



An Roinn Sláinte
Department of Health

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

National Clinical Guideline No. 21

December 2019



Seirbhís Sláinte
Níos Fearr
á Forbairt

Building a
Better Health
Service

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 National Clinical Guideline

This 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

Name	Job title and affiliation
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Ms. Emma Benton	General Manager, Office of NCAGL-HSE Acute Hospitals Division.
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Ms. Karen Finnigan	Senior Pharmacist HSE Medicines Management Programme.
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Ms. Susan Cliff	Deputy Chief Inspector of Social Services, Health Information and Quality Authority.
Ms. Florence Hogan	Quality and Patient Safety Manager, Leopardstown Park Hospital.
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Other group members	
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Ms. Mary Manning	General Manager, National Dementia Office.
Ms. Lorraine McNamee	Nursing & Midwifery Planning & Development Officer; Nurse Lead Dementia, HSE Office of Nursing & Midwifery Services Director.

*Most writing group members sat on all subgroups.

Credits

The role of the NCEC is to prioritise, quality assure and recommend clinical guidelines to the Chief Medical Officer for endorsement by the Minister for Health. It is intended through Ministerial endorsement that full implementation of the guideline will occur through the relevant service plans.

The NCEC and the Department of Health acknowledge and recognise the co-chairs and members of the Guideline Development Group (GDG) for development of the guideline. The NCEC and Department of Health wish to express thanks and sincere gratitude to all persons contributing to this National Clinical Guideline; especially those that gave of their time on a voluntary basis.

Acknowledgments

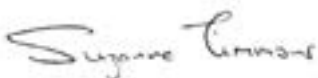
The following credits and acknowledgements are made by the co-chairs of the GDG. The co-chairs wish to acknowledge all members of the GDG as full contributors credited with having given substantial intellectual leadership to the National Clinical Guideline, and the Writing Group for their particular input. Dr. Suzanne Timmons successfully submitted the guideline for NCEC prioritisation in August 2018, following GDG review. The GDG agreed the scope and developed the guideline. The GDG writing subgroup reviewed the evidence, appraised the literature and performed the data extraction and initial evidence synthesis, with particular credit here to Dr. Ashling Murphy. Dr. Ian Maidment and Ciara Kirke performed a separate review of the evidence for Section 3.3. Dr. Siobhan Fox from UCC kindly acted as second reviewer for the guideline and literature quality appraisal.

Dr. Aileen Murphy and Ruth Kelly from UCC conducted the budget impact analysis. Florence Hogan supported the implementation planning. The external review carried out by Prof. Sube Banerjee of Sussex University, and Prof. Louise Allan of Exeter University, is acknowledged. We would like in addition to thank Niamh O'Connor, UCC for administrative and editing support during preparation for publication, and Donna Ó Doibhlin, librarian, UCC for her advice and support of the search strategy. Dr. Suzanne Timmons submitted the guideline for NCEC quality assurance. All authors approved the final guideline.

In particular, the GDG wish to recognise the contribution of the people with dementia and family carers on the GDG and those who took part in focus groups and in the final consultation.

A full list of members of the GDG is available in the previous page/s.

Signed by the Chairs:



Dr. Suzanne Timmons

and



Prof. Stephen Byrne

Date: 5th October 2019

National Clinical Guidelines

Providing standardised clinical care to patients in healthcare is challenging. This is due to a number of factors, among them variations in environments of care and complex patient presentations. It is self-evident that safe, effective care and treatment are important in ensuring that patients get the best outcomes from their care.

The Department of Health is of the view that supporting evidence-based practice, through the clinical effectiveness framework, is a critical element of the health service to deliver safe and high-quality care. The National Clinical Effectiveness Committee (NCEC) is a Ministerial committee set up in 2010 as a key recommendation of the report of the Commission on Patient Safety and Quality Assurance (2008). The establishment of the Commission was prompted by an increasing awareness of patient safety issues in general and high-profile health service system failures at home and abroad.

The NCEC on behalf of the Department of Health has embarked on a quality assured National Clinical Guideline development process linked to service delivery priorities. Furthermore, implementing National Clinical Guidelines sets a standard nationally, to enable doctors, nurses, pharmacists, and health and social care professionals (HSCP) to deliver safe and effective care and treatment while monitoring their individual, team and organisation's performance.

The aim of NCEC National Clinical Guidelines is to reduce unnecessary variations in practice and provide an evidence base for the most appropriate healthcare, in particular circumstances. As a consequence of Ministerial mandate, it is expected that NCEC National Clinical Guidelines are implemented across all relevant services in the Irish healthcare setting.

The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and clinical audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit. The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

NCEC terms of reference

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an annual report.

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This National Clinical Guideline draws on NICE guidance

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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.

Glossary of terms and abbreviations

Acetylcholinesterase inhibitors	An acetylcholinesterase inhibitor (often abbreviated to AChEI), or anticholinesterase, is a drug that inhibits the acetylcholinesterase enzyme from breaking down acetylcholine, thereby increasing both the level and duration of action of the neurotransmitter acetylcholine. These are sometimes referred to as cognitive enhancing drugs, or cognitive enhancers.
Adequate dose	The dose of a medication at which therapeutic effects occurred. This dose will differ for each medication and may need to be adjusted in an individual to address factors that would influence drug absorption, metabolism, elimination, or other pharmacokinetic properties.
Adequate response	A reduction in symptoms as a result of treatment that is deemed to have a clinically significant benefit in functioning and/or quality of life of the individual.
Advance Healthcare Directive	(a) in relation to a person who has capacity, means an advance expression made by the person, in accordance with section 84, of his or her will and preferences concerning treatment decisions that may arise in respect of him or her if he or she subsequently lacks capacity, and (b) in relation to a designated healthcare representative, means the advanced expression under which the representative was designated as such representative (Assisted Decision-Making (Capacity) Act, 2015).
Adverse effects	An undesired harmful effect resulting from a medication or other intervention.
Aggression	Feelings of anger or antipathy resulting in hostile or violent behaviour.
Agitation	A state of excessive motor activity, verbal aggression, or physical aggression to oneself or others, associated with observed or inferred evidence of emotional distress.
Alzheimer's disease (AD)	A condition presenting with symptoms of impaired memory, thinking and/or behaviour. It is a progressive dementia resulting from the degeneration of brain cells affecting mood, behaviour and memory. Is characterised by "plaques" between the dying cells in the brain and "tangles" within the cells (both are due to protein abnormalities). The brain tissue in a person with Alzheimer's has progressively fewer nerve cells and connections, and the total brain size shrinks.
Anticonvulsant medication	A diverse group of pharmacological agents used in the treatment of epileptic seizures. These are sometimes also used as mood stabilisers.
Antidepressant medication	A drug used for the treatment of major depressive disorders and conditions, including dysthymia, social anxiety disorder, obsessive-compulsive disorder, chronic pain, agitation, generalised anxiety disorder, bipolar disorder, childhood enuresis (bedwetting), migraine and sleep disorders.

