognise (or find out from someone who knows the person well) that they are suddenly having difficulties that are not usual for them.

Fluctuation in symptoms A good clue that a person has delirium is that their abilities or awareness seem to fluctuate during the course of a day, or between days. Of note, one form of dementia, Lewy body dementia, can also cause fluctuations, and anyone’s ability can be affected day to day by fatigue and stress, etc. However, marked fluctuations, or fluctuations in someone’s level of alertness should raise the alarm for possible delirium.

Medical illness Whenever delirium is suspected, there needs to be an assessment for a precipitating medical cause (such as new medication, medication withdrawal, infection, electrolyte disturbance, or an acute brain event). Equally, when a person with dementia is ill, people around them need to be more alert to them possibly developing delirium, so maybe asking more often how they are feeling and observing them doing usual tasks, looking for drowsiness and changed mental function that would indicate that delirium may be developing.

<table>
<thead>
<tr>
<th>Table 2.2: Typical delirium features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
</tr>
<tr>
<td>Attention</td>
</tr>
<tr>
<td>Awareness</td>
</tr>
<tr>
<td>Sleep-wake</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Other cognitive and functional changes</td>
</tr>
<tr>
<td>Fluctuation in symptoms</td>
</tr>
<tr>
<td>Medical illness</td>
</tr>
</tbody>
</table>
There are several existing guidelines for the management of delirium, such as the NICE guideline (https://www.nice.org.uk/guidance/cg103), and the recent Scottish Intercollegiate Guideline Network (SIGN, 2018) (https://www.sign.ac.uk/sign-157-delirium.html). It is important to note that this current guideline is not intended to guide the treatment of delirium.

As an acute, serious, and often short-lived condition, the treatment of delirium generally takes precedence over the treatment of chronic non-cognitive symptoms. Some of the guiding principles are the same (need for comprehensive assessment, environmental management strategies, risk benefit analysis, and a clear review plan for discontinuation) and the risks of psychotropic use are the same, but the evidence for effectiveness is different.

### 2.1.4 Non-pharmacological interventions

Whilst non-pharmacological interventions are not within the scope of this guideline, they clearly are “the other side of the coin” to pharmacological interventions, such that the provision of timely and appropriate non-pharmacological interventions may obviate the need for medications, or work in tandem with medications, or allow medications to be reduced once an acute episode of distress has settled. Non-pharmacological interventions are very broad and Table 2.3 is not intended to be an exhaustive list, or to rank interventions in any order:

<table>
<thead>
<tr>
<th>Table 2.3: Examples of non-pharmacological interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Music therapy</strong></td>
</tr>
<tr>
<td><strong>Reality orientation</strong></td>
</tr>
<tr>
<td><strong>Animal-assisted therapy</strong></td>
</tr>
<tr>
<td><strong>Massage/touch</strong></td>
</tr>
</tbody>
</table>

Overall, there is limited evidence on the benefit of various non-pharmacological interventions, with many studies being small and quasi-experimental. However, evidence suggests that **music therapy** and **behaviour management training** are effective for reducing ‘behavioural disturbances’ (see section 3.1.3 for further information on the evidence reviewed for non-pharmacological interventions).

Environmental design is also an important part of the overall approach. Please refer to “Non-cognitive Symptoms in Dementia (NCSD): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners” for detailed evidence and guidance on the indications, choice and use of non-pharmacological interventions (https://dementiapathways.ie/publications).
Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

2.2 Clinical and financial impact of dementia

The current management of non-cognitive symptoms frequently involves the use of psychotropic medications (National Institute of Mental Health, 2012). Defined as substances that affect brain chemicals associated with mood and behaviour, psychotropic medications include antipsychotics, antidepressants, anticonvulsants, benzodiazepines and z-drugs. Acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine are indicated for the treatment of cognitive impairment in dementia (sometimes termed as “cognitive enhancers”) but are also used for non-cognitive symptoms, and therefore they are included in the guideline as psychotropic medications.

Although some psychotropic medications have shown modest efficacy in the treatment of some non-cognitive symptoms, their use has generated controversy within clinical practice due to the increasing recognition of the adverse side effects associated with their use (Mittal et al., 2011; Tampi et al., 2016). Furthermore, in terms of the burden of polypharmacy and inappropriate prescribing, psychotropic medications constitute a significant proportion of culprit medications (Azermai et al., 2013). Inappropriate prescribing of psychotropic medication is an important and possibly preventable risk factor for adverse drug reactions (ADRs) in people with dementia, with hospital-based studies indicating that a large proportion of admission rates are attributable to ADRs (Klarin et al., 2005). Schneider et al. (2005), in a meta-analysis of randomised placebo controlled clinical trials, noted that antipsychotics were associated with an increased risk of death when compared with a placebo. Recent evidence from clinical trials has highlighted the significant adverse effects including stroke and death that are associated with antipsychotic use in people with dementia (Bjerre et al., 2018).

To summarise the key points:

- It is estimated that, at best, only 20% of people experiencing non-cognitive symptoms derive benefit from an antipsychotic (Banerjee, 2009; Maher et al., 2011; Centre for Effective Practice, 2016).
- Antipsychotic usage is considered to triple the risk of developing a stroke (Mittal et al., 2011; Bjerre et al., 2018).
- It is estimated that about 1 in 100 people with dementia treated with an antipsychotic will die due to the medication and about 1 in 60 will have a stroke (Banerjee, 2009).
- The use of antipsychotic medication in people with dementia was estimated to cause an additional 1,600 strokes and 1,800 deaths per year in the UK (Banerjee, 2009).

Thus, potentially, more than 80% of people with non-cognitive symptoms who receive antipsychotics are exposed to a 1:100 risk of death for no potential benefit.

Following the pivotal Banerjee report, the National Health Service in the UK endeavoured to reduce atypical antipsychotic use in people with dementia by two-thirds.

Antidepressants, such as sertraline, citalopram, mirtazapine and trazodone, and benzodiazepines (as well as z-drugs) are widely prescribed for people with dementia and depression, anxiety and/or other non-cognitive symptoms. Additionally, anticonvulsant drugs (used to prevent seizures in people with epilepsy) are sometimes used to treat symptoms of BPSD, as are acetylcholinesterase inhibitors and memantine. The evidence to support the use of these medications is unclear at best and presents a significant challenge to clinicians.
The risk of adverse events is evident with psychotropic medications. Comparing non-users of psychotropic medication to people with dementia receiving antipsychotic medications, haloperidol had an increased mortality risk of 3.8% (95% CI, 1.0%-6.6%; P < .01); risperidone, 3.7% (95% CI, 2.2%-5.3%; P < .01); olanzapine, 2.5% (95% CI, 0.3%-4.7%; P = .02) and quetiapine, 2.0% (95% CI, 0.7%-3.3%; P < .01); antidepressants 12.3% (95% CI, 8.6%-16.0%; P < .01) (Maust et al., 2015).


2.3 Rationale for this National Clinical Guideline

This guideline addresses the appropriate use of psychotropic medications for non-cognitive symptoms in people with dementia. The need for this guideline has been outlined in preceding sections. Until now, no specific guidelines for dementia have been developed in Ireland for the management of non-cognitive symptoms with psychotropic medications. Presently, clinical practice is sometimes based on international guidelines, but only where the healthcare professional is aware of these. As was described in the preceding section, current practice in Ireland seems to over-rely on psychotropic medications, and the process of prescribing these, including clear documentation of indications for prescribing, where it has been assessed, could be improved. Although there are many drivers of psychotropic prescribing, particularly in residential care where overall staff training, numbers and culture are important, many staff are simply not aware of the risks and lack of benefit of the medications in question (Walsh et al., 2018).

2.4 Aim and objectives

This guideline aims to provide clear and evidence based recommendations on appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia for doctors, nurses, pharmacists and health and social care professionals, working in Ireland, by adapting and adopting existing international guidelines where relevant, informed by recent empiric evidence, relevant Irish legislation, and expert stakeholders.

The objectives of this guideline are:

- To facilitate the appropriate use of psychotropic medication for non-cognitive symptoms in people with dementia, by providing clear, evidence based recommendations.
- To improve the safety of psychotropic medication usage for non-cognitive symptoms in people with dementia.
- To raise awareness regarding the risk and benefits associated with psychotropic medication for non-cognitive symptoms in people with dementia.
- To decrease variation, both within and between services and regions, and to guide care to an appropriate standard across the healthcare system.
2.5 Guideline scope

Limitations in translating the evidence to relevant patient cohorts

Individuals that are covered by this guideline are: all adults (18 years and older) with a diagnosis of dementia, of any type. Although this guideline has been written for the general population of people with dementia, as it relies on published evidence from studies in general dementia populations, the GDG didn’t want to exclude people with an intellectual disability in the guideline. Thus, the guideline applies to people with an intellectual disability and dementia, and where available, we have included specific evidence. However, clinicians should use discretion and clinical judgement when extrapolating evidence and recommendations to people with intellectual disability and dementia. Similarly, much of the available evidence is from studies with people with Alzheimer’s disease, vascular dementia and Lewy body dementias, and this needs to be remembered when applying the guideline in other dementia types, for example dementia in Huntington’s disease and multiple sclerosis.

Setting

This guideline applies to all settings that provide care for an adult with dementia. Thus, the person with dementia may be:

- living in the community
- living in a residential setting (be that private, public, or voluntary; including intellectual disability and mental health residential services)
- in a mental health acute care facility (private, public or voluntary)
- in an acute general hospital (private, public or voluntary)
- in a rehabilitation, respite or transitional care unit.

A person with dementia can transition across many services and sectors, and this guideline applies to their care in any and all settings. The above list is not exhaustive.

Medication categories

The following medications are within the scope of this guideline (the Anatomical Therapeutic Chemical (ATC) classification code is shown in brackets):

- Antipsychotic medications (NO5A, excluding N05AN01 Lithium)
- Antidepressant medications (NO6A)
- Anticonvulsant medications (NO3A)
- Benzodiazepines (NO5BA)
- Hypnotics and sedatives including z-drugs (NO5CF), benzodiazepine-derivatives (N05CD) and melatonin (N05CH01)
- Acetylcholinesterase inhibitors (N06DA) and memantine (N06DX), when used for non-cognitive symptoms.

This guideline does not include recommendations for the use of acetylcholinesterase inhibitors and memantine as cognitive enhancers within its scope (although NICE guideline recommendations (2018) are summarised for convenience for clinicians in Appendix 3.5). The guideline scope excludes all other psychotropic medications that are not listed above e.g. stimulant medications, lithium, etc.
Intended users

These guidelines are relevant to all doctors, nurses, pharmacists, health and social care professionals, healthcare assistants, and general support staff involved in the care of people with dementia (e.g. porters who provide a “specialising service”). However, the primary disciplines involved in prescribing and administering psychotropic medications are doctors, nurses and pharmacists. These three groups need to be thoroughly familiar with the recommendations. This National Clinical Guideline has not been presented in an accessible format and some of language may not be easily understood by a person with dementia or their family, although they are very welcome to read it. A specific information leaflet for the person with dementia has been developed to summarise the key content of this National Clinical Guideline (details of this can be found in Appendix 7). We also encourage people with dementia and their family to bring this National Clinical Guideline to the attention of doctors, nurses and pharmacists involved in their care.

When exercising clinical judgement, doctors, nurses, pharmacists and health and social care professionals are expected to take the guideline recommendations into account, alongside the individual needs, preferences and values of the person with dementia. Doctors, nurses, pharmacists and health and social care professionals are expected to facilitate as far as is practicable the person with dementia to participate in the treatment decision. They are also expected to give effect in so far as practicable to the past and present will and preferences of the person with dementia.

Doctors, nurses, pharmacists and health and social care professionals should take into account the beliefs and values of the person with dementia and any other factors which the person with dementia would be likely to consider if he or she was able to do so. The doctor, nurse, pharmacist and health and social care professional should where practicable consider the views of any person named by the person with dementia as a person to be consulted and any Decision Supporter. In ascertaining the will and preferences of the person with dementia, the doctor, nurse, pharmacist and health and social care professional may further consider the views of any person engaged in caring for the person with dementia, any person who has a bona fide interest in their welfare, or other healthcare professionals.

Limits to the scope of the guideline

Table 2.4 outlines important limits to the scope of this Guideline, which should be read by all users of the guideline.

Table 2.4: Issues that are outside the scope of the guideline

| Pre-existing or comorbid mental health issues | A person with dementia may have another indication for psychotropic medication apart from non-cognitive symptoms (e.g. schizophrenia, bipolar disorder), in which case this guideline does not apply for that medication(s). It is important for any such indication for psychotropic medications to be clearly documented in healthcare records and communicated at all transitions of care, to avoid possible inappropriate discontinuations due to an assumption that the medication was for non-cognitive symptoms of dementia. |
| Acetylcholinesterase inhibitors and memantine for cognitive symptoms | Acetylcholinesterase inhibitors and memantine are often used specifically for cognitive symptoms associated with dementia. This guideline specifically considers the evidence for these medications for non-cognitive symptoms and makes recommendations for this indication. (For user convenience, the recommendations from an existing international guideline relating to cognitive symptoms is summarised in Appendix 3.5). |
Psychotropic medication storage, dispensing, administration, formulation and disposal

The focus of this guideline is on the doctor, nurse, pharmacist and health and social care professional assessing the potential risk and benefit of psychotropic medications, involving the person with dementia in decision making, and following best practice in making and communicating treatment decisions and plans. The logistics of medication management are not within scope.Clinicians are referred to existing Medication Management Guidance (https://www.nmbi.ie/Standards-Guidance/Medicines-Management; https://www.hiqa.ie/sites/default/files/2017-01/Medicines-Management-Guidance.pdf).

Prophylaxis or treatment of delirium

Delirium is an acute and life-threatening illness and its treatment takes precedence over the principles of treatment for chronic non-cognitive symptoms. Doctors, nurses, pharmacists, and health and social care professionals are advised to refer to existing international delirium guidelines. Where a person has documented delirium, the recommendations in this guideline can be considered temporarily superseded by local delirium management protocols, until the delirium is fully resolved.

Treatment at end of life

It is important to clarify that as dementia is currently incurable, all dementia care is currently palliative and thus this guideline is highly appropriate to a person who may be receiving palliative care for dementia. In contrast, at the end of life, meaning the last hours and days of life, medication requirements may change. The use of certain psychotropic medications, such as benzodiazepines and antipsychotics, may be required to ensure a comfortable death. Thus, this guideline ceases to apply at end of life, and doctors, nurses and health and social care professionals are referred to the Clinical Guideline on End of Life Care, currently in development.

Non-pharmacological interventions for non-cognitive symptoms or responsive behaviours

The guideline does not include non-pharmacological interventions within its scope, but it was impossible to ignore these altogether, and so a limited review of the evidence for these is included. This is not intended to be a guide for doctors, nurses, pharmacists, and health and social care professionals in deciding when to use certain non-pharmacological interventions, or in selecting between them. Doctors, nurses, pharmacists, and health and social care professionals are referred to the National Dementia Office’s companion document, Non-cognitive Symptoms in Dementia (NCSD): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners for further information on non-pharmacological interventions (https://dementiapathways.ie/publications).

**Off-label prescribing**

The use of many of psychotropic medications tends to be “off-label” within dementia care (European Medicines Association, 2008; Kamble et al., 2010). Similarly, it has been reported that nearly 90% of psychiatric disorders do not have a licenced medication available for treatment, and that atypical antipsychotic medication is the most commonly prescribed off-label medication in psychiatry practice (Devulapalli and Nasrallah, 2009).

Off-label use refers to the use of an authorised medicinal product outside the terms of its marketing authorisation. This can include prescribing the medication for a different indication, or at a different dose, or in a different form (e.g. crushed), than for which it received marketing authorisation. Of note, off-label
prescribing is not prohibited by medicine regulations, but does require particular caution by the prescriber. This practice is safeguarded in legislation in accordance with Medicinal Products (Control of Placing on the Market) Regulations 2007 (SI 540/2007) as amended.

Medications prescribed off-label can be dispensed by pharmacists and administered by nurses (Anonymous, 1992). In addition, the Practice Standards and Guidelines for Nurses and Midwives with Prescriptive Authority (2010; updated 2018) provides guidance on the off-label prescribing of authorised medicinal products by registered nurse prescribers. (https://www.nmbi.ie/NMBI/media/NMBI/NMBI-Practice-Standards-Prescriptive-Authority_1.pdf)


2.6 Conflict of interest statement

At the initial meeting of the GDG, the issue of conflict of interest was addressed and documented. Members of the GDG were requested to complete and sign a conflict of interest form and return to the co-chairs for review. By definition, all members of the GDG had an interest in the development of this guideline, and these were quite varied in their context, for example being a potential recipient or a prescriber of psychotropic medication, being an implementer of the guideline or a person being asked to follow the guideline. However, there were no personal financial interests, or no personal non-financial interests beyond those inherent in the person’s role. One member had received financial assistance from a pharmaceutical company towards a study several years ago that contributed to the evidence (along with several other sources of evidence). This person did not contribute to the decision related to this particular topic. Prior to publication of this document conflict of interest forms were resubmitted and reviewed again by the co-chairs to ensure no new conflicts emerged following guideline development.

2.8 Guideline methodology

A detailed description of the guideline development methodology is provided in the full National Clinical Guideline (2.8 Guideline methodology). The following is a brief summary. The guideline development involved three phases (Figure 2.2).

Phase 1: Existing international guideline evidence reviewed and appraised in line with ADAPTE process (search date 2008-2018)

Phase 2: Systematic search of empiric evidence including systematic reviews, meta analyses and randomised clinical trials (search date 2015-2018 initially, extended later to 2003-2018 (except for antipsychotics)), with quality appraisal

Phase 3: Compilation of evidence and formulation of recommendations for inclusion in the National Clinical Guideline

Figure 2.2: Phases of the evidence review process
Following initial screening of titles and abstracts of potential guidelines for inclusion, selected guidelines were read in full, and graded for methodological rigour according to the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE) II tool (Brouwers et al., 2010). Ultimately, six guidelines were included (with permission), from the United Kingdom (n=2), Australia and New Zealand (n=1), America (n=2), and Canada (n=1). Within these, one UK guidance document (The British Psychological Society (BPS), 2015) specifically dealt with dementia in people with intellectual disabilities and was used only to inform the GDG’s consideration of the use of the new guideline for this population, but this guidance document did not contribute to specific recommendations. Two other guidelines do not include formal recommendations (from the American Medical Directors Association (AMDA), 2013; and Ministry of Health of British Colombia (MHBC), 2012), but these were reviewed by the GDG to inform the overall evidence and context of the recommendations, and some text is quoted.

Thus, our recommendations are primarily based on the recommendations from three high-quality existing guidelines from well-known guideline developers (Table 2.6). For details of existing guideline recommendations relevant to the key questions of this current guideline, please refer to Appendix 3.1.

Table 2.6: International guidelines adapted for this National Clinical Guideline

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline developer</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>National Health and Medical Research Council (NHMRC)</td>
<td>Clinical Practice Guidelines and Principles of Care for People with Dementia.</td>
</tr>
<tr>
<td>2016</td>
<td>American Psychiatric Association (APA)</td>
<td>Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia.</td>
</tr>
<tr>
<td>2018</td>
<td>National Institute for Health and Care Excellence (NICE)</td>
<td>Dementia Assessment, management and support for people living with dementia and their carers.</td>
</tr>
</tbody>
</table>

The titles and abstracts of retrieved articles in the empiric literature were screened with inclusion/exclusion criteria and critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) 2 checklist (Shea et al., 2007).