Antipsychotic medication	One of a group of medications used in the treatment of psychosis. Some of the antipsychotic medications are also approved for use in other conditions such as mood disorders or Tourette's syndrome. Usually referred to as "typical" or "atypical". The first-generation antipsychotic (FGA) medications, referred to as "typical" antipsychotic medications, were the initial medications to be discovered. The FGAs include, but are not limited to, chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, thiothixene, thioridazine, and trifluoperazine. The second generation antipsychotic (SGA) medications, or "atypical" antipsychotic medications, include, but are not limited, to aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.
Apathy	A lack of feeling, emotion, interest, and concern.
Behavioural and psychological symptoms of dementia (BPSD)	A specific range of symptoms of dementia. May include aggression, anxiety, vocalization, restlessness, agitation, walking about, inappropriate behaviour, depressed mood, hallucinations and delusions.
Benzodiazepine	A class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anti-convulsant and muscle relaxant properties. Sometimes referred to as minor tranquilisers.
Best practice guidelines	Systematically developed statements (based on best available evidence) to assist physician, clinician and patient decisions about appropriate healthcare for specific clinical (practice) circumstances. The main purpose of guidelines is to achieve better health outcomes by improving the practice of healthcare professionals and providing consumers with better information about treatment options.
Capacity	<p>A person's ability to understand, at the time that a decision is to be made, the nature and consequences of the decision to be made by him or her in the context of the available choices at that time. A person lacks the capacity to make a decision if he or she is unable—</p> <ul style="list-style-type: none"> (a) to understand the information relevant to the decision, (b) to retain that information long enough to make a voluntary choice, (c) to use or weigh that information as part of the process of making the decision, or (d) to communicate his or her decision (whether by talking, writing, using sign language, assistive technology, or any other means) or, if the implementation of the decision requires the act of a third party, to communicate by any means with that third party (Assisted Decision-Making (Capacity) Act, 2015).
Carer	A family member or nominated representative or co-decision maker/decision representative. It does not refer to any person providing formal care acting in the position of a healthcare professional.

Comprehensive treatment plan	A plan of treatment that is developed as a result of a holistic assessment, that includes the individual's psychosocial and medical requirements and is modified as clinically indicated. Can include non-pharmacological and pharmacological interventions. It is individualised to the person with dementia. There is no prescribed format that a comprehensive treatment plan must follow.
Decision Supporter	A 'Decision Supporter' refers to a Decision-Making Assistant, Co-Decision Maker, Decision-Making Representative, Attorney or Designated Healthcare Representative, if any of these are in place for a person, and have a role in relation to health-related decisions [i.e. an attorney may or may not]. In practice, this person may often be a family member of the person with dementia, but not always. Please refer to the Decision Making (Capacity) Act, 2015 for further details of these terms.
Dementia	A chronic, progressive disease of the brain that affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, judgement, and executive function.
Dementia with Lewy bodies (DwLB)	A particular type of dementia accompanied by changes in behaviour, cognition and movement. Like Parkinson's disease, this is caused by abnormal accumulation of a protein called alpha-synuclein in the brain. However, dementia with Lewy bodies typically presents with dementia within 1-2 years of Parkinson's disease onset (unlike Parkinson's disease dementia) and a typical feature is prominent visual hallucinations and fluctuations in alertness. People with dementia with Lewy bodies can have severe worsening of their Parkinson's symptoms if they receive antipsychotics. (Please see also Lewy body dementia)
Efficacy	Capacity for producing a desired result or effect.
Indication	Specific rational or clinical reasoning for using a specific medication.
Individual	Refers to person(s) with dementia.
Lewy body dementia (LBD)	Lewy body dementia is an umbrella term for any dementia where there are Lewy bodies (i.e. alpha-synuclein protein accumulations in the brain). Within Lewy body dementias, the disease 'dementia with Lewy bodies' presents with prominent early dementia and typically visual hallucinations; while 'Parkinson's disease dementia' typically presents with PD first, and then the person slowly develops dementia several years later. Please refer to 'Dementia with Lewy bodies', and 'Parkinson's disease dementia' for further details.
Medication license	The specific license information pertaining to the produce, supply, possession, prescribing, import or export of medications.
Memantine	A drug used to treat moderate to severe Alzheimer's disease through its act on the glutamatergic system by blocking NMDA receptors.
Mild symptoms	Symptoms that are present but not distressing to the person with dementia.

Mixed dementia	A diagnosis of two or three types occurring together. For instance, a person may have both Alzheimer’s disease and vascular dementia at the same time.
Moderate symptoms	Symptoms that are stressful and upsetting to the person with dementia; may require specific management.
Non-cognitive symptoms	Non-cognitive symptoms associated with dementia include psychosis (delusions, hallucinations), mood disturbances (depression, euphoria, irritability, anxiety), personality changes (disinhibition, apathy), agitation, aggression, pacing, walking about, altered sexual behaviour, changed sleep patterns, and appetite disturbances.
Non-pharmacological	Interventions such as music therapy, relaxation, distraction techniques, and massage, or with cognitive and behavioural interventions, as opposed to pharmacological/medication interventions.
Off label	The use of medications for an unapproved indication or in an unapproved age group, dosage, or route of administration.
Parkinson’s disease dementia (PDD)	The brain changes caused by Parkinson’s disease begin in a region that plays a key role in movement. As these brain changes gradually spread, they often begin to affect mental functions, including memory and the ability to pay attention, make sound judgments and plan the steps needed to complete a task. The key brain changes linked to Parkinson’s disease and Parkinson’s disease dementia are abnormal microscopic deposits composed chiefly of alpha-synuclein.
Pharmacological interventions	The reference to medications with regard to their uses, effects, and modes of action of drugs.
Psychotropic	Chemical substances that action brain function affecting mood and behaviours.
Psychosis	An abnormal condition of the mind that results in difficulties telling what is real and what is not. Symptoms may include false beliefs and seeing or hearing things that others do not see or hear. Other symptoms may include incoherent speech, or behaviour that is inappropriate for the situation. There may also be sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities.
Relevant person	In accordance with the Decision Making (Capacity) Act, 2015 “relevant person” means— <ul style="list-style-type: none"> (a) a person whose capacity is in question or may shortly be in question in respect of one or more than one matter, (b) a person who lacks capacity in respect of one or more than one matter, or (c) a person who falls within paragraphs (a) and (b) at the same time but in respect of different matters.

Serotonin syndrome (SS)	A group of symptoms that may occur following use of certain serotonergic medications. Symptoms can range from mild to severe and can include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhoea.
Selective serotonin reuptake inhibitor	A class of drugs that are typically used as antidepressants in the treatment of major depressive disorder and anxiety disorders.
Severe symptoms	Symptoms that are very stressful and upsetting to the person with dementia; typically requires specific management.
Specialist	Specialist clinicians are those with the appropriate knowledge and skills to be considered a dementia specialist and include secondary care medical specialists (for example psychiatrists in old age, geriatricians and neurologists), some GPs, nurses (Nurse Specialists and Advanced Nurse Practitioners in Dementia) and other health and social care professionals with specialist expertise in diagnosing and treating dementia (e.g. therapists specialising in dementia).
Vascular dementia (VaD)	In vascular dementia, changes in thinking skills sometimes occur suddenly following strokes that block major brain blood vessels. Thinking problems also may begin as mild changes that worsen gradually as a result of multiple minor strokes or other conditions that affect smaller blood vessels, leading to cumulative damage.
Z-drugs	These types of medications work in a similar way to benzodiazepines and are often used to treat sleep problems (insomnia).

Abbreviations

The following abbreviations are used in this document:

AAFP	American Academy of Family Physicians
AC	Anticonvulsant
AChEI	Acetylcholinesterase inhibitor
ACP	American College of Physicians
AD	Alzheimer's disease
ADe	Antidepressants
ADL's	Activities of Daily Living
AGREE	Appraisal of Guidelines for Research & Evaluation
AMDA	American Medical Directors Association
AP	Antipsychotic
APA	American Psychiatric Association
AQuAS	Agency for Health and Assessment of Catalonia
BAP	The British Association for Psychopharmacology
BC	British Columbia
BPSD	Behavioural and Psychological Symptoms of Dementia
CCSMH	Canadian Coalition for Senior Mental Health
CGR	Centre for Gerontology and Rehabilitation
CJD	Creutzfeldt-Jacob Disease
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central Nervous System
CSM	Committee of Safe Medicines
CVE	Cerebrovascular events
DwLB	Dementia with Lewy bodies
EFNS	European Federation of Neurological Societies
EMA	European Medicines Association
FLD	Frontal Lobe Dementia
GMC	General Medical Council
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GDG	Guideline Development Group
GDP	Global Domestic Product
MCI	Mild Cognitive Impairment
MHBC	Ministry of Health British Columbia
MHRA	Medicines and Healthcare products Regulatory Agency
NCEC	National Clinical Effectiveness Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPI	Neuropsychiatric Inventory
PBS	Pharmaceutical Benefit Scheme
PDD	Parkinson's disease dementia
PICOS	Population Intervention Comparison Outcome Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RANZCP	Royal Australian and New Zealand College of Psychiatrists
Resp	Respiratory system
SCIE	Social Care Institute for Excellence
SmCP	Summary of product characteristics
SSRI	Selective serotonin reuptake inhibitor
SWYPFT	South West Yorkshire Partnership NHS Foundation Trust
VaD	Vascular dementia

1 National Clinical Guideline summary

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)

Section	No.	Recommendation	Quality of evidence	Strength of recommendation
General principles of care	1	Prior to considering any psychotropic medication in a person with dementia, a comprehensive assessment¹ should be performed, by an appropriately trained healthcare professional.	Low	Strong
	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 identifiable² risk of harm to the person and/or others.	High	Strong
Antipsychotic medication	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.	High	Strong
	4	People with Alzheimer's disease, vascular dementia or mixed dementias with <i>mild-to-moderate</i> non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of cerebrovascular adverse events and death.	High	Strong
	5	People with dementia with Lewy bodies ³ and Parkinson's disease dementia with <i>mild to moderate</i> non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of severe adverse reactions.	High	Strong
	6	People with Alzheimer's disease, vascular dementia, mixed dementias, dementia with Lewy bodies ³ , or Parkinson's disease dementia, with <i>severe</i> non-cognitive symptoms, causing severe distress, or an identifiable ² risk of harm to the person and/or others, may be offered antipsychotic medication, where appropriate.	Moderate	Conditional
	7	A full discussion with the person and/or their relevant Decision Supporter ⁴ about the benefits and risks, including the increased risk of stroke, transient ischemic attack and mortality, should occur before antipsychotic medication is commenced.	Low	Conditional

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'.