Using existing guideline recommendations, and empiric evidence to address any gaps in the existing guidelines, draft recommendations and good practice points were developed by the Guideline Writing Group, and discussed and agreed by the Guideline Development Group (GDG). Each recommendation was assigned a grade for quality of evidence and strength of recommendation by the GDG, using the GRADE system (see full guideline for details; Table 2.7 and Table 2.8). To summarise briefly, the quality of evidence grade reflects the overall level of evidence upon which the recommendation is based, including the directness of the evidence to the clinical question, and whether further research is likely to change the recommendation. The strength of recommendation is primarily based on the quality of evidence, but does take other factors into account, as explained in each relevant section.

Once the GDG agreed the final recommendations and supporting text, the guideline document was forwarded to two expert reviewers for consultation and was sent for national stakeholder review, as detailed in the full guideline (Appendix 4: Consultation report).
2.11 Implementation

The implementation of the recommendations in this National Clinical Guideline by individual doctors, nurses and pharmacists needs to be supported by an adequately resourced National Implementation programme, including audit and evaluation, as described in Appendix 5b: Budget Impact Analysis; and Appendix 6: Implementation plan, both appendices available in full guideline report only.

The responsibilities within individual settings for supporting implementation of the recommendations are detailed in Appendix 6. In addition, each doctor, nurse, pharmacist and health and social care professional working with people with dementia who experience non-cognitive symptoms should exercise due regard for these recommendations, while still exercising clinical and professional autonomy in line with their own professional standards.

The implementation plan in Appendix 6 outlines facilitators and barriers to implementation, and the specific actions required for successful implementation, along with the responsible parties, expected outcome, and means of verification of the activity and/or outcome. A logic model is also presented to summarise the implementation programme. This National Clinical Guideline will be circulated and disseminated as described. The guideline will also be available on the NCEC and NDO websites.

A suite of multi-modal education and training resources, awareness-raising infographics targeting certain settings and disciplines, and a brief summary version of the National Clinical Guideline, along with a specific information leaflet for the person with dementia, including a decision making support tool, and healthcare professional decision support algorithms, will be developed to support implementation. In addition, a self-audit tool and external audit tool is being developed for each setting to inform local quality improvement initiatives, and to monitor compliance with implementation of the recommendations, respectively. The tools that are being developed or are planned for future development are listed in Appendix 7: Supporting tools.

Successful implementation will require cross-sectoral cooperation and integrated working. It will also require funding, and this in turn is subject to service planning and estimates processes. The Budget Impact Analysis in Appendix 5 (part B) demonstrates the likely cost of implementation and the cost avoidance expected to result from successful implementation.

2.12 Monitoring and audit

The monitoring and evaluation plan for this guideline is detailed in Appendix 8: Monitoring and Auditing (in the full guideline).

2.12.1 Monitoring and evaluation

The key implementation process outcomes for this guideline overall, and for specific recommendations, are listed in the logic model and the implementation table in Appendix 6 (in the full guideline).

A key focus of monitoring and evaluation will be the reach and impact of the training and education programme. Thus, the National Implementation Team will monitor the degree to which the guideline is disseminated and available for use in all clinical areas caring for people with dementia. The aim is that, in acute, residential and community settings, all doctors, nurses, pharmacists, and health and social care professionals are aware of the guideline; and that doctors, nurses and pharmacists will have access to the education programme and be released to participate (or complete the online education module), and
will understand, accept and adopt the guideline. This needs to be monitored during implementation by a combination of methods, to allow the implementation process to be adapted and tailored to the needs of certain settings/groups. The success of the education and training programme should also be formally evaluated at the end of the implementation period, to inform and guide future implementation and maintenance planning, but also to inform other HSE implementation projects.

The key **service outcome** for this guideline is a more appropriate prescribing process when considering psychotropic medications for people with dementia, with an increase in the use of non-pharmacological interventions as first line for non-cognitive symptoms, a reduction in inappropriate prescribing of psychotropic medications, and an increase in the practice of review and tapering of antipsychotic medications. This will be principally monitored through chart audit.

The key **patient-related outcome** of successful implementation of this guideline is improved patient safety, with decreased mortality and morbidity associated with inappropriate prescribing of psychotropic medications. This will need evaluation through review of adverse event data related to psychotropic medications in a sample of hospital admissions pre- and post- implementation. The funding of this evaluation is subject to service planning and estimates processes, with strong consideration of a Health Service Research award application, or a shared funding application to the Health Research Board Applied Partnership Award scheme.

### 2.12.2 Audit

It is important that service outcomes are audited to ensure that this guideline positively impacts on the care of a person with dementia. This needs to occur in all settings where a person with dementia is treated, and mainly involves self-audit by the service/facility. For audit criteria see Appendix 8: Monitoring and Auditing (in the full guideline).

### 2.13 Plan to update this National Clinical Guideline

In accordance with the NCEC requirements, this guideline, published in 2019, will be considered for review by the National Dementia Office (NDO) in three years. Any updates to the guideline in the interim period or as a result of the three-year review will be subject to approval by the NCEC. Updates will be published on the NCEC webpages and made available also on the NDO website.
3.0 Healthcare questions and evidence statements

3.1 General principles of care

This guideline centres on the appropriate use of psychotropic medication in people with dementia and non-cognitive symptoms. As each type of psychotropic medication has specific recommendations, this section commences with general considerations for any psychotropic medication. Subsequent sections deal with specific psychotropic medications in turn (see the medication categories in Section 2.5, Guideline scope).

Recommendations from the reviewed international guidelines and key empiric evidence are presented in tables in Appendix 3.2. This evidence is summarised in the text.

3.1.1 Person-centred, individualised care

Dementia has a big impact on the life of the person and can have huge implications for families, friends and loved ones. People with dementia are supported and are cared for by a vast range of health and social services, public and private, which cross acute hospital, social care (including disability), primary care and mental health sectors.

The National Dementia Strategy (Department of Health, 2014), and its Implementation Plan (2015), aim to “improve dementia care so that people with dementia can live well for as long as possible, can ultimately die with comfort and dignity, and can have services and supports delivered in the best way possible”. Similarly, the Strategic Framework for Reform of the Health Service 2012-2015 commits to a patient-centred, flexible, community-based service that includes natural supports (such as family, friends and social interactions).

The principles of personhood and citizenship underpin the National Dementia Strategy. These principles assert: the human value of people living with dementia and their families; the need for an individualised approach in caring for people living with dementia, with a cognisance of the personal beliefs and values and life experiences; the importance of the person’s own perspective and choice being reflected; the importance of relationships and interactions with others including family members and carers to the person living with dementia; and their potential for promoting health and wellbeing (National Dementia Strategy, 2014).

Translating these principles into practice requires the refocusing of service delivery to address the needs of people with dementia in a way that is responsive and flexible. Legislation and policy now place the rights of people with dementia at the centre of service development and delivery. The United Nation Convention on the Rights of Persons with Disabilities states that people with disabilities, including those with dementia, have the right to live independently and be included in the community; the right to liberty and security of person; to freedom from torture, inhuman or degrading treatment; to legal personhood and to autonomy. It is germane therefore that we address current service provision to ensure that the services and supports provided to people with dementia meet their needs, including the management of any non-cognitive symptoms. The NICE guideline (2018) advocates the need to encourage and enable people living with dementia to give their own views and opinions about their care. In cases where the
individual needs additional or modified resources in order to communicate (e.g. visual aids, hearing aids or simplified text), these should be provided.

This guideline offers best-practice guidance on care and support for people living with dementia who may experience non-cognitive symptoms, and their families. The principles of person-centred care underpin good practice in dementia care. In accordance with the provision of person-centred care, it is important that each person with dementia’s ethical, moral and legal rights are maintained. It is important to involve the person with dementia in all decisions about their care, including the use of psychotropic medications.

Firstly, there is always a presumption of capacity. Secondly, if a person living with dementia does lack the capacity to make a certain decision at a particular time, this does not mean that they will lack it with regards to other decisions they face, or at other times. The Assisted Decision-Making (Capacity) Act (2015) (https://tinyurl.com/y4w6xoh6), which has been passed into law but is not yet commenced, provides clear instructions as to how people who lack capacity can be supported to make decisions about care as well as legislating for how others can aid in making decisions for the person. The Mental Health Act (2008) (http://www.irishstatutebook.ie/eli/2008/act/19/enacted/en/html) may on very rare occasions also be relevant for a person with dementia. In Ireland, doctors, nurses, pharmacists, and health and social care professionals should adhere to the requirements on consent to care and capacity outlined in the Assisted Decision-Making (Capacity) Act (2015) (http://www.irishstatutebook.ie/eli/2015/act/64/enacted/en/html), when this commences. This Act was considered throughout the guideline development, with advice from appropriate experts, including the Decision Support Unit, being sought regarding wording and terms. Refer also to section 3.8 on decision making with regards to psychotropic medication.

Good Practice Point 1: At all times, and throughout the dementia trajectory, an individualised and person-centred approach should be promoted and practiced by all doctors, nurses, pharmacists, and health and social care professionals.

3.1.2 Initial comprehensive assessment

The need for a comprehensive assessment was addressed by several international guidelines. There was general consensus that this needed to occur prior to commencing any type of psychotropic treatment (noting that most guidelines were focussed on one class of psychotropic medications, namely antipsychotic medications). Guidelines were vague as to what this initial assessment should encompass. However, most specified the need to assess the type of symptom and its severity and to explore contributory clinical and environmental causes (Appendix 3.2, table 3.2.1). The need to outrule pain, delirium and other potentially modifiable contributors to symptoms were highlighted in the NICE guideline (2018) and the APA guideline (2016).

Of note, NICE guidelines from 2006 (unchanged in 2016 update, but omitted in the 2018 update) had specified an assessment of: the person's physical health, depression, possible undetected pain or discomfort, side effects of medication, individual biography (including religious beliefs and spiritual and cultural identity), psychosocial factors, physical environmental factors, and behavioural and functional analysis conducted by professionals with specific skills, in conjunction with carers and care workers (NICE, 2016).

The MHBC guideline (2012) doesn’t include specific recommendations but states that “The appropriate
Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

Interventions and management of these behaviours initially requires an assessment to identify possible causes and triggers that may contribute to these behaviours. It also states that “It is vital to identify possible medical causes for the behaviour(s) through a comprehensive assessment and review of medical and psychiatric history, and to distinguish dementia from depression or delirium”.


A supplementary review of literature was not undertaken for this recommendation. The GDG felt that, given the narrow range of indications and the significant risks associated with these medications, a strong recommendation should be made that prior to commencing any psychotropic medication, a thorough assessment should be made, including social and environmental factors. The GDG also felt that it was inherent that this assessment needed to be performed by a suitable trained and qualified person. An appropriately trained person is a person with a suitable qualification and competency to perform a dementia-focussed assessment and also to be able to exclude other causes of distress or agitation, such as undetected pain, delirium, urinary retention, etc. This person would thus usually be a registered doctor or nurse. With our ageing society and the consequent increasing prevalence of dementia, all doctors and nurses who treat adults should expect to treat people with dementia and should have training and skills to support the assessment of a person with dementia. Where a doctor or nurse does not have this competency, the assessment needs to be performed by a colleague who does. Equally, where available and appropriate, a multidisciplinary assessment is likely to yield a more comprehensive assessment to support decision making.

To guide practice, a footnote provides details of the consensus agreement of the GDG as to the necessary components of that assessment, based on their collective expertise and considering the practicality of what can be performed across disparate settings. In addition, the GDG felt that it was important that the assessment should be performed in an appropriate environment that optimises the person’s comfort and ability and includes any support that the individual requires, which may include the presence of a family member, if appropriate. This is also included within the footnote.

**Recommendation 1**
Prior to considering any psychotropic medication in a person with dementia, a comprehensive assessment should be performed, by an appropriately trained healthcare professional.

Quality of evidence: **Low**
Strength of recommendation: **Strong**
Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors, nurses, pharmacists, and health and social care professionals**

The GDG also recognised the importance of elucidating and outlining the risks and benefits of any psychotropic medication being considered, following this assessment, and hence this was included as a good practice point (GPP). Note that the level of evidence to support the need to outline the risks and benefits of antipsychotics is stronger (see section 3.3.2 and recommendation 7).

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1 A comprehensive assessment should include: review of medical history and mental health history (including depression), and medication history; physical examination, including consideration of possible delirium, or undetected pain or discomfort (with an appropriate assessment of same); assessment of the severity, type, frequency, pattern, and timing of symptoms, and other potentially contributory or comorbid factors. This assessment should be performed in an appropriate environment that optimises the person’s comfort and ability and includes any support that the person may require.
3.1.3 Non pharmacological versus pharmacological interventions

The GDG had a specific question pertaining to pharmacological versus non-pharmacological interventions, namely when should pharmacological medication be tried relative to non-pharmacological interventions? To answer this question, the GDG reviewed the available guidelines for evidence-based recommendations relating to pharmacological versus non-pharmacological interventions in the management of non-cognitive symptoms (Appendix 3.2.2). Three guidelines stated that non-pharmacological interventions should be tried initially, prior to pharmacological interventions, for the management of non-cognitive symptoms/BPSD (APA, 2016; NICE, 2018; NHMRC, 2016). There were minor variances in the wording used (non-pharmacological interventions should be used “usually” versus “in non-emergency use” versus “as initial and ongoing management”). Two guidelines specified when medications should be used. The NICE guideline (2018) stated that antipsychotics should be used only when the person with dementia was “at risk of harming themselves or others or experiencing agitation, hallucinations or delusions that are causing them severe distress”; and the NHMRC guideline (2016) stated that pharmacological intervention be only offered first “if the person, their carer(s) or family is severely distressed, pain is the suspected cause, or there is an immediate risk of harm to the person with dementia or others” (Appendix 3.2.2).

Similarly, the BPS guidance (2015) states that “Psychotropic medications have only a limited role in the management of neuropsychiatric symptoms in people with intellectual disabilities and dementia and should only be considered if other environmental/psychosocial approaches have produced only very limited or no benefit and the risk from the symptoms is assessed as high”.

In addition to international guidelines, the empiric evidence for non-pharmacological interventions for non-cognitive symptoms was briefly reviewed by the GDG. Users are referred to the companion document “Non-cognitive Symptoms in Dementia (NCSD): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners” for more detailed information and guidance on non-pharmacological interventions (https://dementiapathways.ie/publications).

Jutkowitz et al. (2016) reviewed 19 RCTs and noted that the strength of evidence was generally insufficient to draw conclusions regarding efficacy or comparative effectiveness of non-pharmacological ‘care-delivery interventions’ (such as dementia care mapping, person centred care, emotion-orientated care) in reducing agitation or aggression in nursing home and assisted living facility residents with dementia.

A ‘review of reviews’ published the following year (38 systematic reviews and 142 primary studies) identified a large number of non-pharmacological interventions for behavioural disturbances (Abraha et al., 2017). The authors noted great variation in how the same type of intervention was defined and applied, the follow-up duration, the type of outcome measured, and the typical modest sample size. Overall, they concluded that music therapy and behavioural management techniques were effective for reducing behavioural disturbances.

In another ‘review of reviews’ by Dyer et al., (which included six systematic reviews of non-pharmacological interventions that were not included in the review by Abraha et al.), a significant

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Good Practice Point 2: The risk and benefits of pharmacological intervention using psychotropic medication should be discussed with the person and/or their relevant Decision Supporter⁴, in all cases where possible.

⁴ Please refer to glossary for definition of a ‘Decision Supporter’.
improvement in BPSD was seen with: functional analysis-based interventions (GRADE quality of evidence was moderate; standardised mean difference (SMD) -0.10, 95%CI -0.20 to 0.00), and music therapy (GRADE quality of evidence was low; SMD -0.49, 95%CI -0.82 to -0.17). The estimate of effect size for most interventions was small. Although some pharmacological interventions had a slightly larger effect size, the authors suggest that functional analysis-based interventions should be used as first line management of BPSD whenever possible due to the lack of associated adverse events. They concluded that music therapy may also be beneficial, but further research was required as the quality of evidence to support its use is low (Dyer et al., 2017).

A cluster randomised trial by Pieper et al. (2016), which included 288 people with advanced dementia and challenging behaviour in twelve nursing homes, found that behavioural management training resulted in less agitation (mean difference in Cohen-Mansfield Agitation Inventory (CMAI): −4.07 points, 95% CI −7.90 to −0.24, p=0.02), and neuropsychiatric symptoms (NPI-NH (Neuropsychiatric Inventory–Questionnaire, Nursing Home version): mean difference −3.57 points, 95% CI −6.30 to −0.84, p=0.005). In addition, there was a significant reduction in the use of antidepressants (Odds Ratio, OR = 0.32).

A recent Cochrane review of music therapy (van der Steen et al., 2018) concluded that providing people with dementia in institutional care with five or more sessions of music therapy "probably reduces depressive symptoms and improves overall behavioural problems at the end of treatment. It may also improve emotional well-being and quality of life and reduce anxiety, but may have little or no effect on agitation or aggression." The authors were uncertain about effects on social behaviour; in addition, the long-term effects were unclear.

Combining the evidence presented in the above section, the GDG made a recommendation. The GDG felt that ‘risk’ was an ambiguous term and felt that this risk needed to be identifiable. Thus, the final recommendation denotes that the risk to the person and/or others must be identifiable. Examples of identifiable risk would include a person threatening another person with an object or attacking another person, without any provocation.

**Recommendation 2**
Non-pharmacological interventions should be used initially to treat non-cognitive symptoms in a person with dementia, unless there is severe distress, or an identifiable risk of harm to the person and/or others.

Quality of evidence: High  
Strength of recommendation: Strong  
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; National Dementia Office; doctors, nurses, pharmacists, and health and social care professionals

Several members of the GDG felt it was important to emphasise that the selection of appropriate non-pharmacological interventions needs to be based on knowing the person with dementia, and a comprehensive assessment of the context and triggers at the time, with the treatment decision ideally made by a multidisciplinary team, rather than having a fixed “menu” of interventions to be tried in turn. It is acknowledged by the GDG that doctors, nurses, pharmacists, and health and social care professionals in many settings will need additional training, support and resources to provide suitable

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2 The presence of evident, real or substantial risk or harm.
non-pharmacological interventions (see implementation plan, Appendix 6).

The recommendation deliberately does not quantify how many different non-pharmacological interventions should be tried, and for how long, as this depends on the exact clinical context. Doctors, nurses, pharmacists, and health and social care professionals are referred to the companion guidance document for non-pharmacological interventions for non-cognitive symptoms to guide treatment choices “Non-cognitive Symptoms in Dementia (NCSD): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners” for more detailed information and guidance on non-pharmacological interventions (https://dementiapathways.ie/publications).

The NHMRC (2016) states that olanzapine is the only antipsychotic approved for parenteral (intramuscular) use in Australia for treating BPSD.

The GDG agreed that when a psychotropic medication is being given, the oral route should always be considered prior to the parenteral route. The GDG felt that parenteral use would and should be an exceptional occurrence, necessitated by either an emergency situation with immediate risk to the person or others, where immediate effects were required, or where a person was unable to swallow and psychotropic administration was deemed essential.
The GDG felt that on the rare occasions when a psychotropic medication was required for non-cognitive symptoms and could not be taken by mouth, the intramuscular route was the preferred route, rather than intravenous, and they agreed with the NHMRC statement that a single agent should be tried first, rather than combination therapy.

The GDG chose not to recommend any one agent, as the best medication in a particular situation would depend on the indication and the person’s other medical issues.

**Good Practice Point 4:** If psychotropic medication is necessary for the management of non-cognitive symptoms, oral medication should be used initially. In the exceptional case where parenteral treatment is necessary, the intramuscular route is preferred to intravenous administration, and single agents are preferred to combination therapy.

**Rapid tranquilisation - emergency situations**

No guideline covered the use of rapid tranquilisation in an emergency situation. The GDG felt that given the urgency and severity of this situation and the risk of the person deteriorating or complications presenting, the most important point was that doctors and nurses should be adequately trained to manage emergency situations. Doctors and nurses are recommended to follow their local policy pertaining to rapid tranquilisation and emergency situations.

**Good Practice Point 5:** If rapid tranquilisation is needed, the attending doctors and nurses should be adequately trained and have access to adequate monitoring and resuscitation facilities, and should consult their local institutional policy.
3.2 Antipsychotic medication

There was general consensus across guidelines that antipsychotic medications should only be used in certain situations. Appendix 3.2.4 presents the guideline recommendations and the empiric evidence that addresses the efficacy and indication for antipsychotics for non-cognitive symptoms. The content of this appendix is summarised below.

3.2.1 Indications for antipsychotics

(i) Symptoms that are likely/not likely to respond:
Several guidelines stated specific symptom indications for antipsychotics, and these were very consistent in naming psychosis (MHBC, 2012; APA, 2016; NHMRC, 2016; NICE, 2018) and agitation (MHBC, 2012; APA, 2016; NHMRC, 2016; RANZCP, 2016; NICE, 2018) as indications for antipsychotics. Aggression was also named as an indication in most of these (MHBC, 2012; NHMRC, 2016; RANZCP, 2016) but not NICE (2018). Appendix 3.2.2 presents the exact wording in these guidelines.

Tampi et al. (2016) in a systematic review of 16 meta-analyses that evaluated the use of antipsychotics in individuals with dementia found that antipsychotics demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia. They noted that their use in individuals with dementia is often limited by their adverse effect profile.

In contrast, antipsychotic medications have been shown to have little effect on several non-cognitive symptoms and behaviours, including walking about, hoarding, repetitive actions, vocal disruptions, inappropriate behaviour, tugging, fidgeting, and inappropriate voiding (Sorbi et al., 2012; AQuAS, 2014; Canadian Coalition for Seniors’ Mental Health, 2006). Reflecting this, the MHBC guideline (2012) states that the following behaviours are not usually amenable to antipsychotic treatment: walking about, vocally disruptive behaviour, inappropriate voiding, hiding and hoarding, inappropriate dressing/undressing, eating inedible objects, repetitive activity, tugging at seatbelts, pushing wheelchair bound residents.

(ii) Severity of symptoms that indicate antipsychotics may be needed:
Several guidelines stated that symptoms needed to be significant or severe, and/or cause significant (severe) distress to warrant an antipsychotic, with minor variations in the exact wording used (MHBC, 2012; NHMRC, 2016; APA, 2016; NICE, 2018).

Tampi et al. (2016) similarly noted that the use of antipsychotics should be reserved for severe symptoms that have failed to respond adequately to non-pharmacological management strategies.

Two guidelines also stated that an indication for the use of antipsychotics was the risk of harm, either to the person with dementia or to others (MHBC, 2012; NICE, 2018).

Taking the guideline recommendations and the recent systematic review by Tampi et al. together, the GDG decided that best practice was that an antipsychotic was used with caution for the management of non-cognitive symptoms, and only when:

i) there was an appropriate target symptom(s), i.e. aggression, agitation or psychosis and either

ii) the symptom(s) are causing severe distress to the person with dementia or

iii) there is an identifiable risk to the person with dementia and/or others.
The GDG felt that in all cases when doctors deem it necessary to prescribe an antipsychotic medication, the Summary of Products Characteristics (SmPC) and specific medication licence should be consulted, noting that most use will be off-label.

**Recommendation 3**

Antipsychotic medication should be used with caution and only in cases where there is aggression, agitation or psychosis that either causes an identifiable risk of harm to the person with dementia and/or others or causes severe distress to the person.

Quality of evidence: **High**

Strength of recommendation: **Strong**

Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurses, nurse prescribers and pharmacists

**Good Practice Point 6:** There is little evidence that antipsychotics are effective in the treatment of certain non-cognitive symptoms such as walking about, hoarding, fidgeting, inappropriate voiding, verbal aggression, screaming, sexual disinhibition and repetitive actions. Therefore, any use in the management of these symptoms needs to be particularly justified.

### 3.2.2 Risks of antipsychotics in dementia

The adverse effects and risks of antipsychotics are well established. The recommendations in international guidelines are presented in Appendix 3.2.5. One guideline advised general “caution” with antipsychotics (APA, 2016). Some guidelines specified the increased risk of cerebrovascular adverse events and death (BPS, 2015; NHMRC, 2016). The MHBC guideline (2012) advises a discussion of the following risks: oversedation, postural hypotension, risk of falls, metabolic syndrome, extrapyramidal symptoms, tardive dyskinesia, stroke, and increased mortality.

In addition, the BPS guidance (2015) states that “Caution should be exercised in the use of antipsychotic medication in the context of the evidence of a high risk for cerebrovascular events and mortality”.

The GDG reviewed the empiric evidence to further delineate the particular risks with antipsychotics, with a particular focus on whether these differed between dementia types.

**Cerebrovascular risk and mortality**

Antipsychotics have been associated with cerebrovascular adverse events and death in people with dementia. Based on pooled analysis of data from four published and unpublished studies of risperidone, which indicated a three-fold risk of cerebrovascular events (3.5% versus 1.2% with placebo), the UK Committee on Safety of Medicines stated in 2004 that risperidone or olanzapine should not be used for the treatment of BPSD, and that prescribers should carefully consider the risks of cerebrovascular events.

In 2005, the US Food and Drug Administration noted that in analyses of 17 placebo-controlled studies of atypical antipsychotics, the mortality rate for older patients with dementia was about 1.6-1.7 times that of placebo. Separately, a meta-analysis of published and unpublished data from RCTs of risperidone (n=5), olanzapine (n=5), quetiapine (n=3) and aripiprazole (n=3), found death rates among the patients with dementia (total 3353) were 3.5% for those taking the medications versus 2.3% for those on placebo (Schneider, Dagerman and Insel, 2005).
In 2008, the US Federal Drugs Authority (FDA) issued an alert that both conventional and atypical antipsychotics were associated with an increased risk of mortality in older people treated for dementia-related psychosis (FDA, 2008). This was in addition to a previous alert by the FDA in 2007 on the association of haloperidol with QT prolongation (an ECG abnormality) and sudden death (www.fda.gov).

A later literature review concluded that antipsychotics increased the risk of cerebrovascular adverse effects and death when used to treat older patients with BPSD (Mittal et al., 2011). Similarly, a review of twelve observational studies published in 2016 with 11,463 total participants showed an overall relative risk of death in Alzheimer’s disease patients receiving antipsychotics versus those not receiving antipsychotic, of 2.08 (95% Confidence Interval (CI) 1.39 to 3.13) (Zhai et al., 2016). The systematic review of meta-analyses published the same year by Tampi et al., found that antipsychotic use in people with dementia results in a greater number of adverse effects compared with placebo, including the risk of stroke and death. The risk of stroke was most prominent in the risperidone-treated group. The risk of death was not associated with any particular antipsychotic (Tampi et al., 2016).

One of the studies within this review is by Ballard et al. (2009) who conducted a discontinuation RCT, reporting as a primary outcome the mortality rate in 165 people with Alzheimer’s disease who had been taking antipsychotics (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for at least 12 months. In the study, people were randomised to either continuing the antipsychotic or to replacing the antipsychotic with placebo. Switching to placebo reduced the risk of mortality (Hazard Ratio 0.58, 95% CI 0.35 to 0.95; P = 0.03). The 24-month survival rate was 46% in people taking antipsychotics compared with 71% in people taking placebo.

**Cognitive side effects**

All antipsychotics have anticholinergic effects to differing degrees, and as such may potentially worsen cognition. The cholinergic system plays an important role in memory, and acetylcholinesterase inhibitors, which increase cholinergic signalling between neurones, are used as cognitive enhancers in dementia. Thus a medication with the opposite effect (anticholinergic) may worsen cognition, especially if also prescribed with one or more other medications with anticholinergic effects (such as certain antidepressants, and some cardiac medications, and some anti-tremor medications for people with Parkinson’s disease).

The GDG felt that there was insufficient evidence currently to make a recommendation about the risk of cognitive side effects with antipsychotics, and that the more definite risk of harm due to stroke and death in a person with dementia was of sufficient concern without additional consideration of whether antipsychotics hastened cognitive decline.

**Recommendation 4**

People with Alzheimer’s disease, vascular dementia or mixed dementias with *mild to moderate* non-cognitive symptoms should **NOT** be prescribed antipsychotic medication due to the increased risk of cerebrovascular adverse events and death.

Quality of evidence: **High**

Strength of recommendation: **Strong**

Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists**
Extrapyramidal effects - particular caution in Parkinson’s disease dementia/dementia with Lewy bodies

Antipsychotics block dopaminergic receptors in the brain, causing motor effects (shuffling, slowness, tardive dyskinesia, etc.). A Cochrane review of haloperidol for agitation in dementia (Lonergan et al., 2011) found that haloperidol was associated with more adverse effects than placebo, with one study reporting 34/101 [34%] of people with dementia had at least one extrapyramidal symptom with haloperidol, compared to 18/103 [18%] with placebo (Odds Ratio 2.3, 95% CI 1.2 to 4.4).

Extrapyramidal symptoms are of particular concern in people with Parkinsonian syndromes and dementia. The mainstay of treatment for Parkinson’s disease is dopaminergic medications; antipsychotics antagonise the effects of dopaminergic medications so that people with Parkinsonian syndromes can be stiffer and slower, which impacts on activities of daily living and quality of life, and comes with attendant risks in terms of falls, fracture, aspiration pneumonia, etc. Parkinsonian syndromes include Parkinson’s disease and also closely related conditions such as Progressive Supranuclear Palsy, Corticobasilar Degeneration and Multiple Systems Atrophy. In all of these, a person may develop dementia as the disease progresses (referred to as Parkinson’s disease dementia).

The risks are even higher in dementia with Lewy bodies, a particular form of Parkinson’s disease where the dementia is a very early and prominent feature, and visual hallucinations are a common symptom. This is caused by the same protein that causes Parkinson’s disease, but in a different distribution within the brain. In Parkinson’s disease, the brainstem is initially more affected, so movement timing and sequencing are affected first, and the person much later develops dementia as the protein slowly spreads to the cortex (Parkinson’s disease dementia). In dementia with Lewy bodies, the cortex is affected early on, causing dementia and visual hallucinations, with a variable degree of Parkinsonian features. Of note, people with dementia with Lewy bodies are highly sensitive to motor disturbances with antipsychotics, with potentially severe consequences, including death.

Reflecting this, some guidelines specifically state that antipsychotics should be avoided in people with dementia with Lewy bodies (NHMRC, 2016). The NICE guideline (2018) affirms caution when using antipsychotics stating “be aware that for people with dementia with Lewy bodies or Parkinson’s disease dementia, antipsychotics can worsen motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions”.

The AMDA guideline (2013) states that people who have dementia with Lewy bodies generally have an increased sensitivity to antipsychotics, and that second-generation antipsychotics may have a lower frequency of extrapyramidal side effects, but all antipsychotics have some ‘significant’ associated risks.

The GDG also reviewed the Scottish Intercollegiate Guidelines Network (SIGN) guideline (2010) for Parkinson’s disease (https://www.sign.ac.uk/assets/sign113.pdf), as this was highly relevant to this particular question. This states that people with Parkinson’s disease dementia with moderate to severe psychosis should be considered for treatment with low-dose clozapine, with appropriate blood monitoring as it causes blood dyscrasias. If blood monitoring is not possible, the SIGN guideline recommends low-dose quetiapine be considered as an alternative antipsychotic. In contrast, the NICE guideline for Parkinson’s disease (2017) (https://www.nice.org.uk/guidance/ng71) recommends consideration of quetiapine to treat hallucinations and delusions in people with Parkinson’s disease who have no cognitive impairment (not treating at all if well tolerated), stating that if standard treatment is not effective, clozapine should be offered to treat hallucinations and delusions (being aware that registration with a patient monitoring service and ongoing monitoring is needed due to the serious risk of agranulocytosis). This guideline also reminds clinicians to “be aware that lower doses of quetiapine and clozapine are
appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia

needed for people with Parkinson’s disease than in other indications” and specifically states that olanzapine should not be used.

The GDG agreed that there are significant risks with antipsychotics in dementia with Lewy bodies and Parkinson’s disease dementia, above and beyond the usual risks of stroke and increased mortality in people with other dementias, and felt that a specific recommendation was required. Although the GDG agreed that clozapine can be useful for the treatment of Parkinson’s disease dementia as it doesn’t have the propensity to worsen Parkinson’s disease motor function, they felt that due to its own significant risks, it should only be prescribed by a team who specialise in clozapine prescribing and monitoring, and who have the facility to monitor bloods regularly, and know what to do if a blood dyscrasia develops. In practice, this limits safe clozapine prescribing to a mental health service. Equally, although the GDG agreed that low dose quetiapine does not worsen motor control to the same degree as other antipsychotics, members questioned the efficacy of low dose quetiapine for moderate to severe psychosis. In reviewing the evidence to support this recommendation in the SIGN guideline, this recommendation appears to be based on trials involving drug-induced psychosis and not trials on primary Parkinson’s disease dementia psychosis (e.g. Frieling et al., 2007).

The GDG felt that given the available evidence, a recommendation for the use of clozapine and/or quetiapine could not be made at this time. The GDG discussed this with experts in clinical practice and concluded that best practice was that in cases of Parkinson’s disease dementia psychosis where antipsychotic medication is deemed necessary, the clinician should base the choice of antipsychotic on a full assessment and target specific symptoms. The clinician is strongly advised to contact a specialist team with experience in treating people with Parkinson’s disease dementia/dementia with Lewy bodies for direct advice on an individual person with Parkinson’s disease dementia or dementia with Lewy bodies who has distressing psychosis.

**Recommendation 5**
People with dementia with Lewy bodies and Parkinson’s disease dementia with mild to moderate non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of severe adverse reactions.

Quality of evidence: **High**
Strength of recommendation: **Strong**
Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists**

**Recommendation 6**
People with Alzheimer’s disease, vascular dementia, mixed dementias, dementia with Lewy bodies, or Parkinson’s disease dementia, with severe non-cognitive symptoms, causing severe distress, or an identifiable risk of harm to the person and/or others, may be offered antipsychotic medication, where appropriate.

Quality of evidence: **Moderate**
Strength of recommendation: **Conditional**
Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists**

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2 The presence of evident, real or substantial risk or harm.
3 Please refer to glossary for definitions of Parkinson’s disease dementia and dementia with Lewy bodies. Extreme caution is required in prescribing antipsychotics to a person with dementia with Lewy bodies, as they can have life-threatening adverse reactions to antipsychotic medications.
3.2.3 Risk/benefit discussion with family

The recommendations from existing guidelines are presented in Appendix 3.2.5. The MHBC guideline (2012) advises clinicians to “Carefully weigh the potential benefits of pharmacological intervention versus the potential for harm. Recognise that the evidence base for drug therapy is modest. Engage the resident/family/substitute decision-maker in the health care planning and decision-making process. Obtain consent for health care treatment from the appropriate decision-maker before administering antipsychotic medication.”

It further states that “All information should be provided in a language or method that the resident/family/substitute decision maker can understand... written information be provided so that all are aware of what to expect and also to indicate that the family/substitute decision maker are welcome to actively participate in developing the plan of care. Information should be culturally appropriate, available in other languages and be accessible to persons with disabilities such as hearing loss”.

Similarly, the AMDA guideline (2013) states that “while there is no regulatory requirement for informed consent for antipsychotic medication, the relatively high risk to benefit ratio and the lack of evidence for BPSD make it prudent to pursue a reasonable and thoughtful discussion of the value and risk of these medications, as wells as alternatives, with the relevant parties. Such conversations should be documented in the clinical record”.

The NICE guideline (2018) states in a footnote that informed consent should be obtained and documented prior to prescription of an antipsychotic for non-cognitive symptoms.

Given the consensus across the existing guidelines, an empiric evidence review was not performed. The GDG fully supported the principle that doctors, nurses, pharmacists and health and social care professionals should be expected to facilitate participation in decision-making by the person with dementia wherever possible, and/or their relevant Decision Supporter, where appropriate, given the significant risks associated with antipsychotic medications for non-cognitive symptoms. The GDG use the term Decision Supporter rather than “family” in line with the terminology used in the ADMA (2015), as it is not assumed that the Decision Supporter (e.g. the Decision-Making Representative, Attorney, etc.) will always be a family member. Using this term does not reduce the importance of the relationship between a person with dementia and their family, and it is recognised that the family will also have information needs if they are administering the medication or being asked to watch out for side effects.

Although the GDG felt this discussion was a highly important component of appropriate prescribing, the recommendation was made conditional to reflect the acknowledged challenges and complexities of following this recommendation in clinical practice in every situation, and the evolving legal position of surrogate decision making in Ireland currently.

**Good Practice Point 7:** Doctors, nurses, pharmacists and health and social care professionals are strongly advised to contact a specialist team with experience in treating people with Lewy body dementias for direct advice on a person with Parkinson’s disease dementia or dementia with Lewy bodies who has distressing psychosis.
Recommendation 7
A full discussion with the person and/or their relevant Decision Supporter\(^1\) about the benefits and risks, including the increased risk of stroke, transient ischemic attack and mortality, should occur before antipsychotic medication is commenced.

Quality of evidence: Low
Strength of recommendation: Conditional
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; Decision Support Unit; doctors, nurses, pharmacists and health and social care professionals

3.2.4 Choice of antipsychotic medication
Antipsychotic medication can be broadly categorised into typical (first generation) antipsychotics, which were discovered first, and then atypical (second generation) which were developed later. Within these broad categories, there are several antipsychotics in each group. The overall evidence for choice of antipsychotics from international guidelines and empiric literature review is presented in Appendix 3.2.6, and is discussed below, firstly in terms of which class of antipsychotic to prescribe, and then in terms of individual antipsychotics.

Choice of atypical versus typical antipsychotic medication
In terms of atypical (second generation) versus typical (first generation) antipsychotics, several guidelines recommended that atypical antipsychotics are preferred, given the reduced incidence of adverse effects associated with their use (APA, 2016; AMDA, 2013; NHMRC, 2016; MHBC, 2012).

Consistent with this, a review by Holmes and Badrakalimuthu in 2015 noted that of all agents currently used for ‘behaviour problems’, atypical (second generation) antipsychotics had the strongest evidence base. Similarly, a systematic review by Preuss et al. in 2016 concluded that the evidence base for atypical antipsychotics was strongest, although their benefits are moderate at best (effect size 0.16–0.31). This included moderate- to high-quality evidence from 17 RCTs containing 5,028 people, which found improvements in the NPI, Brief Psychiatric Rating Scale, CMAI and Clinical Global Impression of Change with atypical antipsychotics versus placebo, but higher rates of mortality, somnolence, and extrapyramidal and cerebrovascular adverse events compared to placebo.

A meta-analysis by Rao et al. (2016) suggested that second generation antipsychotic medications had no increased risk of stroke compared to first generation, based on population based studies with a total of 79,910 people who were treated with second generation antipsychotic medications, with 1,287 cases of stroke reported. The relative risk of stroke was 1.02 (95% CI 0.56-1.84) for the second generation antipsychotic medication group. There was no significant difference in the risk of stroke (p = 0.96) between groups, but significant heterogeneity was found among the results of included studies (p < 0.001).