Section	No.	Recommendation	Quality of evidence	Strength of recommendation
Antipsychotic medication	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 ⁵ .	Moderate	Strong
	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.	Moderate	Strong
	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 Supporter⁴.	Low	Strong
	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 Supporter⁴.	Moderate	Strong
	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 ⁶ .	Moderate	Strong
Acetylcholinesterase inhibitors and memantine	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.	High	Conditional
	14	Due to the particular risks with antipsychotics in people with Parkinson's disease dementia and dementia with Lewy bodies ³ , rivastigmine or donepezil may be considered for non-cognitive symptoms causing severe distress when non-pharmacological interventions have proved ineffective.	Moderate	Conditional
	15	People with vascular dementia or frontotemporal dementia who develop non-cognitive symptoms should NOT be prescribed acetylcholinesterase inhibitors.	Moderate	Strong
	16	Memantine is indicated as a cognitive enhancer in people with moderate ⁷ 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.	Moderate	Strong

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'.

⁵ Prescribing an antipsychotic for BPSD, other than risperidone for short-term treatment of persistent aggression in Alzheimer's dementia, is **off-label**.

⁶ 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.

⁷ 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.

Section	No.	Recommendation	Quality of evidence	Strength of recommendation
Antidepressant medication	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.	Moderate	Conditional
Anticonvulsant medication	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.	Low	Strong
Benzodiazepines, z-drugs, and other hypnotics	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 episodes⁹.	Low	Strong
	20	A personalised sleep management regimen ¹⁰ may be considered for sleep disorders in a person with dementia.	Moderate	Conditional
	21	Melatonin should NOT be used for sleep disorders in people with dementia.	Moderate	Strong

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.

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.

⁹ For maximum duration of use refer to the Summary of Product Characteristics (SmPC). The Medicine Management Programme guidance (2018) contains an appendix with useful details on dosage and maximum duration for the benzodiazepines licenced in Ireland, for both anxiety and insomnia. (<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxiety-insomnia/bzraguidancemmpfeb18.pdf>). Appendix D.

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.

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

<ol style="list-style-type: none"> 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.
<ol style="list-style-type: none"> 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.
<ol style="list-style-type: none"> 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.
<ol style="list-style-type: none"> 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).

2**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).

2.1.1 Prevalence and types of dementia

Globally, dementia affects approximately 46 million people (Global Burden of Disease (GBD), 2016) categorising dementia as a major healthcare concern and global issue. Increasing dementia rates, costs and burden of disease assert significant pressures on health, economic and social care systems in several countries. In Ireland, there are currently around 55,266 people living with dementia and this is expected to rise to 95,863 by 2031 and 157,883 people by 2046 (O’ Shea et al., 2015). Although there are several hundred types of dementia, most of these are rare. The most common types include Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, Parkinson’s disease dementia and mixed dementia. Other forms of dementia include frontotemporal dementia, Huntington’s disease dementia, and Creutzfeldt-Jacob disease (European Medicines Agency (EMA), 2008). Alzheimer’s disease is the most common type of dementia with evidence suggesting that in people aged over 65, approximately 60% or more of dementias are due to Alzheimer’s disease, 17% are vascular dementia, 10% are of mixed aetiologies, 4% are dementia with Lewy bodies, 2% are Parkinson’s disease dementia, 2% are frontotemporal dementia, and 3% are attributable to other causes (Dementia UK, 2014; Department of Health, 2014). In people with younger onset dementia (symptoms developing before the age of 65 years), these proportions differ, with Alzheimer’s disease representing lower numbers (about 33%), and a greater incidence of frontotemporal dementia (12%) (Young Dementia UK, 2018, Alzheimer Society of Ireland, 2017).

A particular subgroup of people with young onset dementia are people with a pre-morbid intellectual disability. Adults with Down syndrome are at higher risk of Alzheimer’s disease than their peers. By the age of 40 years of age, nearly all adults with Down syndrome will have evidence of the neuropathology of Alzheimer’s disease (Lamar et al., 2011). Diagnosis in this population is challenging due to a lack of clear diagnostic criteria suitable for adults with intellectual disability. As baseline normal functioning may not be easily defined in adults with intellectual disability, progression of dementia may be difficult to assess (Krinsky-McHale and Silverman, 2013).

It was estimated that there were 700 people with Down syndrome living with dementia in Ireland, based on the 2008 National Disability Survey (Creating Excellence Report, 2011), but the true figure is likely to be significantly higher. In Ireland, in a prospective follow up study of 77 people with Down syndrome in an intellectual disability service in Dublin aged 35 years and older, over the 20-year period, 97.7% developed dementia, with a mean age at diagnosis of 55 years (McCarron et al., 2017a). In Wave 3 (2016/2017) of IDS-TILDA, a nationally representative longitudinal study of older adults with intellectual disability in Ireland, the prevalence of dementia among adults with intellectual disability who had Down syndrome was 35.5% (McCarron et al., 2017b).

The diagnosis of the type of dementia is important as treatment decisions are often dependent on this knowledge. Similarities in symptoms and presentations can present a challenge in appropriately diagnosing dementia in some cases, so that a definitive sub-type of dementia diagnosis can not be made until post mortem. But in most people, it is possible for an appropriately trained specialist to diagnose the probable sub-type. In Ireland, many people with dementia are not formally diagnosed (Timmons et al., 2015), and many of those diagnosed do not have a sub-type diagnosis. This needs to be considered when applying evidence based on a particular dementia sub-type to the care of a person with dementia.

Note: The diagnosing of dementia is beyond the scope of these guidelines. Please refer to Dementia: Diagnosis and Management in General Practice (Irish College of General Practitioners, 2014, and updated 2019) (http://dementiapathways.ie/filecache/e74/e54/839-dementia_qrg_15th_april_2019-1.pdf) and the NICE National Clinical Guideline on 'Dementia Assessment, management and support for people living with dementia and their carers' (NICE, 2018) (<https://www.nice.org.uk/guidance/ng97/resources/dementia-assessment-management-and-support-for-people-living-with-dementia-and-their-carers-pdf-1837760199109>) for appropriate guidance on diagnosing dementia. The following online resource from the National Dementia Office on pathways for dementia diagnosis may be useful (<https://dementiapathways.ie/care-pathways/diagnosis-of-dementia-and-cognitive-impairment>).

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).