A meta-analysis by Hsu et al. in 2017 concluded that second generations had a lower risk of stroke (Odds Ratio 1.31; 95% CI 0.74-2.30), compared with first generation antipsychotics (Odds Ratio 1.49; 95% CI 1.24-1.77). The GDG would like to point out that the 95% CI of these Odds Ratios overlap, which suggests that there may not be any difference in risk. A meta-analysis the same year by Farlow et al. reported that atypical antipsychotics are associated with lower risk of all-cause mortality and extrapyramidal symptoms but higher risk of stroke when compared with conventional antipsychotics (Appendix 3.2.6).

\(^1\) Please refer to glossary for definition of a ‘Decision Supporter’.
**Choice of specific antipsychotic medication**

The MHBC guideline (2012) and NHMRC guideline (2016) both preferentially recommend risperidone for treating psychosis, and risperidone or olanzapine for treating agitation/aggression. The MHBC guideline (2012) states that "while risperidone and olanzapine are useful in reducing aggression, risperidone is more effective in reducing psychosis. Risperidone is the only atypical antipsychotic medication approved for the short term treatment of aggression/psychosis in severe dementia".

Similarly, risperidone is recommended as the first choice in antipsychotic treatment by the Royal Australian and New Zealand College of Psychiatrists (2016) given that it is "the only oral medication approved in Australia and New Zealand for use in behavioural disturbances associated with Alzheimer’s type dementia". This group specifically states that other medications (e.g. quetiapine, aripiprazole and olanzapine) if used for BPSD are off-label and hence should be considered only when risperidone is not tolerated or is inappropriate.

The NICE guideline (2018) similarly notes that the only antipsychotic with a UK marketing authorisation for use in dementia is risperidone; this marketing authorisation only covers short-term treatment (<6 weeks) of persistent aggression in people with moderate to severe Alzheimer’s disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

A review of quetiapine in Parkinsonian syndromes found seven RCTs with a total of 241 participants, where quetiapine did not cause any motor deterioration, but failed to significantly reduce psychotic symptoms when compared to placebo when objectively assessed on the Brief Psychotic Rating Scale (Desmarais et al., 2016). However, they noted that high loss to follow-up and dropout rates as well as significant improvement in psychotic symptoms in the placebo groups may have affected the outcome measures.

A larger systematic review of studies reporting safety data for quetiapine in older adults (El-Saifi et al., 2016), found that compared to placebo, quetiapine resulted in significantly greater cognitive impairment, higher rates of falls and injury. Quetiapine was not associated with increased mortality in people with dementia, compared to placebo (single case control study). Compared with risperidone and olanzapine, quetiapine had a significantly lower risk of mortality (five observational studies) and possibly reduced rate of cerebrovascular events (four observational studies, with conflicting results), but possibly increased rate of falls and injury (two observational studies with non-significant increases).

A recent review included one high-quality meta-analysis and data from 8 RCTs and 12 large observational studies of people with dementia (Farlow et al., 2017). Compared to placebo, aripiprazole, risperidone, and olanzapine but not quetiapine resulted in modest improvement in neuropsychiatric symptoms. Aripiprazole, risperidone, quetiapine, and olanzapine were associated with increased odds of acute myocardial infarction, and risperidone and olanzapine with increased odds of hip fractures. Observational studies suggest no differences in all-cause mortality between atypical antipsychotics (Farlow et al., 2017).

Thus, the GDG agreed that where an antipsychotic is required, atypical (second generation) antipsychotic medications should be used as they have less risk of extrapyramidal effects (although the stroke/mortality risk compared to typical antipsychotics is not clear). There was much discussion about whether to only recommend risperidone, as the only licensed antipsychotic for BPSD (licensed for short term use for refractory and persistent aggression with risk of harm). Members of the GDG noted that the evidence for olanzapine was not dissimilar to risperidone, and that quetiapine was far more commonly used in Ireland due to its lower risks of adverse effects (although less effective). The GDG finally agreed that the individual clinician would have to weigh up the risk and benefit in the individual circumstances, and that it was not appropriate to make a blanket recommendation. The GDG do however highlight to doctors and nurse prescribers that if they prescribe an antipsychotic other than risperidone for non-cognitive symptoms, and if they prescribe risperidone for an indication other than persistent aggression, they are doing so off-label.
Recommendation 8
Atypical (second generation) antipsychotic medications are associated with fewer extrapyramidal effects and risks than typical (first generation) antipsychotics, and therefore second generation medication should be used if antipsychotic therapy is necessary for the management of non-cognitive symptoms.

Quality of evidence: Moderate
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

3.2.5 Initiation and titration of antipsychotics
To reiterate, non-pharmacological intervention should be used as first line management of non-cognitive symptoms, and prior to the initiation of any psychotropic medication a comprehensive assessment should be performed, with psychotropic medications only used in cases where non-pharmacological intervention has proved ineffective or where there is severe distress in the person with dementia, or risk of harm to the individual and/or others. Following this process, if an antipsychotic is being prescribed, it should be done as safely as possible. It is important that non-pharmacological interventions (unless ineffective) are not discontinued just because a psychotropic medication is temporarily required. In addition, following a period of treatment with psychotropic medication, a person may have a better response to a previously ineffective non-pharmacological intervention.

Existing guidelines state that when an antipsychotic is being initiated it should be done so at a low dose (MHBC, 2012; NHMRC, 2016) and titrated upwards (NHMRC, 2016). The APA guideline (2016) similarly recommends that an antipsychotic for behavioural/psychological symptoms in people with dementia “should be initiated at a low dose to be titrated up to the minimum effective dose as tolerated”. The NICE guideline (2018) recommends using the lowest effective dose of antipsychotics.

The GDG agreed that this is a basic principle of good care. The GDG noted that as many people with dementia are older and have co-morbidities, and may have polypharmacy, prescribers should be mindful of the risk of drug accumulation due to renal or hepatic dysfunction and drug-drug interactions when deciding safe doses and titration/review frequency. It is not possible to give specific direction, but titration decisions should be informed by a comprehensive assessment that includes symptoms and their severity, general health and co-morbidities.

Recommendation 9
If a risk and benefit assessment favours the use of antipsychotic medication, treatment should be initiated at the lowest possible dose and titrated slowly, as tolerated, to the minimum effective dose.

Quality of evidence: Moderate
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

1 Prescribing an antipsychotic for BPSD, other than risperidone for short-term treatment of persistent aggression in Alzheimer’s dementia, is off-label.
3.2.6 Review and discontinuation of the antipsychotic medication

The following section applies to a person with non-cognitive symptoms where there has been a recent commencement of antipsychotic medication for one or more non-cognitive symptoms of dementia. It does not apply to people with a pre-existing, co-morbid mental health illness that may require life-long antipsychotics. Particular care must be taken in attempting to withdraw a long-term antipsychotic where the indication for its commencement is not clear. In this case, the clinician is advised to consult with the initial prescriber to ascertain the exact indication for the antipsychotic medication. If it can be ascertained that the indication for a long-term antipsychotic prescription was non-cognitive symptoms in the context of dementia and not a primary mental health illness, the recommendations can be followed.

Appendix 3.2.7 summarises the recommendations in existing guidelines. A review of the empiric evidence was not performed for this clinical question.

Need to review appropriateness of antipsychotic prescription, and discontinue, if no clear benefit or presence of side effects:

There was inconsistency between guidelines in terms of the optimum duration of a trial of an antipsychotic medication for non-cognitive symptoms before the clinician would conclude that the medication was ineffective. The MHBC guideline (2012) states that antipsychotics should be withdrawn if no improvement in the targeted behaviour or if undue adverse effects occur. They note that a response usually occurs in 1-2 weeks and recommend to taper/discontinue if no improvement within 12 weeks and reassess, “when an alternative antipsychotic may be tried”.

The APA guideline (2016) states that if clinically significant side effects are experienced, the potential risks and benefits of antipsychotics should be reviewed to determine if tapering/ discontinuing of the medication is indicated. If there is no clinically significant response after 4-week trial of an adequate dose, the medication should be tapered and withdrawn.

The NICE guideline (2018) recommends that treatment with antipsychotics should be stopped if there is not a clear, ongoing benefit for the person taking them and after discussion with the person taking them and their family members or carers. The timeline is not specified.

Trial of tapering or withdrawal after a positive response in symptoms

The MHBC guideline (2012) states that “All medication should initially be considered as a trial. If the medication is found to be effective, consideration should be given to tapering/discontinuation” and that “clinicians should consider tapering and withdrawing antipsychotics and all other medications used to treat BPSD after 3 months of behavioural stability, and following careful clinical review.”

The APA guideline (2016) states that if there is a positive response to treatment, decision making about possible tapering of antipsychotics should be accompanied by a discussion with the person with
dementia/their surrogate decision maker (if relevant). An attempt to taper and withdraw the drug should be made within 4 months, unless the person experiences a recurrence of symptoms with prior attempts at tapering.

The NICE guideline (2018) recommends to use antipsychotics for the ‘shortest possible time’ and reassessing the person at least every 6 weeks to check whether they still need the medication. Of note, the NICE evidence review for the guideline describes high-quality evidence from 7 RCTs containing 366 people, which found a higher proportion of people who discontinued antipsychotics had a worsening of BPSD/non-cognitive symptoms compared with those who continued. In addition, there was low- to moderate-quality evidence from up to 6 RCTs containing 462 people which could not differentiate overall levels of BPSD/non-cognitive symptoms, or rates of early study termination or mortality (NICE, 2018). It also describes moderate-quality evidence from one RCT that could not differentiate neuropsychiatric symptoms between people who continued antipsychotic medication compared with those who discontinued. There was however high-quality evidence from one RCT finding higher levels of neuropsychiatric symptoms (NPI) in people who discontinued antipsychotic medication compared with those who continued.

Within the NICE review, one small clinical trial of risperidone for hallucinations found 13 of the 17 (76.5%) participants who were randomised to discontinuing risperidone relapsed, compared with 10 of the 26 (38.5%) who continued treatment (p<0.02). NPI domain scores did not affect relapse rates but people with severe auditory hallucinations at baseline had a higher likelihood of relapse once risperidone was stopped (Hazard Ratio 2.96, 95% CI=1.52, 5.76) (Patel et al., 2017). This effect was not present in the subgroup with visual hallucinations. With the caveat that this is a single study, this indicates that particular caution may be required when discontinuing antipsychotics for severe auditory hallucinations, with a need for close monitoring for relapse.

The GDG felt that it was important that the guideline recommendations were feasible in clinical practice. Within a residential care setting or an acute hospital, it would be feasible for staff to review a person regularly (even if the person was not seen by the prescriber in person, but instead by an appropriately qualified other staff member). Many felt that it would however be unreasonable to expect a General Practitioner (GP) or a prescriber in a clinic (out-patient setting) to review a person within 1-2 weeks, and this frequency of review might be onerous for the person with dementia. Other options such as a telephone call to their family/carer were discussed, noting that this would not always be equivalent to an in-person review. Some GDG members felt that the length of time before a review should be individualized as it may depend on the person’s functional status, the nature of the non-cognitive symptoms, and the duration, persistence, and severity of symptoms.

Thus, a decision was made by the GDG not to recommend a specific time for initial review for early efficacy or side effects, or to specify the duration of a trial of treatment before the treating MDT would conclude that treatment had failed. However, the GDG also felt it was very important that people with a positive response to antipsychotics were not continued on antipsychotics indefinitely. Based on the timelines recommended in international guidelines (MHBC: after 3 months; APA: within 4 months; NICE: no time specified), the GDG chose to specify that a review for possible trial of discontinuation needed to occur within 3 months.
The final recommendations are as below:

**Recommendation 10**
If there is a positive response to treatment with antipsychotic medication, decision making about possible tapering of the medication should occur within 3 months, accompanied by a discussion with the person with dementia and/or their relevant Decision Supporter.4

Quality of evidence: **Low**
Strength of recommendation: **Strong**
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurses and pharmacists

**Recommendation 11**
If a person with dementia is taking an adequate therapeutic dose of antipsychotic medication without clear clinical benefit, the medication should be tapered and stopped; where possible after discussion with the person and/or their relevant Decision Supporter.4

Quality of evidence: **Moderate**
Strength of recommendation: **Strong**
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

**Monitoring during withdrawal of an antipsychotic**
The APA guideline (2016) states that if an antipsychotic is being tapered, assessment of symptoms should occur at least monthly during taper and for at least 4 months after discontinuation (strong recommendation based on low quality evidence - see Appendix 9 for APA grading explanation).

The MHBC guideline (2012) includes anecdotal clinical experience that some residents with BPSD/non-cognitive symptoms may require ongoing maintenance therapy where the consequences of symptom relapse are deemed to be unacceptably severe and no alternative treatment approaches have been deemed effective. Those residents should continue to be reviewed, at a minimum annually.

The GDG felt that review during tapering was an important part of deprescribing, given the risk of relapse. The GDG felt that it should be a rare occurrence to not consider attempting to discontinue antipsychotic medication when the indicator symptoms had settled, but that equally a person who suffers repeated (distressing) relapses should not have persistent attempts to discontinue antipsychotic medication. It was felt that pragmatically, two failed attempts at discontinuation were sufficient to indicate that the person required ongoing treatment with that same agent (or on occasions switching on recommencement to a different agent, if the clinical scenario indicated that a change in medication would be better). However, the person on long-term medication would still require regular review for emerging side effects or change in the risk-benefit balance of continuing the medications.

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4 Please refer to glossary for definition of a ‘Decision Supporter’.
**Recommendation 12**
If antipsychotic treatment is being tapered, assessment of symptoms for re-emergence should occur regularly during tapering, and for a period after discontinuation of antipsychotic medication.

Quality of evidence: **Moderate**
Strength of recommendation: **Strong**
Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors and nurses**

**Good Practice Point 9**: In rare cases where a person with dementia has had two or more failed attempts of antipsychotic withdrawal and requires ongoing maintenance therapy with an antipsychotic, the person should be reviewed at the point of re-prescribing and at least 6 monthly thereafter.

### 3.2.7 Cost effectiveness of antipsychotic medication
Kirbach et al. (2008) modelled the cost effectiveness of olanzapine, compared with no treatment, for **agitation** and **psychosis** in people with Alzheimer’s disease (AD), living in the community and in nursing homes in the USA. Effectiveness estimates of olanzapine were taken from the CATIE-AD study by Schneider et al. (2006), modelled over 13 years. Prescription costs, inpatient and outpatient care costs and memantine costs were included in the cost analysis. The total 13-year cost for a person with AD who was prescribed olanzapine was $39,781, compared to the “no treatment” cost of $35,899. However, while treatment with olanzapine incurred higher costs, it afforded quality adjusted life years (QALY) gains, with an incremental cost-effectiveness ratio (ICER) of $37,104 per QALY. These results suggest that olanzapine is cost-effective in terms of QALY gained for the treatment of agitation and psychosis in individuals with AD, when compared with no treatment.

Rosenheck et al. (2007) conducted a cost utility analysis comparing the cost effectiveness of atypical antipsychotic medications with placebo in the treatment of psychosis and aggression in people with AD in the USA. Like Kirbach et al. (2008), the analysis used effectiveness estimates of antipsychotic drugs (olanzapine, risperidone and quetiapine) from the CATIE-AD study by Schneider et al. (2006). The net ‘health benefit’ of each drug was calculated by subtracting monthly healthcare costs from the monthly health benefits, measured in QALYs gained. Results indicated that on average, the group prescribed a placebo had significantly lower total health costs compared to those assigned an atypical antipsychotic. The analysis also suggested that there were no differences in QALYs gained with the atypical antipsychotics. Thus, no treatment was considered to be a less costly alternative that achieved better health benefits.

These studies, both using CATIE-AD data, have conflicting results, with one concluding that olanzapine is cost effective for **agitation** and **psychosis**, and the other finding that atypical antipsychotic medications are not cost effective for **aggression** and **psychosis**. There are limitations to both studies, with more details available on both in Appendix 5, Part A.

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*This assessment should usually occur at least monthly during tapering and also for at least 4 months after discontinuation of antipsychotic medication. The exact frequency and duration of monitoring will depend on factors such as the severity and duration of symptoms and also the duration of antipsychotic treatment. The person and their family should be informed of the potential for re-emergence of symptoms, which would necessitate earlier review than might have been planned.*
3.2.8 Summary of evidence and recommendations for antipsychotics

The evidence suggests that where possible, people with dementia who experience non-cognitive symptoms should be made aware of the risk and benefits associated with the use of antipsychotic medications. Given the severe adverse events associated with them, antipsychotic medications should be used with caution, and should not be the first line of treatment in non-cognitive symptoms. Non-pharmacological interventions should be tried initially and only when these have failed or are inappropriate (e.g. urgent treatment needed) should antipsychotic medications be considered. The decision to commence antipsychotic medication should be made only: when a comprehensive assessment of the person has taken place; in cases where symptoms are severe and there is an identifiable risk to the person or others; and when non-pharmacological interventions have proved ineffective on their own.

Antipsychotic medications should be used cautiously using a targeted approach towards symptoms that are proven to respond (i.e. aggression, severe agitation, and psychosis). The choice of an individual antipsychotic medication should be based on the particular person’s risks and their symptoms, with evidence suggesting that atypical antipsychotics may have fewer risks and side effects associated with them than typical (first generation) antipsychotics, and noting that risperidone is the only antipsychotic medication licensed for BPSD/non-cognitive symptoms, and even this is only licenced for short term use for refractory aggression in Alzheimer’s disease.

Once the decision to commence an antipsychotic medication has been deemed appropriate, the person with dementia should be reviewed regularly, and the effect of the medication on symptom improvement or worsening should be monitored and recorded. The antipsychotic medication should be stopped if not improving symptoms after a reasonable trial (using the clinician’s judgement as to final dose tried and the duration of trial at this dose, based on initial symptoms, and side effects). In addition, there should be a trial of tapering or withdrawing medication within three months of symptom stability, with regular monitoring for symptom re-emergence, suggested to be for at least four months after antipsychotic withdrawal.
Several international guidelines reviewed the evidence for acetylcholinesterase inhibitors and memantine in the treatment of cognitive symptoms, where they are used as cognitive enhancers (i.e. they do not modify the progression of the damage and dying of neurones, but they help cholinergic and other signalling between surviving neurones). This current guideline does not include recommendations for the use of acetylcholinesterase inhibitors as cognitive enhancers within its scope, but for convenience, the NICE guideline (2018) (https://www.nice.org.uk/guidance/ta217/chapter/1-Guidance) recommendations are summarised in Appendix 3.5.

Although many people with dementia will be receiving acetylcholinesterase inhibitors and/or memantine, targeting their cognition, this is not always the case. Therefore this guideline specifically deals with the scenario where a person is not already prescribed these medications and the clinician is considering the prescription of these medications for the management of non-cognitive symptoms.

Only the BPS guidance (2015), which is specific to the use of psychotropic medications in people with intellectual disability, gave a recommendation about the use of acetylcholinesterase inhibitors and/or memantine in relation to the management of BPSD/non-cognitive symptoms. This guidance document states that “these medications can be used in certain circumstances in the management of BPSD in people with intellectual disability and Alzheimer’s disease and dementia with Lewy bodies where psychological and/or environmental measures alone are unsuccessful.” The guidance document also states that “as well as improving symptoms of BPSD in people with dementia, the available evidence suggests that they may improve the quality of life of both the person and their carer”. Although the NICE guideline 2018 presents useful evidence regarding the efficacy of acetylcholinesterase inhibitors and memantine for non-cognitive symptoms in non-Alzheimer’s disease dementias, there is not a specific recommendation given for non-cognitive symptoms. In contrast, the previous NICE guideline update in 2016 had given specific recommendations, as follows: “In people with dementia with Lewy bodies who have non-cognitive symptoms causing significant distress, or leading to behaviour that challenges, an acetylcholinesterase inhibitor should be offered. Individuals with vascular dementia who develop behavioural and psychological symptoms of dementia should not be prescribed acetylcholinesterase inhibitors, except as part of properly constructed clinical studies”.

Thus, the GDG performed a literature search of the evidence for the use of acetylcholinesterase inhibitors and memantine, reviewing evidence published from 2003 to 2018. This empiric evidence is presented in tabular format in Appendix 3.3, and summarised below, for common dementia subtypes. Of note, the most commonly used assessment tool for non-cognitive symptoms is the Neuropsychiatric Inventory (NPI), where the total score can range from 0 to 144. A clinical response had been defined in the literature as a minimum change on the NPI of four points (Mega et al., 1996) or nine points (Kaufer et al., 1996). The NPI website says that generally a decrease in four points or a 30% reduction from baseline total NPI score would be regarded as clinically meaningful, unless otherwise specified in a study for a particular reason (http://npitest.net/faqs.html).

### 3.3.1 Acetylcholinesterase inhibitors for non-cognitive symptoms in Alzheimer’s disease

In a systematic review and meta-analysis of acetylcholinesterase inhibitors given for at least 12 weeks at optimal dose (Hansen et al., 2008), seven studies reported change in behaviour using the NPI; four studies using donepezil and three galantamine. Donepezil performed better than galantamine; the pooled weighted mean difference in NPI score between active treatment and placebo was -4.3 (95% CI -5.95 to -2.65) for donepezil and -1.44 (95% CI -2.39 to -0.48) for galantamine respectively.
A further systematic review by Rodda et al. the following year (2009) included 14 studies, four of which had behavioural outcomes as the primary outcome measure, while it was a secondary outcome in the remaining trials. Three studies reported either an improvement in overall NPI score (5.6 (donepezil), 6.2 (donepezil) and 2.1 points (galantamine)) or in the agitation/aggression item of the NPI only. These changes are at best, of modest clinical benefit. A further ten studies did not find a significant improvement in scores with acetylcholinesterase inhibitors, but the majority were not specifically designed or powered to detect changes in neuropsychiatric outcomes. Another limitation noted by the authors was the generally low NPI scores at baseline, such that improvement was difficult.

A large review (Butler and Radhakrishnan, 2012) noted four previous systematic reviews (Birks, 2011; NICE, 2006; Hansen et al., 2008; Rodda et al., 2009) that assessed acetylcholinesterase inhibitors in people with dementia. The authors concluded that acetylcholinesterase inhibitors improved neuropsychiatric symptoms compared with placebo at 26 weeks (measured by the NPI: 2 RCTs of donepezil; 1 RCT of galantamine; total 1005 people); with a pooled weighted mean difference of -2.4 (95% CI -4.1 to -0.8). This level of improvement is not clinically significant. A more recent review of psychotropic agents in the treatment of BPSD concluded that the use of acetylcholinesterase inhibitors is controversial for BPSD (Preuss et al., 2016).

Finally, a recent, focussed Cochrane Systematic Review entitled ‘Donepezil for dementia due to Alzheimer’s disease’ was conducted by Birk & Harvey (2018) to assess the clinical safety and efficacy of donepezil in people with mild, moderate or severe dementia due to Alzheimer’s disease. In total, 30 studies (n=8,257) were included in the review, of which 28 were included in a meta-analysis. Most studies were of six months’ duration or less. Four studies (n=1,035) assessed behavioural symptoms using the NPI in people taking donepezil 10mg/day versus placebo after 24-26 weeks of treatment and one study (n=194) used the Behavioural Pathology in Alzheimer’s disease (BEHAVE-AD) score. The changes from baseline at 24-26 weeks on the NPI and BEHAVE-AD scores were (Mean Difference -1.62, 95% CI -3.43 to 0.19, p= 0.08) and (Mean Difference 0.40, 95% CI -1.28 to 2.08, p= 0.64) respectively; thus there was no statistically significant difference between donepezil and placebo at 24 - 26 weeks for either score. A limitation identified in this review was that participants did not suffer from more than mild behavioural problems at baseline, in any of the four studies in the meta-analysis.

To summarise, there are limitations in many of the studies performed to date regarding the efficacy of acetylcholinesterase inhibitors in non-cognitive symptoms, with earlier studies reporting some benefits in behaviour changes, but where these were not the primary outcome of the study, and also noting that these studies were often funded by pharmaceutical companies. The studies (such as CALM-AD and later studies) that were specifically designed to study behaviour changes were generally equivocal or negative. While initially donepezil seemed to out-perform galantamine, the recent Cochrane review of donepezil concluded there was no benefit for donepezil in BPSD.

Thus, the GDG felt that although acetylcholinesterase inhibitors had a definite indication for the treatment of cognitive symptoms in Alzheimer’s disease (in all stages) they could not be recommended for the treatment of non-cognitive symptoms in Alzheimer’s disease at this time.
Recommendation 13
Acetylcholinesterase inhibitors are indicated for cognitive enhancement in people with mild to moderate Alzheimer’s disease but are NOT recommended solely for the treatment of non-cognitive symptoms in a person with Alzheimer’s disease.

Quality of evidence: High
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

3.3.2 Acetylcholinesterase inhibitors for non-cognitive symptoms in people with Lewy body dementias

As detailed in section 3.2.2 (Extrapyramidal effects- particular caution in Parkinson’s disease dementia/ dementia with Lewy bodies), there are two Lewy body dementias. In Parkinson’s disease, the brainstem is initially more affected, so movement timing and sequencing are affected first, and the person much later develops dementia as the protein slowly spreads to the cortex (Parkinson’s disease dementia). In ‘dementia with Lewy bodies’, the cortex is affected early on, causing dementia and visual hallucinations, with a variable degree of Parkinsonian features.

The NICE guideline (2016) stated that in people with dementia with Lewy bodies who have non-cognitive symptoms causing significant distress, or leading to behaviour that challenges, an acetylcholinesterase inhibitor should be offered. The NICE guideline in 2018 does not include a recommendation, but does present a summary of evidence, which is presented at the end of this section.

Looking at the empiric evidence, Wild et al. (2003) and the subsequent evidence review for the NICE guideline in 2006 found only one randomised, double-blind trial (McKeith et al., 2000) comparing rivastigmine and placebo in people with dementia with Lewy bodies who suffered from behavioural disturbances or psychiatric problems. In this 20-week study (n=120), rivastigmine was associated with a reduction in neuropsychiatric symptoms compared with placebo (NPI), but differences between groups did not reach significance (Standard Mean Difference = −0.28, 95% CI = −0.67 to +0.12). An RCT by Emre et al. (2004) demonstrated a ‘statistically significant’ improvement in NPI score with rivastigmine in people with Parkinson’s disease dementia (but note the reduction of two points is not clinically significant).

A subsequent review by Ballard et al. (2011) on the treatment of dementia with Lewy bodies and Parkinson’s disease dementia again reported the McKeith (2000) study but didn’t find any more recent acetylcholinesterase inhibitor studies.

Stinton et al. (2015) performed a large review of multiple medications for Parkinson’s disease dementia or dementia with Lewy bodies. They identified six RCTs of acetylcholinesterase inhibitors in Parkinson’s disease dementia or dementia with Lewy bodies that used the 10-item NPI to assess psychiatric symptoms and performed a meta-analysis of these six studies. Subgroup analyses within this indicated small benefits for total neuropsychiatric symptoms in Parkinson’s disease dementia from both donepezil (weighted mean difference = −1.17, 95% CI = −2.26, −0.08) and rivastigmine (weighted mean difference = −2.00, 95% CI = −3.91, −0.09), but not in dementia with Lewy bodies for either medication. Two studies assessed psychiatric symptoms in dementia with Lewy bodies using the 4-item NPI (the sum of...
scores for apathy, delusions, depression, and hallucinations, total possible score = 48). A significant effect favouring acetylcholinesterase inhibitors was observed (weighted mean difference=−3.36; 95% CI: −5.85, −0.87). Subgroup analysis indicated a benefit from donepezil (weighted mean difference=−4.80, 95% CI: −8.63, −0.97) but not rivastigmine.

The NICE guideline (2018) evidence review summarises these studies again:

- **Dementia with Lewy bodies**: High-quality evidence from 2 RCTs suggests that donepezil significantly improves carer burden. Low-quality evidence from 3 RCTs could not differentiate an effect on neuropsychiatric symptoms of acetylcholinesterase inhibitors while high-quality evidence from 2 RCTs suggests that acetylcholinesterase inhibitors significantly improve neuropsychiatric symptoms (hallucinations, delusions, dysphoria and apathy). Low-quality evidence from 2 RCTs could not differentiate an effect on neuropsychiatric symptoms of donepezil.

- **Parkinson’s disease dementia**: Moderate-quality evidence from 2 RCTs suggests that acetylcholinesterase inhibitors significantly reduce the risk of hallucinations. High-quality evidence from 2 RCTs suggests that acetylcholinesterase inhibitors significantly improve neuropsychiatric symptoms.

- **Mixed Parkinson’s disease dementia or dementia with Lewy bodies**: High-quality evidence from 5 RCTs suggests that acetylcholinesterase inhibitors significantly improve neuropsychiatric symptoms.

- **Moderate- to high-quality evidence from a network meta-analysis by the NICE guideline team of 9 RCTs showed that acetylcholinesterase inhibitors are associated with a significant increase in any adverse events, but not serious adverse events.**

To summarise, there is emerging evidence for the benefit of donepezil and rivastigmine for non-cognitive symptoms in Lewy body dementias, particularly Parkinson’s disease dementia. The GDG were cautious about the clinical significance of the meta-analysis results (Stinton et al., 2015), where although statistically significant benefits were found for acetylcholinesterase inhibitors, the actual clinical benefit may be modest (noting that the 10-item NPI was used). However, the GDG felt that given the particular risks of antipsychotic medication worsening motor function in Lewy body dementias (especially in dementia with Lewy bodies), and the caution with using clozapine in practice (see section 3.2.2), clinicians can struggle to find any suitable medication when a person with dementia with Lewy bodies or Parkinson’s disease dementia has significant distress due to non-cognitive symptoms. The lack of serious adverse events shown in the NICE meta-analysis for acetylcholinesterase inhibitor in Lewy body dementias was also noted.

Thus, it was felt that rivastigmine and donepezil could be cautiously recommended for non-cognitive symptoms in people with Lewy body dementias (be that dementia with Lewy bodies or Parkinson’s disease dementia), noting that this use is off-label. The GDG didn’t feel the current evidence adequately differentiated between rivastigmine and donepezil to preferentially recommend either agent.
Recommendation 14
Due to the particular risks with antipsychotic medications in people with Parkinson’s disease dementia and dementia with Lewy bodies, rivastigmine or donepezil may be considered for non-cognitive symptoms causing severe distress when non-pharmacological interventions have proved ineffective.

Quality of evidence: Moderate
Strength of recommendation: Conditional
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

3.3.3 Acetylcholinesterase inhibitors for non-cognitive symptoms in vascular dementia and frontotemporal dementia
The NICE guideline update in 2016 had stated that individuals with vascular dementia with non-cognitive symptoms or behaviour that challenges should not be prescribed acetylcholinesterase inhibitors, “except as part of properly constructed clinical studies” (NICE, 2016). The NICE guideline in 2018 didn’t contain any specific recommendation for non-cognitive symptoms in vascular dementia, but did recommend that acetylcholinesterase inhibitors not be prescribed for cognitive symptoms in vascular dementia.

The evidence review for the NICE guideline in 2006 had found two RCTs of donepezil and one RCT of galantamine versus placebo in people with vascular dementia. The review concluded that acetylcholinesterase inhibitors significantly reduced neuropsychiatric symptoms compared with placebo in people with vascular dementia (measured by NPI: SMD –0.21, 95% CI –0.41 to –0.01). Of note, this reduction is not clinically significant.

A subsequent RCT (Auchus et al., 2007) with 788 people with vascular dementia found no improvement in neuropsychiatric symptoms measured by NPI at 26 weeks with galantamine versus placebo (mean change: +0.6 with galantamine versus –1.2 with placebo).

The NICE guideline (2018) evidence review summarises these studies as follows: High-quality evidence found neuropsychiatric symptoms were significantly worse in people receiving acetylcholinesterase inhibitors, but moderate-quality evidence found no difference. No new studies were included in this review.

The GDG noted the lack of evidence to support the use of acetylcholinesterase inhibitors for cognitive symptoms or non-cognitive symptoms in vascular dementia. Thus, the agreed recommendation was to NOT prescribe acetylcholinesterase inhibitors for non-cognitive symptoms in vascular dementia. The GDG do note however that many people clinically diagnosed as possible or probable vascular dementia based on clinical diagnostic criteria actually have pathological features of mixed vascular dementia/Alzheimer’s disease at autopsy, and so caution is needed in being overly prescriptive based on a clinical diagnosis of ‘vascular dementia’. If the clinician feels there may be overlap of vascular dementia with Alzheimer’s disease or Lewy body dementias, it may be appropriate to trial an acetylcholinesterase inhibitor.

A recent review of clinical trials and systematic reviews found that cholinesterase inhibitors did not demonstrate efficacy in ameliorating frontotemporal dementia symptoms, and the review did not offer
conclusive evidence to support their use in BPSD (Young et al., 2018). Thus, frontotemporal dementia was included in this recommendation.

**Recommendation 15**
People with vascular dementia or frontotemporal dementia who develop non-cognitive symptoms should **NOT** be prescribed acetylcholinesterase inhibitors.

Quality of evidence: **Moderate**  
Strength of recommendation: **Strong**  
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

It was not possible to make a recommendation for people with undifferentiated or mixed dementias, based on the current evidence. However, as the evidence does not support the use of acetylcholinesterase inhibitors for non-cognitive symptoms in Alzheimer’s disease, vascular dementia or frontotemporal dementia, the GDG felt that unless the clinician suspected an element of Lewy body dementia, an acetylcholinesterase inhibitor was probably unlikely to help the person.

### 3.3.4 Memantine for non-cognitive symptoms

**Alzheimer’s disease:**

A Cochrane systematic review entitled ‘Memantine for Dementia’ was conducted to determine the efficacy and safety of memantine for people with Alzheimer’s disease, vascular dementia and mixed dementia (McShane et al., 2006). Pooled data from three unpublished studies with people with mild to moderate Alzheimer’s disease indicated no effect on behaviour. People with moderate to severe Alzheimer’s disease taking memantine had significantly less worsening of mood and behaviour as assessed on the NPI at six months (2.76 NPI points, 95% CI 0.88 to 4.63, p=0.004) but this degree of change is not clinically significant. The participants were less likely to develop new agitation with memantine (12% v 18%; Odds Ratio 0.6; 95% CI 0.42 to 0.86, p=0.005). However, no evidence was presented to suggest that mood and behaviour problems which were apparent at the time of study entry were more likely to resolve in those taking memantine.

Two systematic reviews in 2008 compared memantine to placebo for the treatment of people with BPSD (Maidment et al.; and Gauthier et al.). The reviews identified the same 6 RCTs. The systematic review and meta-analysis conducted by Maidment et al. reported that 3 RCTs were high quality and three RCTs were moderate, and losses to follow-up ranged from 11% to 27% between studies. The meta-analysis only included people with Alzheimer’s disease and found that memantine had a statistically significant but not clinically relevant reduction in NPI scores compared with placebo (1730 people; total difference in mean NPI value: −1.99, 95% CI −3.91 to −0.08; P = 0.04). Gauthier et al. (2008) reported on ‘any improvement in total NPI score’ and found a statistically significant difference in favour of memantine, but the absolute difference in NPI scores were the same as that described by Maidment et al. (2008), i.e. a change of approximately 2 points in the NPI, which is not clinically significant (total score 0-144). A further “pooled analysis” of three of these trials, by Wilcock et al. (2008) is presented in Appendix 3.3

A later meta-analysis by Schneider et al. 2011, based all the same evidence again, assessed the efficacy of memantine in Alzheimer’s disease. In the three trials included, there was no evidence for the efficacy...
of memantine in the subset of people with mild Alzheimer’s disease on any outcome in an individual trial or in the meta-analysis, including the NPI score (0.09; 95% CI, −2.11 to 2.29; p=0.94). For the subset of people with moderate Alzheimer’s disease, there was no significant effect on the NPI (0.25; 95% CI, −1.48 to 1.99; p=0.77) in any of the individual trials or the meta-analysis.

A large review (Butler and Radhakrishnan, 2012) suggested that compared with placebo, memantine may be marginally more effective at reducing neuropsychiatric symptoms (measured by NPI scores) in people with Alzheimer’s disease (rated as very low-quality evidence).

A recent double-blind antipsychotic withdrawal trial (Ballard et al., 2015), randomised 199 people with probable Alzheimer’s disease in residential care and already receiving an antipsychotic to either switch to memantine or to continue the antipsychotic. The primary outcomes were function and agitation (CMAI). Secondary outcomes were NPI, cognition and mortality. At 24 weeks, there were no significant differences in BADLS or CMAI. There were non-significant differences in total NPI at weeks 12 and 24 favouring antipsychotics. The authors concluded that there were no benefits for memantine in the long-term treatment and prophylaxis of clinically significant neuropsychiatric symptoms.

Lewy body dementias:
A pharmaceutical industry-funded RCT assessed memantine in people with Parkinson’s disease dementia or dementia with Lewy bodies (Emre et al., 2010). In the subgroup of people with dementia with Lewy bodies (n=75), at 24 weeks, people taking memantine had improved NPI scores compared with those taking placebo (change from baseline: −4.3 with memantine versus +1.7 with placebo; mean difference −5.9, 95% CI -11.6 to -0.2; p=0.041). This effect was not seen in the subgroup with Parkinson’s disease dementia (n=120), or the combined population.

The NICE 2018 evidence review summarises this and other studies as follows:

- **Dementia with Lewy bodies:** Moderate-quality evidence from one RCT could not differentiate the effect of memantine on care burden. Moderate-quality evidence from one RCT could not differentiate the effect of memantine on neuropsychiatric symptoms.
- **Parkinson’s disease dementia:** Moderate-quality evidence from two RCTs could not differentiate the effect on care burden of memantine. Moderate-quality evidence from two RCTs could not differentiate an effect on neuropsychiatric symptoms for memantine.
- **Mixed Parkinson’s disease dementia or dementia with Lewy bodies:** Moderate-quality evidence from two RCTs could not differentiate an effect on care burden with memantine. Moderate-quality evidence from three RCTs could not differentiate an effect on neuropsychiatric symptoms for memantine.

Moderate to high-quality evidence from a network meta-analysis by the NICE guideline team of nine RCTs showed that memantine has less adverse effects than acetylcholinesterase inhibitors.

**Vascular dementia:**
A Cochrane systematic review (Mc Shane et al., 2006) found that pooled data from two studies indicated a very small beneficial effect of memantine on behaviour (NPI) in people with mild to moderate vascular dementia.

**Frontotemporal dementia:**
The NICE guideline evidence review (2018) stated that low to moderate-quality evidence could not differentiate an effect on neuropsychiatric symptoms in frontotemporal dementia with memantine.
**Summary of the evidence for memantine for non-cognitive symptoms in dementia:**

In summary, the evidence suggests that memantine has **at best** a small benefit for non-cognitive symptoms in Alzheimer’s disease, which may not be clinically significant. The evidence to support the use of memantine in the treatment of non-cognitive symptoms in other dementias remains very limited and not sufficient to generate specific recommendations with regard to its use.

**Recommendation 16**

Memantine is indicated as a cognitive enhancer in people with moderate to severe Alzheimer’s disease, Parkinson’s disease dementia and dementia with Lewy bodies, but it is **NOT** recommended to be prescribed solely for the treatment of **non-cognitive symptoms** in a person with dementia.