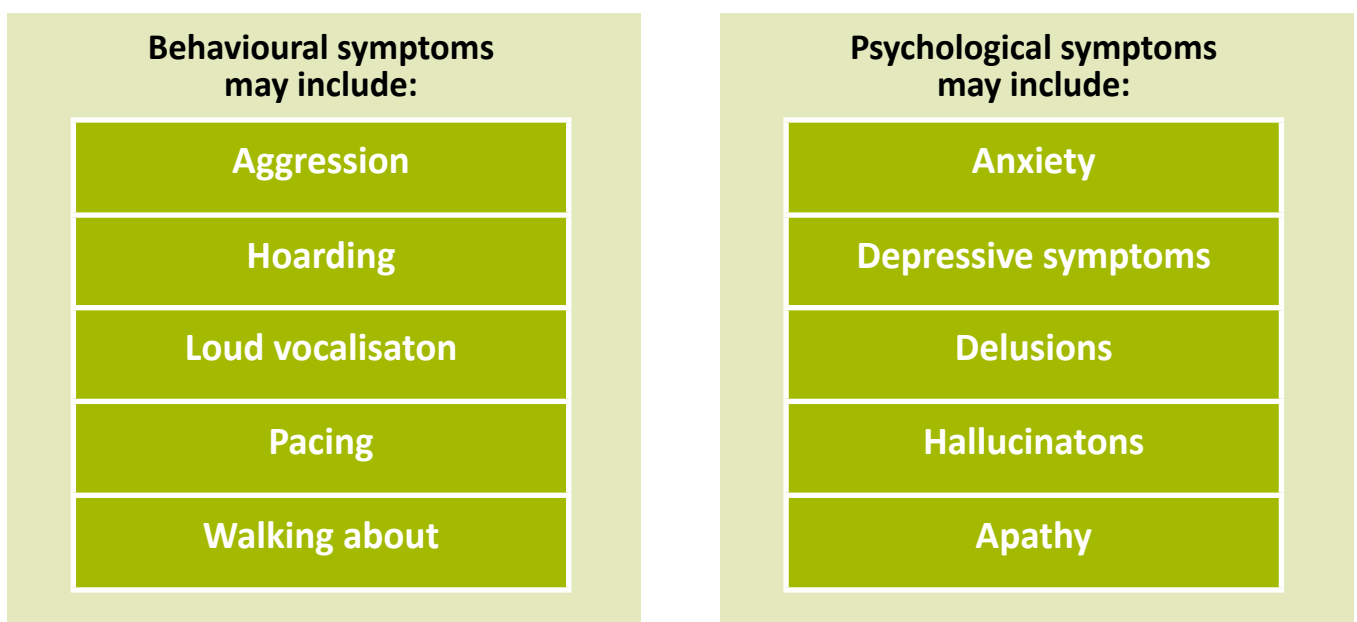


Figure 2.1: Examples of BPSD

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).

Table 2.1: Non-cognitive symptom severity

Mild symptoms	Present but not distressing to the person
Moderate symptoms	Stressful and upsetting; may require specific management
Severe symptoms	Very stressful and upsetting; typically requires specific management

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).

Clinicians are referred to the NICE guideline for delirium (2010) (<https://www.nice.org.uk/guidance/cg103>), and the more recent Scottish Intercollegiate Guideline Network (SIGN, 2018) (<https://www.sign.ac.uk/sign-157-delirium.html>), for further details on indicators and the assessment of delirium.

Table 2.2: Typical delirium features

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.

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 2.3: Examples of non-pharmacological interventions

Music therapy	Reminiscence therapy	Art therapy	Multisensory stimulation
Reality orientation	Validation therapy	Aromatherapy	Physical activity
Animal-assisted therapy	Environmental design	Recreational activities	Bright light therapy
Massage/touch	Cognitive behavioural therapy	Carer interventions	Emotion-oriented therapy

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://dementiathways.ie/publications>).

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 (Azermi 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).

The Health Service Executive (HSE) Medicines Management Programme recently published guidance on the appropriate prescribing of benzodiazepines and z-drugs in the treatment of anxiety and insomnia (HSE, 2018) (<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxietyinsomnia/bzraguidancemmpfeb18.pdf>). The guidance highlights safety concerns and problems associated with the use of these medicines including dependency, tolerance and withdrawal.

2.2.1 Scale of psychotropic prescribing for non-cognitive symptoms

Despite warnings, the use of antipsychotics for treating people with dementia has increased over the past two decades (Tampi et al., 2016). Thirty-seven studies on antipsychotic drug use, and 27 studies on antidepressant drug use, conducted in 12 different European countries, noted that antipsychotic use in nursing homes ranged from 12% to 59% and antidepressant use from 19% to 68% (Janus et al. 2016). In the US, it is estimated that 16% of all nursing homes residents are prescribed an antipsychotic (Gurwitz et al., 2017) and 19% in England (Szczepura et al., 2016). A study in the Netherlands showed that prevalence of antipsychotic prescribing in 1,090 people with dementia was 31% overall, highest in large, urban facilities with below average staffing levels and poorer resident rating of personal care and recreational activities (Kleijer et al., 2014).

Irish data on psychotropic prescribing for people with dementia

Unpublished work estimated that nationally, 40% of people with dementia are prescribed an antipsychotic (Sexton et al., 2015). Of note, this data was derived from the Irish Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS) community pharmacy claims database, where cognitive-enhancing drugs were used as a surrogate for a diagnosis of dementia (due to the lack of diagnostic information on this database), and so people with mild dementia or paradoxically very advanced dementia would be under-represented (as less likely to be receiving cognitive-enhancing medications). Another limitation of the HSE-PCRS is the lack of generalisability for those aged <70 years due to more limited eligibility for the scheme in this age group.

People with dementia in residential care

There is limited information on the prevalence of antipsychotic prescribing in the Irish context, however one study conducted in a residential care setting found that 30% of residents with dementia were prescribed an antipsychotic (Shortall, 2012). One small and retrospective study of 14 publicly funded residential care facilities in Cork, which reported on data collected in 2009, found that 37% of all residents were prescribed antipsychotic medication (Bermingham et al., 2017). Similarly, a recent feasibility study in one HSE provided residential care unit (baseline data from end of 2017) found a 44% rate of prescribing of antipsychotics at baseline (Walsh, 2018).