Quality of evidence: **Moderate**  
Strength of recommendation: **Strong**  
Responsible for implementation: **National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists**

**3.3.5 Combination therapy (acetylcholinesterase inhibitors with memantine) for non-cognitive symptoms**

A pharmaceutical industry-funded review by Gauthier et al. (2013) examined the evidence for short- and long-term efficacy of combination therapy with acetylcholinesterase inhibitors and memantine in the treatment of moderate-severe Alzheimer’s disease. It included one study (Porsteinsson et al., 2008) which found that for people with moderate-severe Alzheimer’s disease, combination treatment (donepezil and memantine) provided an advantage over donepezil monotherapy in the items of agitation/aggression (p<0.001), irritability/lability (p<0.01), and appetite/eating change (p<0.05). In addition, there was less emergence of new agitation/aggression, irritability/lability, and night-time behaviour (p<0.05) in people receiving combination therapy who were asymptomatic for these symptoms at baseline. However, the change in NPI score from baseline to week 24 in people on combination therapy was a reduction of 0.1. This very small change is not clinically significant.

The GDG felt the scarce evidence available for the effect of combination therapy on non-cognitive symptoms prevented a specific recommendation.

**3.3.6 Summary of evidence and recommendations for acetylcholinesterase inhibitors and memantine**

In summary, the published evidence does not support the use of acetylcholinesterase inhibitors or memantine to treat non-cognitive symptoms in people with Alzheimer’s disease, vascular dementia or frontotemporal dementia. The evidence for the benefit of acetylcholinesterase inhibitors for non-cognitive symptoms in Parkinson’s disease dementia and dementia with Lewy bodies, although weak, coupled with the significant risks of antipsychotics in this population, currently supports their use.

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3 As per the NICE guideline (2018), memantine **monotherapy** is recommended as an option for managing severe Alzheimer’s disease, and in moderate Alzheimer’s disease when acetylcholinesterase inhibitors are not tolerated or contraindicated. For people with Alzheimer’s disease who are already taking an AChE inhibitor, the recommendation from NICE 2018 is to **consider** memantine in addition to an AChE inhibitor in moderate disease and **offer** memantine in severe disease. At this current time, memantine has a licence for use in Ireland in moderate and severe Alzheimer’s disease.
Motivational and affective disturbances may arise in dementia without biological depression (which would be amenable to antidepressant medication). Therefore, clinical judgement based on any history of mood disturbance and the current clinical picture is required when considering antidepressant use in dementia.

Antidepressants were included within the scope of two guidelines (NICE, 2018; NHMRC, 2016) with exact recommendations detailed in Appendix 3.2.8. In summary, the NICE guideline (2018) advised psychological treatments, and not routine antidepressants, for mild to moderate depression. The NHMRC guideline (2016) advised selective serotonin reuptake inhibitors (SSRIs) for agitation if non-pharmacological treatments are inappropriate or have failed. Both guidelines felt it was appropriate to give antidepressants where a person had a pre-existing “major depression” that was ongoing, or relapsed. Of note, the NICE guideline (2018) also included within its review scope the treatment of co-morbid mental health disease (e.g. anxiety, depression) in a person with dementia. However, no supporting evidence was found, and no clinical recommendation was made.

The GDG were reluctant to adapt the wording of the NICE or NHMRC guidelines without reviewing the evidence for antidepressants for depressive symptoms, but also for other non-cognitive symptoms. Thus, the GDG performed a literature search of the evidence for the use of antidepressants in dementia, reviewing evidence published from 2003 to 2018. Appendix 3.2.8 contains details of this empiric evidence.

Of note, the BPS guidance (2015) stated that “Antidepressant medications are useful in the management of depressive symptoms in people with dementia and intellectual disabilities”. However, no evidence is presented to support this statement, and clinicians are advised to consider the evidence below and the final recommendation when deciding on treatment for a person with intellectual disability and dementia.

**3.4 Antidepressant medication**

**Antidepressants for the treatment of depression**

A systematic review examined a total of seven RCTs in people with depression and dementia (Nelson and Devanand, 2011). Two studies demonstrated a beneficial effect from the use of an antidepressant on global depression ratings, and participants taking clomipramine had significantly lower scores and higher remission rates than those on the placebo. The remaining five studies showed no statistically significant difference between the treatment and placebo groups in depression scores. In the meta-analysis of six studies, the Odds Ratio for response to antidepressant versus placebo was 2.12 (95% confidence interval (CI) 0.95–4.70; p=0.07) and for remission was 1.97 (95% CI 0.85–4.55; p=0.11). Neither result is statistically significant. The authors noted that the trials were significantly underpowered to detect differences (Nelson and Devanand, 2011).

A large study with 326 people with probable or possible Alzheimer’s disease (the HTA-SADD study), and depression for at least four weeks, who were randomised to either placebo, sertraline or mirtazapine, failed to demonstrate significant differences in outcome (Cornell Scale for Depression in Dementia (CSDD) score) across all groups (Banerjee et al., 2011). Decreases in depression scores at 13 weeks did not differ between controls and participants receiving sertraline (mean difference 1.17, 95% CI −0.23 to 2.58; p=0.10), or between controls and those receiving mirtazapine (mean difference 0.01, −1.37 to 1.38; p=0.99), or between the mirtazapine and sertraline groups (mean difference 1.16, −0.25 to 2.57;
p=0.11); these findings persisted to 39 weeks. A significant proportion of people had adverse events with the antidepressants (43% with sertraline and 41% with mirtazapine versus 26% with placebo; p=0.01) (Banerjee et al., 2011).

A review in 2012 of 12 studies to determine the efficacy of SSRI and serotonin–noradrenaline reuptake inhibitor (SNRI) therapy for alleviation of comorbid depression in Alzheimer’s disease found that effect size estimates were non-significant, non-heterogeneous and ‘small to null’. The authors concluded that the evidence does not support the efficacy of SSRI/SNRI treatment for symptoms of comorbid depression in Alzheimer’s disease. However, the authors noted that studies differed in terms of criteria for diagnosis of depression, the antidepressant tested, and the outcome measures used (Sepehry et al., 2012).

Similarly, a review by Preuss et al. (2016) concluded that antidepressants have shown limited benefit for depression in dementia. They cautioned that this may be attributed to clinical trials often excluding severely depressed people, so that the apparent treatment benefit may be reduced.

Another recent review on antidepressants found mixed results, with positive effects for apathy shown only for agomelatine (Harrison et al., 2016). The evidence to support the use of antidepressants was found to be limited and equivocal. The authors concluded that due to the absence of benefit compared with placebo, and the increased risk of adverse events, the present practice of using antidepressants as first-line treatment of depression in dementia requires further rationale prior to it being deemed acceptable.

In line with the above evidence, the NICE guideline evidence review (2018) found three (low quality) negative RCTs of sertraline, and one (low quality) negative RCT of mirtazapine, and low quality evidence from a systematic review of 10 RCTs that antidepressants did not have significant benefit compared with placebo for the management of depressive symptoms in people with dementia.

In addition, moderate-quality evidence from three RCTs found higher levels of adverse events in people taking sertraline compared with placebo, but very low-quality evidence from two RCTs could not differentiate levels of serious adverse events. Moderate-quality evidence from 1 RCT containing 215 people found higher levels of adverse events in people taking mirtazapine compared with placebo, but low-quality evidence from the same study could not differentiate levels of serious adverse events.

A recent Cochrane review of antidepressants for depression in dementia, published in August 2018 (after our systematic review ended, but of such relevance that it is included here), included ten studies and found high quality evidence that antidepressants did not lead to significant differences in depression rating scales compared to placebo, but found moderate quality evidence that antidepressants led to more remission of depression (40% versus 21%).

To summarise, current evidence does not show strong support for the use of antidepressants to treat depression in a person with dementia. However, it should be noted that the evidence above does not relate to severe depression, and also studies did not include people with severe dementia.

Antidepressants for the treatment of non-cognitive symptoms

Due to the significant risks of antipsychotic medications, there has been a move in recent years towards considering antidepressants as an alternative treatment for non-cognitive symptoms. In a direct head to head study, in people with dementia hospitalised for BPSD, citalopram (n=53) had similar efficacy to risperidone (n=50) in reducing psychosis (32% reduction with citalopram versus 35% reduction with
Risperidone), rated using the Neurobehavioural Rating Scale (NBRS) (Pollock, 2007). Citalopram had a slightly better effect on reducing agitation (12% versus 8%). Of note, there was a 44% drop-out rate during the trial. Citalopram was associated with a significantly lower burden of adverse side effects (4% versus 19%). The authors cautioned that other studies were needed before citalopram could be recommended for psychosis in dementia.

A narrative review of available evidence in 2011 concluded that antidepressants can be effective in the treatment of BPSD and are ‘generally well tolerated’ in older people with dementia (Henry et al., 2011). Eight of the 15 studies involving an SSRI and three of the four involving trazodone showed benefit in the treatment of BPSD. In the ten trials with a placebo arm and tolerability data, the SSRI was stated to be well tolerated or not significantly different to placebo in seven studies and had worse side effects in three.

A Cochrane review by Seitz et al., that same year, of antidepressants for agitation and psychosis in dementia found relatively few studies of sufficient quality for inclusion. Overall, there was a significant reduction with antidepressants compared to placebo in the CMAI total score (mean difference -0.89; 95% CI -1.22 to -0.57), noting that results were heavily influenced by one large study. There were no significant differences in NPI score with SSRIs compared to placebo in one study. Another study found citalopram improved the NBRS after controlling for baseline severity of the NBRS score although the unadjusted mean difference was not statistically significant (-7.70, 95% CI: -16.57 to 1.17). One study of trazodone compared to placebo did not find any significant difference in the change in CMAI total scores (mean difference 5.18, 95% CI, -2.86 to 13.22). There was no difference in the rates of trial withdrawals due to adverse events for SSRIs compared to placebo for four studies reporting this outcome. Three other studies compared SSRIs to typical antipsychotics, with two included in a meta-analysis where there was no statistically significant difference in the change in the CMAI total scores with treatment (mean difference 4.66, 95% CI: -3.58 to 12.90). There was also no difference in adverse events for SSRIs compared to typical antipsychotics.

Seitz et al. concluded that “sertraline and citalopram were associated with a reduction in symptoms of agitation, and that SSRIs and trazodone appear to be well tolerated”. However, they concluded that more studies are required to determine if antidepressants are safe and effective treatments for agitation and psychosis.

The more recent Cit-AD study, a multicentre RCT which explored the efficacy of a 30-mg daily dose of citalopram for agitation in people with Alzheimer’s disease, showed a significant decrease in agitation (consistent across several outcome measures) and caregiver distress (Porsteinsson et al., 2014). It should be noted that this dose exceeds current recommended doses for older people - refer to the cardiac conduction disturbance section below.

A recent review of antidepressants for people with dementia and concomitant depression included one study (n=44) that reported on global BPSD outcomes. No significant effect was observed with antidepressants (standard mean difference −0.25, 95%CI −0.85 to 0.35; very low-quality evidence) (Dyer et al., 2017).

The evidence review for the NICE guidelines (2018) looked at antidepressants for “other non-cognitive symptoms” (i.e. not depression and anxiety) and determined that there was very low- to moderate-quality evidence from up to four RCTs containing 419 people which found improvements in CMAI scores with SSRIs versus placebo, but could not differentiate total neuropsychiatric symptoms or behavioural symptoms. Adverse events were also similar to placebo. In addition, there was very low- to moderate-
quality evidence from up to two RCTs containing 103 people which could not differentiate any outcome measures between: SSRIs and atypical antipsychotics; SSRIs and typical antipsychotics; trazodone and placebo: or trazadone and typical antipsychotics.

In a recent review of frontotemporal dementia by Young et al. (2018), a small number of studies are summarised relating to the treatment of BPSD in frontotemporal dementia with antidepressants (mainly SSRIs). Within these, Herrmann et al. (2012) found citalopram at 40 mg daily (note this high dose is not recommended for older people) led to a decrease in symptoms including irritability, depression, apathy, and disinhibition, while also improving overall NPI scores. Studies of sertraline in treating frontotemporal dementia symptoms were limited to mainly observational studies. An RCT of trazadone at dosages of at least 300 mg/day over 12 weeks reported decreased symptoms of problematic eating, agitation, irritability, dysphoria, and depression, although mild adverse events were noted, including fatigue, dizziness, and hypotension (Lebert et al., 2004).

To summarise, evidence suggests a possible benefit from SSRIs (sertraline and citalopram) in reducing symptoms of non-cognitive symptoms and in particular agitation and psychosis, but there is not a strong evidence base to support this, and there are significant risks with SSRIs, despite their apparent tolerability in reported studies of people with non-cognitive symptoms (see section 3.5.2). It is not clear if usual doses of citalopram would have the same benefit as the excessively high doses used in some of the positive RCTs.

**Antidepressants for sexual disinhibition**

Guay et al (2008) performed a review of treatments for “inappropriate sexual behaviours”, in people with dementia, finding mainly observational studies. The authors concluded that there was potentially a role for antidepressants (preferentially SSRIs) for this indication.

A more recent review (Cipriani et al., 2015) included two more recent case studies and noted that there have still been no RCTs on the efficacy or safety of any medication for sexual disinhibition. This was still the case as of 2016 (De Giorgi et al., 2016). Thus the GDG rated the evidence for antidepressants for the treatment of sexual disinhibition as very low quality and felt that a specific recommendation could not be made. Instead, clinicians are recommended to try non-pharmacological interventions (seeking triggers, using distraction, etc.) and to seek specialist advice.

**Antidepressants for sleep problems**

Apart from hypnotics and z-drugs, trazodone and mirtazapine are prescribed at night and can cause drowsiness, and so clinicians may consider their use to improve sleep. A short-term RCT of mirtazapine for sleep problems in dementia (Scoralick et al., 2017), where 24 people with Alzheimer’s disease and a sleep disorder received either mirtazapine or placebo for two weeks, found increased daytime sleepiness with mirtazapine but no improvement in the duration or efficiency of nocturnal sleep.

The evidence review for the NICE guideline (2018) and a separate Cochrane review (McCleery et al., 2016) both described one (moderate to high quality) RCT containing 30 people (Camargos et al., 2014) which found higher levels of total night-time sleep and better sleep efficiency in people with sleep problems taking low dose trazodone (50mg) versus placebo over a two week period, but no difference in number of night-time awakenings, total daytime sleep, number of daytime naps or activities of daily living. Compared with the placebo group, trazodone users slept 42.5 more minutes per night and had their night time ‘percent of time asleep’ increased by 8.5%. Trazodone did not cause significant daytime sleepiness or naps, or affect cognition or function. There were no differences in frequency or severity rating of adverse events between the groups (Camargos et al., 2014).
To summarise, the evidence for trazodone improving sleep is based on one small and short-term RCT, and there is no evidence relating to mirtazapine, and thus a recommendation can not be made for these with regards to treating sleep disturbance at this time.

### 3.4.2 Particular cautions with antidepressants

**Serotonin syndrome**

This is a syndrome induced by excessive blood levels of serotonin. Symptoms can range from mild to severe and can include hyperthermia, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhoea. Complications may include seizures and rhabdomyolysis (muscle breakdown), and death.

An AMDA guideline on “Delirium and acute problematic behaviour in the long-term care setting” discusses that ‘inappropriately prescribed’ SSRIs in residential care can lead to exacerbation of agitation and delirium and hence should be used cautiously (AMDA, 2013). In particular, consecutive (or concurrent) use of numerous antidepressants for diverse symptoms (e.g., depression, anxiety and pain) can increase the risk of adverse effects including a higher risk of developing serotonin syndrome.

Of note, other medications apart from antidepressants can contribute to this syndrome, and therefore care is needed when co-prescribing SSRIs, SNRIs or tricyclic antidepressants with each other, or with other commonly prescribed medications such as opioids or anti-nausea medications.

**Anticholinergic effects**

There was general consensus among the guidelines that antidepressants with anticholinergic effects (i.e. tricyclic antidepressants) should be avoided in people with dementia (NICE, 2016; NHMRC, 2016). Some SSRIs may also have weak anticholinergic effects (e.g. paroxetine, fluoxetine). If this is a concern, prescribers are referred to individual medication SmPCs for more details (see: [http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine](http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine)).

**Other risks**

In the Cit-AD study, a multicentre RCT which explored the efficacy of a 30-mg daily dose of citalopram for agitation in people with Alzheimer’s disease (and showed a significant decrease in agitation), there was a concerning level of QTc prolongation on electrocardiograms, as well as cognitive worsening, in the citalopram treated people (Porsteinsson et al., 2014). The current recommendation is that citalopram dose is not increased beyond 20mg in an older person. The risks of cardiac conduction disturbance with TCAs are also well recognised.

The risk of hyponatraemia with most antidepressants is well recognised, and if it occurs, can mimic worsening of dementia symptoms (e.g. confusion, falls). Antidepressants have been reported to increase the risk of falls in nursing home residents with dementia (Sterke et al., 2008).

Taking all the above evidence together, there is no current evidence to support the use of antidepressants to treat depression in a person with dementia. However, there is a strong evidence base for the benefit of antidepressants for depression outside of dementia, and the GDG felt a person with dementia and severe comorbid depression should be treated on the same basis as a person without dementia. The GDG agreed with the NICE guideline (2018) position that if someone has previously responded well to antidepressant treatment, then it would be appropriate to use the same treatment if the person later develops dementia and has a suspected recurrence of depression. However, it must be acknowledged that it can be challenging to accurately diagnose depression in more advanced stages of dementia, even using appropriate tools such as the Cornell Scale for Depression in Dementia, and the clinician has to carefully weigh up the risks of a trial of an antidepressant with the likelihood that symptoms may represent a recurrence of depression (e.g. apathy, refusing food).
The GDG felt that given the good evidence base to demonstrate a lack of benefit, and the risk of side effects, antidepressants should not be used for mild depression in a person with dementia, and instead the person should receive non-pharmacological treatments, including psychological treatment.

In moderate depression, the GDG felt that episodes that have not responded to psychological treatment, might then warrant a cautious trial of antidepressants. And in severe depression, the GDG similarly felt that antidepressants, despite no studies to guide treatment decisions, warranted consideration based on evidence in other populations.

Although there is some evidence for antidepressants (specifically SSRIs) reducing non-cognitive symptoms (particularly agitation), the GDG were cautious, given the risk of side effects, and felt that more evidence is required to make a definitive recommendation. Hence this is included as a Good Practice Point only.

Given the extremely limited evidence base, the GDG did not feel a recommendation could be made for trazodone or mirtazapine improving sleep in person with dementia at this time.

**Recommendation 17**

In people with mild to moderate dementia\(^8\), and mild to moderate depression and/or anxiety, psychological treatments should be considered. Antidepressants may be considered to treat severe comorbid depressive episodes in people with dementia, or moderate depressive episodes that have not responded to psychological treatment.

Quality of evidence: Moderate
Strength of recommendation: Conditional
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurses, pharmacists and health and social care professionals

**Good Practice Point 10:** Apart from their role in the treatment of depression, antidepressants may have a role in the treatment of other severe non-cognitive symptoms in a person with dementia (such as agitation), where pharmacological treatment has been deemed necessary. If trialled for other non-cognitive symptoms, antidepressants should be used with caution, with close monitoring for side effects.

### 3.4.3 Cost effectiveness of antidepressants for depression in a person with dementia

Banerjee et al. (2013) compared the cost effectiveness of two antidepressants, mirtazapine and sertraline, with placebo in the treatment of depression in people with dementia, as part of the HTA-SADD randomised control trial, conducted in nine old age psychiatry services in England. No significant differences in costs and quality adjusted life years (QALY) gains was reported between treatment groups. Neither mirtazapine nor sertraline were considered cost effective when compared with placebo if depression scores were the primary outcome. When costs and QALYs were considered alongside each other, mirtazapine was the most likely to be cost effective. It must be noted that the economic evaluation did not extend beyond the short time frame of the clinical study (39 weeks); nor are the findings extrapolated to people with severe dementia or severe depression, where effectiveness and cost effectiveness may be different. Appendix 5, Part A, has more details of this cost effectiveness study.