In admissions to hospital, captured in the 2013 Irish National Audit of Dementia Care in Acute Hospitals (INAD) audit (see below) from residential care ($n=243$), 45% were receiving antipsychotic medication (de Siún et al., 2014). Although any sub-group of a population admitted to hospital may not be entirely representative of the overall population, there is a consistency in the four sources of data that suggests the rate of prescribing of antipsychotic medication to people with dementia in residential care in Ireland may be about 40%, which is substantially higher than the European average of 27%, and the rate in the

UK of 19% (De Siun et al., 2014).

People with dementia requiring admission to hospital

In another study, conducted in six acute hospitals, 14% of people with dementia (many only diagnosed as part of the research) were receiving an antipsychotic prior to admission to hospital, compared to 5% of 450 older people without dementia (Walsh et al., 2016). In addition, 37% of people with dementia were receiving multiple psychotropic medications. Of note, 70% of the people with dementia in this study were admitted from home and many had not yet had a formal diagnosis of dementia (i.e. diagnosed de novo in the research study), which would be expected to be associated with lower prescribing rates of all dementia-related medications.

The INAD audit (de Siún et al., 2014)

(<https://www.ucc.ie/en/media/research/irishnationalauditofdementia/INADFullReportLR.pdf>) identified that antipsychotic drugs were prescribed to 29% of 660 people with known dementia (identified through national hospital discharge data) prior to acute hospitalisation. This is in contrast to the corresponding rates of antipsychotic receipt of 15.6% in 2010, then 9.4% in 2012, among people with dementia on admission to hospitals in England and Wales (Royal College of Psychiatrists, 2011 and 2013), and the 21% in Northern Ireland (O'Shea et al., 2015). Of note, 19% of the 409 people with dementia admitted to hospital from home were receiving antipsychotics (de Siun et al., 2014; Gallagher et al., 2016).

People with dementia during hospitalisation

In addition, 41% of acute hospital in-patients with dementia were prescribed an antipsychotic during hospitalisation in Ireland, one quarter of which were new or additional prescriptions (Gallagher et al., 2016). In total, 41% of patients prescribed antipsychotic medications before admission were discharged on higher doses, while 12% of patients not prescribed an antipsychotic before admission were discharged with a new regular prescription (Gallagher et al., 2016). Concerningly, the indication for any new antipsychotic medication was only documented in 78% of cases. Where documented, 'agitation' was the most common indication (61%), which, without qualification (severe, with risk of harm to self or others, or caused by/suspicion of psychosis), is not in itself an appropriate indication for a high risk medication whose primary indication is for treating psychosis. Assessments for treatable underlying causes of non-cognitive symptoms were poorly performed – ruling out delirium (45%), or pain (76%), assessing mood (26%), and seeking information from family about distress-provoking factors (3%) or calming actions (2%) (Gallagher et al., 2016). Thus, it appears that clinicians were prescribing antipsychotics in hospital without much evidence of consideration of alternatives.

Adults with intellectual disability

Results from Wave 1 of the intellectual disability Supplement to the Irish Longitudinal study on Ageing (IDS-TILDA 2009/2010; n= 753 older adults with intellectual disability), indicated that of the 37 people with reported dementia/Alzheimer's disease, 40.5% reported antipsychotic use (O'Dwyer et al., 2018b). Linked to this, 51.4% with reported dementia/Alzheimer's disease reported a doctor's diagnosis of an emotional/nervous or psychiatric condition. At Wave 2 of the study (2013/2014), of the 65 participants with reported dementia/Alzheimer's disease who had available medication information, 49.2% reported antipsychotic exposure and 54.1% reported a doctor's diagnosis of an emotional/nervous/psychiatric condition (O'Dwyer et al., 2018b). Information was not established as to whether any of these antipsychotics were initiated for non-cognitive symptoms or psychiatric morbidities.

The risk of potential harm from inappropriate use of antipsychotics in people with intellectual disability

who have dementia is compounded by the potential for idiosyncratic responses to antipsychotics and other psychotropic medicines due to the presence of organic dysfunction associated with the intellectual disability (O'Dwyer et al., 2018a).

2.2.2 Financial impact of dementia

Due to its progressive nature, as well as the need for a vast array of services, the financial impact of dementia is considerable. Worldwide, dementia costs over €682 billion, representing 1.09% of global gross domestic product (GDP) (Trepel, 2010) with this cost anticipated to rise to over a trillion by 2018 (Prince et al., 2015). Direct medical care costs account for approximately 20% of global dementia costs, while direct social sector costs and informal care costs each account for roughly 40% of costs (Prince et al., 2015). As a result of increased longevity and ageing populations, the economic burden of dementia currently ranks higher than stroke, heart disease and cancer combined (Prince et al., 2015). However, healthcare allocations for dementia care continue to be substantially lower than each of these individual disease groups (Trepel, 2010).

Dementia is estimated to cost the Irish health service over €1.69 billion annually, with this expected to increase substantially in the forthcoming years, given dementia prevalence rates and the ageing population (Pierce et al., 2014). Similar to the global situation, it is estimated that half this cost (48%) is for informal care (i.e. borne by the person with dementia and their family), while the other half is a cost to the state, mainly for residential care (43%) rather than healthcare costs (9%) (Connolly et al., 2014). The “extra” cost of acute hospital care for patients with dementia is due to longer lengths of stay, estimated to be €200 million per year (Connolly and O’Shea, 2015). It is worth noting that Ireland is anticipated to have the largest growth in terms of ageing population within all European countries and hence, diagnoses of dementia are expected to increase substantially in the coming years (Trepel, 2010). The expected dramatic rise in the resources required for dementia care in Ireland over the coming years make it a key priority area in terms of health economic planning.

2.2.3 Cost of psychotropic medications

Although psychotropic medications are considered relatively inexpensive in terms of manufacturing costs, the high frequency of their use in Ireland means their overall cost is not insignificant. The total annual cost of dementia-related medication in Ireland is estimated to be almost €16 million, of which 85% is accounted for by ‘anti-dementia’ drugs (i.e. cognitive enhancers), while the estimated combined cost of antipsychotics, anxiolytics and antidepressants for non-cognitive symptoms is €2.4 million per annum (Creating Excellence Report, 2011).

However, this cost is only a small part of the true cost of psychotropic medications, if these are prescribed inappropriately. Thus, there are significant healthcare costs incurred as a direct result of adverse events e.g. falls, fractures, pneumonia, strokes, and associated hospitalisation/rehabilitation costs. Extrapolating from UK figures (Banerjee, 2009), there are potentially 100 preventable strokes (50% of which are severe), and 110 preventable deaths, from antipsychotics alone in Ireland each year (assuming a conservative 20% of people with dementia in Ireland receive antipsychotics each year), which will double by 2036 unless we reduce the rates of prescribing.

Unfortunately, it is difficult to estimate other morbidity due to antipsychotics apart from stroke and death, or to estimate deaths or morbidities due to other inappropriately prescribed psychotropic medications, such as benzodiazepines and antidepressants. However, 40% of hospital admissions in people with dementia are reported to be due to psychotropic medications (Gustafsson et al., 2016).

In addition, there may also be other significant health and social costs arising from inappropriate psychotropic medications, related to the need for increased social care, including admission to residential care. A full depiction of these costs is presented in Appendix 5: Economic Assessment.

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).

2.3.1 Evidence that current practice is amenable to change

Other countries have seen dramatic reductions in their use of psychotropic medications in dementia following the implementation of guidelines (Bjerre et al., 2018). In the USA, there was a 33% reduction in antipsychotic prescribing in residential care from 2012 to 2017 (from 24% to 16.0%), when a national initiative was launched (Gurwitz et al., 2017). In the UK, there was a large reduction in overall antipsychotic drug prescription in dementia, from 22.1% in 2005 to 11.4% by 2015 (Donegan et al., 2017), associated with national monitoring of usage. Within acute hospitals in the UK, the Banerjee report (2009), in conjunction with the UK National Dementia Strategy (2009), is reported to have resulted in a 51.8% reduction in the use of antipsychotic medications for hospitalised patients with dementia in England and Wales from 2008 to 2011 (Gallagher et al., 2016).

Of note, national targets to reduce antipsychotic prescribing have sometimes been associated with a rise in the prescription of other psychotropic medications, or other 'work arounds', such as a surprising 19% rise in the rate of diagnosis of schizophrenia in residential care in the US, assumed to be in order to recategorise a prescription of an antipsychotic as 'appropriate' (Donegan et al., 2017; Westbury, 2017). Our strategy has therefore been to include all psychotropic medications, not just antipsychotic medications, to reduce the risk of 'medication switching'; while education, stakeholder support and culture change will hopefully reduce the risk of 'diagnosis switching'. Additionally, the focus of this guideline is on the process of prescribing, not second-guessing the final decision to prescribe or not, and therefore there is not a fixed 'target' for prescribing rates for a particular medication for any service, sector, or unit.

In one cluster randomised control trial in the UK, a training and support intervention targeting nursing home care staff across several nursing homes reduced antipsychotic use by 19% in residents with dementia, without worsening behavioural symptoms. This reduction was sustained for 12 months (Fossey et al., 2006).

In Ireland, one public residential care unit (where 60-80% of residents have dementia) reports that it reduced its rate of prescribing of psychotropic medications dramatically between 2016 and 2017, by introducing a new procedure requiring initial trials of psychosocial interventions prior to medications (personal communication, 21st November 2017). Prescribing fell from a baseline of 40/160 (25%)

residents prescribed a benzodiazepine ‘as needed’ to just nine residents at six weeks, with this new practice maintained over many months (while recorded). Similarly, a gradual, targeted approach to reducing hypnotics in the same unit led to a reduction in residents being prescribed ‘as needed’ hypnotics from 18 at baseline to zero, and regular prescriptions falling from 25 to 19.

A recent feasibility study in another 75-bed HSE residential care facility (Walsh, 2019) has shown that staff are willing to attend education sessions and to improve their practice in this area, with the prescription of regular antipsychotic medication to the residents with dementia there decreasing from 44% to 36% over the three-month intervention period, and the absolute number of ‘as required’ psychotropic medications administered monthly also decreasing. This study has also highlighted some of the practicalities of implementing the practice change, which have been incorporated into the implementation plan (Appendix 6). The potential cost avoidance from improved practice is discussed in Appendix 5b (Budget Impact Analysis).

2.3.2 National context for this guideline

The National Dementia Strategy (2014) (<https://www.gov.ie/en/publication/62d6a5-national-dementia-strategy/>) sets out the Department of Health’s strategy to improve dementia care in Ireland.

The priority action areas for implementation included:

- Better awareness and understanding;
- Timely diagnosis and intervention;
- Integrated services, supports and care for people with dementia and their carers;
- Training and education;
- Research and information systems;
- Leadership.

Under “Timely Diagnosis and Intervention”; the National Dementia Strategy Implementation plan (2015) stated that “The Health Service Executive (HSE) 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” (Priority Action 2.3). The Clinical Lead of the National Dementia Office was tasked with developing this guidance material in November 2017.

Similarly, one of the ‘Key Priorities and Actions to Deliver on Goals’ of the HSE Social Care Division’s Operational Plan in 2016 had been to “Implement a Quality Improvement Initiative in the safe prescribing of antipsychotic medication in a number of early adopter sites in Older Persons Residential Services by Quarter 4” (HSE, 2016). Based on this, the division proposed to “develop clinical guidelines on the appropriate prescribing and management of Psychotropic medicines in long-term care settings for older people, to ensure that such medicines are managed in line with best practice”.

The “Draft Project Initiation document” was used as an initial basis for developing the guidance, modified by 1) increasing the scope to people with dementia in any setting, not just residential care units and 2) narrowing the focus from medication “management” (which would include storage, dispensing, formulations etc.) to “prescribing”. The latter change reflected the core intent within the National Dementia Strategy, also cognisant that there is a HSE Medicines Management Programme in existence. This modification was agreed by the National Dementia Strategy implementation monitoring group,

which is chaired by the Department of Health.