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\(^8\) There is no evidence as yet to guide the treatment of depression in people with severe dementia, as they were excluded from trials. Thus, the recommendation only applies to people with mild to moderate dementia.
3.5 Anticonvulsant medication

There is evidence to support the use of anticonvulsants as mood stabilisers in major depressive disorders. These are sometimes also used in non-cognitive symptoms, so it was decided by the GDG to include these within the scope of this guideline. Anticonvulsants were referred to in just one guideline (NICE, 2018). The GDG thus performed a literature search of the evidence for the use of anticonvulsants, reviewing evidence published from 2003 to 2018.

The BPS guidance on Dementia and People with Intellectual Disabilities (2015) states that medications such as carbamazepine or valproate may be considered if there is evidence of rapid cycling mood disorder or significant mood fluctuations, but not to offer mood stabilisers to manage agitation or aggression in people living with dementia, unless they are indicated for another condition.

The NICE (2018) guideline used the term ‘mood stabilisers’ to refer to carbamazepine and valproate in the context of non-cognitive symptoms. The recommendation is as follows: “Do not offer mood stabilisers to manage agitation or aggression in people living with dementia, unless they are indicated for another condition”.

A review of the use of anticonvulsant mood stabilisers (carbamazepine, valproic acid, gabapentin, lamotrigine, topiramate) in the treatment of BPSD (Konovolov et al., 2008), which included seven RCTs (two of carbamazepine and five of valproate), found that one study showed statistically significant improvement of BPSD; five studies showed no significant difference; one study showed statistically significant worsening of symptoms. The majority of the studies reported significantly more frequent adverse effects in the medication group. The authors concluded that although clearly beneficial in some people, anticonvulsant mood stabilisers could not be recommended for routine use in the treatment of BPSD (Konovalov et al., 2008).

The following sections provide the evidence for specific anticonvulsants.

3.5.1 Carbamazepine

A review by Butler and Radhakrishnan (2012) concluded that compared with placebo, carbamazepine may be more effective at improving symptoms (measured by Brief Psychiatric Rating Scale [BPRS]) in people with dementia. Of note, this contained the same two carbamazepine studies as the review by Konovalov et al. (2008).

There was a specific evidence review by NICE in 2015 (Evidence summary [ESUOM40]: Management of aggression, agitation and behavioural disturbances in dementia: carbamazepine). This described four very small and short term RCTs from 1982-2001 (two included in the above reviews also) with a total population size of 97, which had notable limitations, and provided conflicting results about the efficacy of carbamazepine for managing aggression, agitation and behavioural disturbances in people with dementia. The evidence summary concluded that larger, longer-term RCTs are required to confirm efficacy and safety.

3.5.2 Gabapentin

Only one review was found that focused on gabapentin in treating BPSD (Kim et al., 2008). This contained 11 case reports, 3 case series and 1 retrospective chart review. In most of these studies and reports, gabapentin was reported to be ‘well-tolerated’ and an effective treatment for BPSD. A further chart review in 2012 (Tampi et al; n= 20) found gabapentin to be well tolerated as an adjunct to an antipsychotic in BPSD. However, there has been no RCT of gabapentin performed to date. The GDG note the significant side effect profile of gabapentin, particularly somnolence and dizziness.
3.5.3 Sodium valproate

Sodium valproate is also known as sodium valproic acid and in the US is also marketed as its derivative, Divalproex Sodium. These can be taken as broadly equivalent in terms of extrapolating results from studies.

An early review noted that valproate preparations are ineffective in treating agitation among individuals with dementia and valproate therapy is associated with an unacceptable rate of adverse effects (Lonergan et al., 2009).

The review by Butler and Radhakrishnan (2012) found three RCTs of sodium valproate/valproic acid of ‘sufficient quality’, none of which found a significant difference between groups in outcomes measured by the BPRS or the Bech-Rafaelsen Mania Scale.

A Cochrane review published in October 2018 (after our systematic review ended but being of such relevance that it is included here) included five studies with 430 participants. The two moderate quality studies found no benefit with valproate, based on the BPRS, and the three very low-quality studies found no benefit using the CMAI. The authors concluded that “valproate therapy cannot be recommended for management of agitation in dementia. Further research may not be justified, particularly in light of the increased risk of adverse effects in this often frail group of people. Research would be better focused on effective non-pharmacological interventions for this patient group, or, for those situations where medication may be needed, further investigation of how to use other medications as effectively and safely as possible”.

3.5.4 Lamotrigine

In a 16-week, preliminary open-label trial (n=40 people with Alzheimer’s disease), mean changes from baseline NPI scores and the two NPI subscales (anxiety and irritability) were not significantly different compared to placebo. The mean decrease from baseline on the NPI agitation subscale, however, was significantly greater in the lamotrigine therapy (p<0.05) (Suzuki and Gen, 2015). Furthermore, the mean decrease from baseline in the diazepam-equivalent dose co-prescribed was significantly greater in the lamotrigine therapy group than in the control group (p<0.05). Although promising, this is the only study to date of lamotrigine for BPSD.

3.5.5 Summary of evidence and recommendations for anticonvulsant medication

In summary, there is currently very limited evidence to support the use of anticonvulsants in non-cognitive symptoms, with either no available RCTs (gabapentin), one small open label trial only (lamotrigine), several negative RCTs (carbamazepine), and a negative Cochrane review (valproate).

Thus, the quality of evidence is very low for gabapentin and lamotrigine; low for carbamazepine; and moderate for valproate. The GDG have thus assigned the quality of evidence overall for anticonvulsant medication as low.

Recommendation 18

Anticonvulsant medication is indicated for the treatment of seizures, bipolar disorder, or as an adjunctive therapy for pain, but is NOT recommended as a treatment for non-cognitive symptoms in a person with dementia.

Quality of evidence: Low
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists
3.6 Benzodiazepines

Benzodiazepines are anxiolytic medications, i.e. they reduce anxiety, and thus it is understandable that a clinician may consider using them to treat anxiety in a person with dementia. It is estimated that 8.5-20% of people with dementia receive benzodiazepines (Defrancesco et al., 2015). However, benzodiazepines have significant risks. Benzodiazepines can be classified as short, intermediate or long acting depending on the half-life.

There is useful guidance from the HSE’s Medicines Management Programme (2018) (https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxiety-insomnia/bzraguidancemmpfeb18.pdf) on the appropriate prescribing of benzodiazepines and z-drugs (BZRA) in the treatment of anxiety and insomnia (not specifically in people with dementia). This advises caution with the use of benzodiazepines especially in older aged populations, due to the risks associated with them, including sedation, drowsiness, and lethargy. GDG members also note the significant issues with acute withdrawal from benzodiazepines. There are also concerns about benzodiazepines worsening cognitive decline (Billioti de Gage et al., 2015), the evidence for which is not clear at present, and which is outside the scope of this guideline.

The MMP guidance (2018) recommends that:

- “Benzodiazepines should be prescribed for the shortest possible duration and to a maximum period of two to four weeks for the treatment of anxiety”.
- “BZRA (benzodiazepines and z-drugs) should only be prescribed for a period of a few days to two weeks for insomnia”.

Please refer to this guidance document for further details of individual medication licence with regards to dose and duration (Appendix D). In addition, the MMP guidance contains useful information on deprescribing benzodiazepines following short-term and long-term use (Medicines Management Programme, 2018; section 11, page 25), including a sample letter to patients (Appendix E), a patient information leaflet (Appendix F), and two user guides on sleep and relaxation and sleep (Appendix B and C).

Benzodiazepines were not included in any dementia guideline and so a systematic review of empiric evidence published from 2003 to 2018 was performed. However, the comments in the AMDA Clinical Guideline for “Delirium and Acute Problematic Behaviour in the Long Term Care Setting” (2013) with regards to benzodiazepines are worth noting. This guideline noted the ‘inappropriate use’ of benzodiazepines in people with delirium and psychosis and stated that “all benzodiazepines are associated to some degree with adverse consequences such as increased confusion, sedation, falls, and hip fractures in a susceptible population. In addition, they may cause increased agitation, insomnia, and other side effects”. The guideline also stated that tolerance occurs rapidly with short half-life benzodiazepines and that these are “best avoided, being often ineffective and commonly causing oversedation and rebound effects (anxiety and insomnia) after each dose”.

Butler and Radhakrishnan (2012) found no new RCTs of benzodiazepines for the treatment of BPSD since the 2006 NICE guideline which had identified one RCT of 135 people with Alzheimer’s disease or vascular dementia (from 2002) comparing intramuscular lorazepam versus placebo, with a follow-up of only 24 hours (NICE, 2006). (The lorazepam significantly reduced aggressive behaviour or agitation as measured by the CMAI at 2 hours (SMD –0.40; 95% CI –0.74 to –0.06)).
A review by Tampi et al. (2014) of five RCTs included one RCT comparing alprazolam to lorazepam (1991). Although agitation was reduced more with alprazolam, it is not possible to know what the placebo response would have been. Another trial compared lorazepam to haloperidol (1998) in nursing home residents already receiving haloperidol, who then entered a cross-over trial without deterioration in BPSD while on alprazolam. The third trial compared intramuscular (IM) lorazepam to IM olanzapine and placebo (summarised above) and the fourth trial (1975) compared diazepam to thioridazine. The final trial compared oxazepam to haloperidol and diphenhydramine (1990), with all having “modest” effects on behaviours. Overall, there was no significant difference in efficacy between these active drugs, except thioridazine was superior to diazepam. There also was no significant difference between the active drugs in terms of tolerability. A slightly later review (Defrancesco et al., 2015) did not find any other RCTs.

Thus the evidence for the use of benzodiazepines in non-cognitive symptoms remains limited with no RCTs in the last 15 years. However, the GDG felt the well-recognised risks of benzodiazepines most likely applied as much, or even more, to a person with dementia. The GDG also noted that in clinical practice, benzodiazepines can sometimes paradoxically increase agitation in a person with dementia. The GDG did however recognise a need occasionally for short-term benzodiazepine use for severe anxiety, where a trial of a benzodiazepine would be justified given the person’s obvious distress, and anticipating that in such a highly anxious state, non-pharmacological interventions may not be feasible. The following recommendation takes this clinical experience into account, despite the lack of evidence to date.

**Recommendation 19**

Due to the very limited evidence to support the use of benzodiazepines in the management of non-cognitive symptoms in a person with dementia, and their significant adverse effects, they should be avoided for the treatment of non-cognitive symptoms, and usage strictly limited to the management of short-term severe anxiety episodes.

Quality of evidence: Low
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

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3.7 Z-drugs (hypnotics) and melatonin


Among international guidelines, only one included sleep disturbance in dementia in their scope (NICE, 2018), Appendix 3.2 (Appendix table 3.2.8). This recommended to consider a “personalised multicomponent sleep management approach”, and not offer melatonin for insomnia, but did not specifically address z-drugs.

The BPS guidance on Dementia and People with Intellectual Disabilities (2015) similarly states that in individuals with intellectual disability with dementia, non-pharmacological intervention should be attempted initially to treat sleep disorders. If these approaches do not produce any significant benefits and the risks continue, a pharmacological approach may be considered along with non-pharmacological approaches.

A review of the treatment of sleep disturbances in Alzheimer’s disease found no RCTs of Z-type medications for insomnia in dementia (Salami et al., 2011). A later review by Ooms et al. (2016) similarly found no trials of z-drugs.

In a recent Cochrane review that included four melatonin trials with a total of 222 participants (McCleery et al., 2016), although no serious harms were reported, there was reasonable evidence that melatonin did not improve sleep in people with Alzheimer’s disease. The NICE 2018 guideline included three of these studies (rating them as low- to moderate-quality), and concluded that they could not detect a difference in total night-time sleep time, ratio of daytime to night-time sleep, sleep efficiency, nocturnal time awake, number of night-time awakenings, carer-rated sleep activity, activities of daily living, sleep latency or numbers of adverse events between people taking melatonin versus placebo.

Thus, evidence to support z-drugs improving sleep in dementia is weak. The available melatonin trials were consistently negative, indicating that it should not be used for the treatment of sleep disturbance in a person with dementia. The single (negative) study assessing mirtazapine for sleep problems in dementia is detailed in section 3.4.1.

Recommendation 20
A personalised sleep management regimen may be considered for sleep disorders in a person with dementia.

Quality of evidence: Moderate
Strength of recommendation: Conditional
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurses, pharmacists and health and social care professionals
Recommendation 21
Melatonin should NOT be used for sleep disorders in people with dementia.

Quality of evidence: Moderate
Strength of recommendation: Strong
Responsible for implementation: National Implementation Team; Local Implementation teams; Local service managers; doctors, nurse prescribers and pharmacists

Good Practice Point 11: There are no studies of z-drugs for sleep disorders in people with dementia. Due to their significant side effects, if z-drugs are considered, it should be for the shortest period possible (or as specified by medication license).
3.8 Supporting decision making with regards to psychotropic medications

Consent is the giving of permission or agreement for an intervention, receipt or use of a service or participation in research following a process of communication in which the service user has received sufficient information to enable him/her to understand the nature, potential risks and benefits of the proposed intervention or service. The National Consent Policy (May 2017) (https://www.hse.ie/eng/services/list/3/acutehospitals/hospitals/ulh/staff/resources/pppgs/nationalconsentpolicy/nationalconsentpolicy.pdf) notes that the need for consent extends to all interventions conducted by or on behalf of the HSE on service users in all locations.

Of note, on very rare occasions, a person with dementia may require treatment on an involuntary basis under the Mental Health Act (2008) (http://www.irishstatutebook.ie/eli/2008/act/19/enacted/en/html) for a co-existing mental health disease, noting that most people in mental health units are there on a voluntary basis. The Mental Health Act places limits on consent with regard to the provision of treatment to involuntary patients. Part 4 (Section 56) allows for an exception to consent for treatment, where the consultant psychiatrist who is responsible for the care and treatment of the person deems the treatment to be necessary to safeguard the person’s life, to restore his/her health, to alleviate his/her condition or to relieve his/her suffering, and where the person because of his/her mental disorder is regarded to be incapable of giving consent. The basis on which any person (with dementia or otherwise) might be detained under the Mental Health Act is outside the scope of this guideline. The following sections assume a person is not being treated under Section 56 of the Mental Health Act.

3.8.1 What information must be discussed?

A general rule is to provide information that a reasonable person in the service user’s situation would expect to be told. This is in line with ethical and professional standards as well as the legal standard applied by Irish courts. Such information includes the likelihood of:

- side effects or complications of an intervention;
- failure of an intervention to achieve the desired aim; and
- the risks associated with taking no action or with taking an alternative approach.

A risk is material (significant) if someone in the person’s position would attach significance to it. Such risks must be disclosed to the person. Thus, common, even if minor, side effects should be disclosed as should rare but serious adverse outcomes.

Material risks when prescribing antipsychotic drugs, for example, will include (depending on the particular medication and any comorbidities) sedation, parkinsonism, falls, cardiac arrhythmias, metabolic syndrome, stroke and death. The fact that a person might be upset or refuse treatment as a result of receiving information as part of the consent process is not a valid reason for withholding information that they need or are entitled to know.

3.8.2 Capacity of a person to make decisions

For consent to an intervention to be valid, the service user must:

- have received sufficient information in a comprehensible manner about the nature, purpose, benefits and risks of an intervention;
- not be acting under duress; and
- have the capacity to make the particular decision.
Best practice favours a ‘functional’ or decision-specific approach to defining decision-making capacity: that capacity is to be judged in relation to a particular decision to be made, at the time it is to be made - in other words it should be issue specific and time specific – and depends upon the ability of an individual to comprehend, reason with and express a choice with regard to information about the specific decision. This approach is also adopted in the Assisted Decision Making (Capacity) Act; (http://www.irishstatutebook.ie/eli/2015/act/64/enacted/en/html).

There is a presumption of capacity and it must not be assumed that someone lacks capacity to make a decision solely because they have dementia. It is important to give those who may have difficulty making decisions the time and support they need to maximise their ability to make decisions for themselves.

3.8.3 Making decisions if capacity is absent

The National Consent Policy notes:

No other person such as a family member, friend or carer and no organisation can give or refuse consent to a health or social care service on behalf of an adult service user who lacks capacity to consent unless they have specific legal authority to do so.

However, it may be helpful to include those who have a close, ongoing, personal relationship with the service user, in particular anyone chosen by the service user to be involved in treatment decisions, in the discussion and decision-making process pertaining to health and social care interventions.

Their role in such situations is not to make the final decision, but rather to provide greater insight into the individual’s previously expressed views and preferences and to outline what they believe the individual would have wanted. In some cases, involvement of those close to the service user will facilitate the service user in reaching a decision in conjunction with health/social care providers.

Such ‘specific legal authority’ to consent (or refuse consent) on behalf of another person is rarely available at present unless, for example, the person is a Ward of Court.

The Assisted Decision Making (Capacity) Act will, when it is fully commenced, provide for a number of formal mechanisms to support someone, where possible, to make their own decisions and, if this is not possible, for appointment of a Designated Healthcare Representative by the circuit court to make specific decisions, such as regarding psychotropic use, on the person’s behalf. The Enduring Power of Attorney provisions will be altered so that someone can appoint an Attorney to make healthcare decisions on their behalf if they later lose capacity to make such decisions. (The current Enduring Power of Attorney law does not cover healthcare decisions). Finally, a person may draw up an Advance Healthcare Directive describing legally-binding treatments they wish to refuse in advance.

In addition, the role of an independent advocate is referenced in the Assisted Decision-Making (Capacity) Act. An advocate is a person who acts on behalf of and in the interests of a person or group. The advocate facilitates a person or group to express their wishes and preferences and to state their views on matters affecting their lives and well-being (SAGE Advocacy, 2015). It has been agreed through amendments to the Assisted Decision-Making (Capacity) Act that an ‘advocate’ will be included as an ‘Intervenor’ within the meaning of the legislation. It is proposed that Codes of Practice will be developed for the role of an independent advocate within the Assisted Decision-Making (Capacity) Act 2015.
Relevance to this guideline
The principles and guidance provided in the National Consent Policy apply to all decisions regarding the prescribing of psychotropic medication in people with dementia. As with other proposed interventions, people must be informed of all significant risks when prescription of psychotropic drugs is proposed. Material risks when prescribing antipsychotic drugs, for example, will include (depending on the particular medication and any comorbidities) sedation, parkinsonism, falls, cardiac arrhythmias, metabolic syndrome, stroke and death.

If a person with dementia lacks capacity to make a decision regarding psychotropic medications, it may be helpful to include those who have a close, ongoing, personal relationship with the person, in particular anyone chosen by the person to be involved in treatment decisions (including an independent advocate), in the discussion and decision-making process. In this guideline, such people are described as ‘Decision Supporters’.

When the Assisted Decision Making (Capacity) Act is fully commenced, there may in some situations be people with decision-making authority under this legislation who must be consulted regarding use of psychotropic and who will then give or withhold consent regarding the use of these medications. One of the codes of practice under section 103 of the Assisted Decision Making (Capacity) Act will provide guidance to health care professionals about circumstances in which urgent treatment may be carried out without consent and what type of treatment may be provided in these circumstances.

3.8.4 Covert administration of medications
Non-adherence rates for psychotropic medications are estimated to be between 20% to 50% and this can increase considerably in people with psychosis or mental health issues (70%) (Whitty and Devitt, 2005). If an appropriate, and legal, decision has been made that the person requires medication, but the person personally refuses to take it, it is essential to re-consider the necessity of the treatment, and whether it is so essential that it needs to be given by deception (Whitty and Devitt, 2005). Efforts should be made to gain an understanding of the person’s reasons for refusal, where possible. As well as a risk-benefit of the medication itself, there also needs to be consideration of the additional risks of giving the medication covertly. The decision to use covert medication must be a multidisciplinary discussion which includes all practitioners directly or indirectly involved in the covert medication, and with the expert guidance of a pharmacist, in addition to the person’s ‘relevant supporter or representative’.

It is outside the scope of this guideline to make a recommendation on the use of covert administration of psychotropic medications. Doctors, nurses, pharmacists and health and social care professionals who may be required to administer covert medication should make themselves fully aware of guidance from their own Professional Bodies with regard to covert administration and they should ensure that they are acting in accordance with the Assisted Decision Making (Capacity) Act 2015, when it is fully commenced.
Appendices

Only appendices 3 and 7 are presented here as they are key to interpretation of the recommendations in this summary guideline (appendix 3.3 and 3.4 in full version only).

Refer to the full guideline report for the remaining appendices:

- **Appendix 1** Guideline Development Group terms of reference
- **Appendix 2** Search strategy
- **Appendix 4** Consultation report
- **Appendix 5** Economic assessment
  - Part A: Economic evidence summary
  - Part B: Budget impact analysis
- **Appendix 6** Implementation plan
- **Appendix 8** Monitoring and audit
- **Appendix 9** Levels of evidence in international guidelines
- **Appendix 10** Flowchart for guideline development process
- **Appendix 11** Side effects associated with psychotropic medications
### Appendix 3: Evidence tables

#### Appendix 3.1: Coverage within international guidelines of evidence related to key questions

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* AGREE II scoring performed by two independent raters; full item scoring available on request
** No robust guideline recommendation found for Acetylcholinesterase inhibitors and memantine, or for Benzodiazepines
### Appendix 3.2: Matrix tables for evidence from guidelines and systematic empiric literature pertaining to recommendations

### Appendix 3.2.1: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 1

**Key Question 1a:** What is the process that needs to take place when considering the use of psychotropic medication in a person with dementia, to optimise safety and efficacy?

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<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA 2016</td>
<td>APA recommends that patients with dementia be assessed for the type, frequency, severity, pattern, and timing of symptoms. APA recommends that patients with dementia be assessed for pain and other potentially modifiable contributors to symptoms as well as for factors, such as the subtype of dementia, that may influence choices of treatment. APA recommends that before non-emergency treatment with an antipsychotic is initiated in patients with dementia, the potential risks and benefits from antipsychotic medication be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient’s surrogate decision maker (if relevant) with input from family or others involved with the patient.</td>
<td>1C= low evidence, but strong rec. 1C= low evidence, but strong rec. 1C= low evidence, but strong rec.</td>
<td>Adapted as recommendation 1 (plus detail in footnote) Adapted as recommendation 1 (plus detail in footnote) Adapted as GPP (for psychotropic medication)</td>
</tr>
<tr>
<td>NICE 2018</td>
<td>Before starting non-pharmacological or pharmacological treatment for distress in people living with dementia, conduct a structured assessment to: • explore possible reasons for the person’s distress and • check for and address clinical or environmental causes (for example pain, delirium or inappropriate care)</td>
<td>Not stated but wording is strong</td>
<td>Adapted as recommendation 1</td>
</tr>
</tbody>
</table>
### Appendix 3.2.2: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 2

#### Key Question

i) and ii)

When should non-pharmacological interventions be used in the management of non-cognitive symptoms?

When should pharmacological interventions be used in the management of non-cognitive symptoms?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA 2016</td>
<td>APA recommends reviewing the clinical response to nonpharmacological interventions prior to nonemergency use of antipsychotic medication to treat agitation or psychosis</td>
<td>1C= low evidence, but strong rec.</td>
<td>Adapted as recommendation 2</td>
</tr>
<tr>
<td>NHMRC 2016</td>
<td>People with dementia who develop BPSD should usually be treated using non-pharmacological approaches in the first instance. If pharmacological management is used, this should complement, not replace, non-pharmacological approaches. Pharmacological intervention should usually only be offered first if the person, their carer(s) or family is severely distressed, pain is the suspected cause, or there is an immediate risk of harm to the person with dementia or others (i.e., very severe symptoms).</td>
<td>Practice Point</td>
<td>Adapted as recommendation 2</td>
</tr>
<tr>
<td>NICE 2018</td>
<td>As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia. Ensure that people living with dementia can continue to access psychosocial and environmental interventions for distress while they are taking antipsychotics and after they have stopped taking them. Only offer antipsychotics for people living with dementia who are either: • at risk of harming themselves or others or • experiencing agitation, hallucinations or delusions that are causing them severe distress.</td>
<td>Not stated but strong wording</td>
<td>Adapted as recommendation 2</td>
</tr>
</tbody>
</table>

#### Systematic Reviews

<table>
<thead>
<tr>
<th>Reference</th>
<th>Conclusions</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jutkowitz et al., 2016</td>
<td>Strength of evidence was generally insufficient to draw conclusions regarding efficacy or comparative effectiveness of care delivery interventions for agitation and aggression in people with dementia in residential care.</td>
<td>Low</td>
</tr>
<tr>
<td>Abraha et al., 2017</td>
<td>Music therapy and behavioural management techniques were effective for reducing BPSD.</td>
<td>Low</td>
</tr>
<tr>
<td>Dyer et al., 2017</td>
<td>A significant improvement in BPSD was seen with: functional analysis-based interventions (GRADE quality of evidence moderate; standardized mean difference (SMD) -0.10, 95% CI -0.20 to 0.00).</td>
<td>Moderate</td>
</tr>
<tr>
<td>van der Steen et al., 2018</td>
<td>Music therapy probably reduces depressive symptoms and improves overall behavioural problems (in the short term). It may also improve emotional well-being and quality of life and reduce anxiety, but may have little or no effect on agitation or aggression. Long-term effects weren't clear.</td>
<td>Moderate (for depression, behaviour, agitation, aggression)</td>
</tr>
</tbody>
</table>

#### RCT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Conclusions</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieper et al., 2016</td>
<td>Behavioural management training for staff resulted in improved agitation and neuropsychiatric symptoms and less antidepressant medication use.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
### Appendix 3.2.3: Matrix table for evidence from guidelines and systematic empiric literature pertaining to route of administration of psychotropic medications (GPP 4 and 5)

<table>
<thead>
<tr>
<th>Key Question 2</th>
<th>What route of administration should be used if psychotropic medication is deemed necessary for the management of BPSD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline</td>
<td>Recommendation</td>
</tr>
<tr>
<td>NHMRC 2016</td>
<td>If medications are necessary for the control of violence, aggression and extreme agitation in people with dementia, oral medication <strong>should</strong> be offered before parenteral medication.</td>
</tr>
<tr>
<td></td>
<td>If parenteral treatment is necessary for the control of violence, aggression and extreme agitation, intramuscular administration is preferable because it is safer than intravenous administration.</td>
</tr>
<tr>
<td></td>
<td>Intravenous administration should be used only in exceptional circumstances. Vital signs <strong>should</strong> be monitored after parenteral treatment. Health professionals should be aware that loss of consciousness can be mistaken for sleep. If the person appears to be or is asleep, more intensive monitoring is required because of the risk of loss of consciousness.</td>
</tr>
<tr>
<td></td>
<td>If parenteral medication is necessary for the control of violence, aggression and extreme agitation in people with dementia, olanzapine or lorazepam are preferred.</td>
</tr>
<tr>
<td></td>
<td>Wherever possible, a single agent <strong>should</strong> be used in preference to a combination.</td>
</tr>
<tr>
<td></td>
<td><strong>Practice point</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Practice point</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Consensus Based Recommendation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Consensus Based Recommendation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Consensus Based Recommendation</strong></td>
</tr>
</tbody>
</table>

**Strength of recommendation**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC 2016</td>
<td>Adapted as GPP</td>
</tr>
<tr>
<td></td>
<td>Adapted as GPP</td>
</tr>
<tr>
<td></td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>Adapted as GPP</td>
</tr>
</tbody>
</table>
**Appendix 3.2.4: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 3**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA 2016</td>
<td>APA recommends that nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient.</td>
<td>1B= moderate evidence, and strong rec.</td>
<td>Adapted as Recommendation 3</td>
</tr>
<tr>
<td>NICE 2018</td>
<td>Only offer antipsychotics for people living with dementia who are either: • at risk of harming themselves or others or • experiencing agitation, hallucinations or delusions that are causing them severe distress.</td>
<td>Not stated</td>
<td>Adapted as Recommendation 3</td>
</tr>
<tr>
<td>NHMRC 2016</td>
<td>People with dementia and severe BPSD (i.e. psychosis and/or agitation/aggression) causing significant distress to themselves or others, may be offered treatment with an antipsychotic.</td>
<td>Evidence Based Recommendation (conditional)</td>
<td>Adapted as Recommendation 3</td>
</tr>
<tr>
<td>MHBC 2012</td>
<td>Antipsychotic medications are indicated only if aggression, agitation or psychotic symptoms cause severe distress or an immediate risk of harm to the resident or others</td>
<td>Strong</td>
<td>Adapted as Recommendation 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Conclusions</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tampi et al., 2016</td>
<td>Antipsychotics demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia. Their use in individuals with dementia is often limited by their adverse effect profile.</td>
<td>High</td>
</tr>
</tbody>
</table>
### Appendix 3.2.5: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 7

**Key Question 4**

a) What are the risks and contraindications to the use of an antipsychotic medication in the management of non-cognitive symptoms (including in different dementia sub-types)?

b) What discussion should take place with a person with dementia or their family about risks?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE 2018</td>
<td>Before starting antipsychotics, discuss the benefits and harms with the person and their family members or carers (as appropriate). Consider using a decision aid to support this discussion. Be aware that for people with dementia with Lewy bodies or Parkinson’s disease dementia, antipsychotics can worsen the <strong>motor features</strong> of the condition, and in some cases cause severe antipsychotic sensitivity reactions.</td>
<td>Not stated but wording implies strong.</td>
<td>Adapted as Recommendation 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditional</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not stated</td>
<td>Adapted as Recommendation 5</td>
</tr>
<tr>
<td>NHMRC 2016</td>
<td>People with AD, VaD or mixed dementias with mild-moderate BPSD should not usually be prescribed antipsychotic medications due to increased risk of cerebrovascular adverse events and death. As far as possible, antipsychotics should be avoided in people with Dementia with Lewy bodies due to the risk of <strong>severe untoward reactions, particularly extrapyramidal side effects</strong>. There should be a full discussion with the person with dementia and their carers and family about the possible benefits and risks of treatment. In particular, cerebrovascular risk factors should be assessed and the possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition discussed.</td>
<td>Evidence Based Recommendation (strong)</td>
<td>Adapted as Recommendation 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Practice Point</td>
<td>Adapted as Recommendation 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evidence Based Recommendation (strong)</td>
<td>Adapted as Recommendation 7</td>
</tr>
<tr>
<td>APA 2016</td>
<td>APA recommends that before non-emergency treatment with an antipsychotic is initiated in patients with dementia, the potential risks and benefits from antipsychotic medication be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient’s surrogate decision maker (if relevant) with input from family or others involved with the patient.</td>
<td>1B = moderate evidence, and strong rec.</td>
<td>Adapted as Recommendation 7</td>
</tr>
</tbody>
</table>
### Key Question 5

If antipsychotic medication is deemed necessary for the management of non-cognitive symptoms, which is the most appropriate choice of antipsychotic to use?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
</table>
| **NHMRC 2016**

The choice of antipsychotic should be made after an individual risk–benefit analysis.

(Risperidone has the strongest evidence for treating psychosis. Risperidone and olanzapine have the strongest evidence for treating agitation/aggression, with weaker evidence for aripiprazole).

In dementia with Lewy bodies, if antipsychotics are used for severe BPSD, atypical or second generation antipsychotics with low propensity to cause extrapyramidal side effects should be used; quetiapine and olanzapine are considered to have the best tolerability.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
</table>
| **APA 2016**

In the absence of delirium, if non-emergency antipsychotic treatment indicated, **HALOPERIDOL** should **not** be used as a first-line agent.

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al. 2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atypical antipsychotics have the strongest evidence base, although these benefits are moderate.

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preuss et al. 2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atypical antipsychotics (SGA) have the strongest evidence base, although their benefits are moderate at best.

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al. 2017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A significant increased risk of cerebrovascular accidents with typical antipsychotics (OR 1.49; 95% CI 1.24-1.77) when compared with atypical antipsychotics (OR 1.31; 95% CI 0.74-2.30)

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kales et al. 2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Olanzapine and risperidone were more efficacious than quetiapine or placebo, but quetiapine and placebo were better tolerated.

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmarals 2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quetiapine failed to significantly reduce psychotic symptoms when compared to placebo.

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Saifi et al. 2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In older adults, compared with risperidone and olanzapine, quetiapine had significantly lower risk of mortality, possibly reduced rate of cerebrovascular events, and possibly increased rate of falls and injury.

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farlow et al. 2017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Compared with placebo, aripiprazole, risperidone, and olanzapine but not quetiapine resulted in modest (standardized mean difference <0.5 SD) improvement in neuropsychiatric symptoms. Observational studies suggest that atypical antipsychotics have lower risk of all-cause mortality and extrapyramidal symptoms but higher risk of stroke than conventional antipsychotics.

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Summary</th>
<th>GRADE level of evidence</th>
</tr>
</thead>
</table>

Meta-analysis of population-based data suggested that the use of SGAs as opposed to FGAs to control BPSD is not associated with significantly increased risk of CVA.
### Appendix 3.2.7: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendations 10 and 11

<table>
<thead>
<tr>
<th>Key Question 6</th>
</tr>
</thead>
</table>
| **a)** When should a review of a person with non-cognitive symptoms who has commenced antipsychotic medication occur with regards to discontinuing the antipsychotic?  
| **b)** What is the process that needs to take place when tapering/withdrawing antipsychotic medication in the management of non-cognitive symptoms?  

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
</table>
| **NICE 2018** | When using antipsychotics  
• use the lowest effective dose of antipsychotics and use them for the shortest possible time  
• reassess the person **at least every 6 weeks**, to check whether they still need medication.  
Stop treatment with antipsychotics if:  
• the person is not getting a clear ongoing benefit from taking them **and**  
• after discussion with the person taking them and their family members or carers (as appropriate).  |
| Not stated but wording implies strong  | Adapted as recommendation 10 |
| APA 2016 | APA recommends that if a patient with dementia experiences a clinically significant side effect of antipsychotic treatment, the potential risks and benefits of antipsychotic medication should be reviewed by the clinician to determine if tapering and discontinuing of the medication is indicated.  
APA recommends that in patients with dementia with agitation or psychosis, if there is no clinically significant response after a **4-week trial** of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn.  
APA recommends that in a patient who has shown a positive response to treatment, decision making about possible tapering of antipsychotics should be accompanied by a discussion with the patient (if clinically feasible) as well as with the patient’s surrogate decision maker (if relevant) with input from family or others involved with the patient.  
APA recommends that in patients with dementia who show **adequate response** of BPSD to treatment with an antipsychotic drug, an attempt to taper and withdraw the drug should be made **within 4 months of initiation**, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication.  
APA recommends that in patients with dementia whose antipsychotic is being tapered, assessment of symptoms should occur at least monthly during taper and for at least 4 months after discontinuation.  |
| 1C= weak evidence, and strong rec.  | Adapted as recommendation 11 |

| 1B= moderate evidence, and strong rec.  | Adapted as recommendation 10 |
| 1C= weak evidence, and strong rec.  | Adapted as recommendation 12 |
Appendix 3.2.8: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendations 17, 19 and 20

### Key Question 8
What is the evidence to support the use of antidepressants in people with dementia in the management of non-cognitive symptoms?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC 2016</td>
<td>People with dementia who experience agitation should be offered a trial of selective serotonin reuptake inhibitor (SSRI) antidepressants (the strongest evidence for effectiveness exists for citalopram) if non-pharmacological treatments are inappropriate or have failed. Review with evaluation of efficacy and consideration of de-prescribing should occur after two months. The need for adherence, time to onset of action and risk of withdrawal effects and possible side effects should be explained at the start of treatment. Antidepressant medications with anticholinergic effects (e.g., tricyclic antidepressants) should be avoided because they may adversely affect cognition. The role of antidepressants in the treatment of depression in people with dementia is uncertain. Larger trials conducted in people with dementia have not shown benefit (in group data) for antidepressants for treatment of depression per se. Nevertheless, it is considered that those with a pre-existing history of major depression (prior to developing dementia) who develop a co-morbid major depression should be treated in the usual way.</td>
<td>EBR (strong)</td>
<td>Adopted (as good practice point)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP</td>
<td>Not included</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBR (strong)</td>
<td>Adopted as recommendation 17</td>
</tr>
<tr>
<td>NICE 2018</td>
<td>For people living with mild to moderate dementia who have mild to moderate depression and/or anxiety, consider psychological treatments. Do not routinely offer antidepressants to manage mild to moderate depression in people living with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health condition.</td>
<td>Conditional</td>
<td>Adopted as recommendation 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not stated; but strong wording</td>
<td>Adopted as recommendation 17</td>
</tr>
</tbody>
</table>

### Key Question 11
What is the evidence to support the use of z-type medications and melatonin in people with dementia with non-cognitive symptoms?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Adapted or adopted by GDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE 2018</td>
<td>For people living with dementia who have sleep problems, consider a personalized multicomponent sleep management approach that includes sleep hygiene education, exposure to daylight, exercise and personalized activities. Do not offer melatonin to manage insomnia in people living with Alzheimer’s disease.</td>
<td>Not stated but wording implies Conditional</td>
<td>Adopted as recommendation 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not stated but wording implies Strong</td>
<td>Adopted as recommendation 20</td>
</tr>
</tbody>
</table>
Appendix 3.5: Summary of NICE guideline (NG97) recommendations for acetylcholinesterase inhibitors and memantine in the treatment of cognitive symptoms

- Donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer’s disease.

- Memantine monotherapy is recommended as an option for managing Alzheimer’s disease for people with moderate Alzheimer’s disease who are intolerant of or have a contraindication to acetylcholinesterase inhibitors, or severe Alzheimer’s disease.

- Clinicians should ‘consider’ memantine in addition to an acetylcholinesterase inhibitor in moderate Alzheimer’s disease, and should offer memantine in addition to an acetylcholinesterase inhibitor in severe Alzheimer’s disease.

- Clinicians should offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies (galantamine only if these not tolerated) and should ‘consider’ donepezil or rivastigmine in severe disease.

- Clinicians should consider memantine for people with dementia with Lewy bodies if acetylcholinesterase inhibitors are not tolerated or are contraindicated. (Parkinson’s disease dementia is not included in this guideline as it is covered in a separate Parkinson’s disease guideline).

- Clinicians should only consider acetylcholinesterase inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer’s disease, Parkinson’s disease dementia or dementia with Lewy bodies.

- Clinicians should not offer acetylcholinesterase inhibitors or memantine to people with frontotemporal dementia, or cognitive impairment caused by multiple sclerosis.
Appendix 7: Supporting tools

The following supporting tools are already available from the National Dementia Office website: https://dementiapathways.ie/the-national-dementia-office


Clinicians are also referred to the HSE Medication Management Programme’s document on benzodiazepines and related medications https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxiety-insomnia/bzraguidancemmpfeb18.pdf)