As the GDG was being formed, the utility of a simple “guidance document” was questioned. It was felt by many parties that such a document being “made available in all relevant settings, including nursing homes” may not necessarily result in it being read or consulted, and that poorly ‘psychotropic risk aware’ services or facilities may be less likely to use the guidance document. It was also felt that the proposed strategy for the HSE to distribute the guidance document to private residential care units, where many of the people with dementia living in residential care reside, would not necessarily lead to its adoption in this setting in the absence of other resources to change culture and practice.

Thus, in consultation with the National Dementia Strategy implementation monitoring group, a decision was made to develop a robust Clinical Guideline for the Appropriate Use of Psychotropic Medication for non-cognitive symptoms in People with Dementia and to apply for this to be endorsed as a NCEC National Clinical Guideline. This would include an intrinsic implementation plan, key quality improvement metrics, and associated audit tools, to drive improvements in clinical practice.

2.3.3 Alignment with national policy/strategy

The following Irish legislation, policy and guidance documents are relevant to this guideline.

Legislation and statutory guidance:

- Health and Social Care Professionals Act 2005.
- Health and Social Care Professionals (Amendment) Act 2012, 2017.
- Mental Health Act 2001, 2008.
- Health Act 2007 (Care and Welfare of Residents In Designated Centres For Older People) Regulations 2013.
- Mental Health (Amendment) Act 2015.
- Assisted Decision-Making (Capacity) Act 2015 (<http://www.irishstatutebook.ie/eli/2015/act/64/enacted/en/html>).

Policies and non-statutory guidance

- The Irish National Dementia Strategy (2014) (<https://assets.gov.ie/10870/3276adf5273f4a9aa67e7f3a970d9cb1.pdf>).
- HSE Framework for Improving Quality in our Health Service (2016).
- Healthy Ireland – A Framework for Improved Health and Wellbeing (2013- 2025).
- The National Positive Ageing Strategy: Positive Ageing Starts Now (2013).
- National Carers’ Strategy: Recognised, Supported, Empowered (2012).
- National Standards for Safer Better Healthcare (HIQA, 2012).
- National Standards for Residential Services for Children and Adults with Disabilities (HIQA, 2014).
- National Standards for Residential Care Settings for Older People in Ireland (HIQA, 2015).
- Future Health: A Strategic Framework for Reform of the Health Service (2012- 2015).
- HSE National Consent Policy (2017) (<https://www.hse.ie/eng/services/list/3/acutehospitals/hospitals/ulh/staff/resources/pppgs/nationalconsentpolicy/nationalconsentpolicy.pdf>).

- Sláintecare Report (2017) and Implementation Strategy (2018).
- Nursing and Midwifery Board of Ireland's Guidance to Nurses and Midwives on Medication Management (2007, under review 2019).
- Health Information and Quality Authority's Medicines Management Guidance (2015).

In addition, the new Quality Care Metrics (QCM) for Older Persons has a metric for 'responsive behaviour support' (<https://healthservice.hse.ie/filelibrary/onmsd/national-guideline-for-nursing-and-midwifery-quality-care-metrics-data-measurement-in-older-person-services-2018.pdf>).

Within this, there are two relevant indicators:

- a) there is documented evidence that PRN (as needed) psychotropic medicines are administered as a last resort only, following review and employment of non-pharmaceutical interventions.
- b) a record of all PRN psychotropic medication administered is maintained.

The GDG has liaised with the QCM lead to ensure the psychotropic guideline aligns well with the QCM, and relevant members of the QCM team received drafts of the guideline during its development.

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 (NO5CD) 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 “specialling 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

<p>Pre-existing or comorbid mental health issues</p>	<p>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.</p>
<p>Acetylcholinesterase inhibitors and memantine for cognitive symptoms</p>	<p>Acetylcholinesterase inhibitors and memantine are often used specifically for <u>cognitive symptoms</u> associated with dementia. This guideline specifically considers the evidence for these medications for <u>non-cognitive symptoms</u> 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).</p>

<p>Psychotropic medication storage, dispensing, administration, formulation and disposal</p>	<p>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)</p>
<p>Prophylaxis or treatment of delirium</p>	<p>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 <u>documented</u> delirium, the recommendations in this guideline can be considered temporarily superseded by local delirium management protocols, until the delirium is fully resolved.</p>
<p>Treatment at end of life</p>	<p>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.</p>
<p>Non-pharmacological interventions for non-cognitive symptoms or responsive behaviours</p>	<p>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, <i>Non-cognitive Symptoms in Dementia (NCSD): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners</i> for further information on non-pharmacological interventions (https://dementiapathways.ie/publications).</p>

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

The Irish Medical Council Guide to Professional Conduct and Ethics for Registered Medical Practitioners (2016) does not give specific guidance on off-label prescribing but states that “you must ensure as far as possible that any treatment, medication or therapy prescribed for a patient is safe, evidence-based and in the patient’s best interests”

<https://www.medicalcouncil.ie/News-and-Publications/Reports/Guide-to-Professional-Conduct-and-Ethics-8th-Edition-2016-.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.

2.7 Sources of funding

The salary for a postdoctoral researcher (0.6 FTE for 6 months) to perform guideline and literature searching was funded by the National Dementia Office. Two members of the NDO were members of the GDG (Co-chair and member). In addition, funding was provided by the Department of Health for health economist support for the Budget Impact Analysis, and for the cost of international guideline agreement fees.

2.8 Guideline methodology

The GDG agreed that no one existing guideline could be simply adopted for use in Ireland, given the particular scope of the guideline and contextual factors of the Irish healthcare system. Equally, it would be time-inefficient to develop a guideline *de novo* from empiric evidence. Thus, the GDG aimed to adapt existing international guidelines wherever possible, supplemented by *de novo* recommendation development where needed for a particular clinical question.

The ADAPTE principles for guideline adaptation were used to ensure rigour in our adaptation process (ADAPTE Collaboration, 2009). ADAPTE had a robust development process, and has been used by many

international guideline development groups, and is the adaptation process suggested within the NCEC Guideline Developers Manual (2019).

The *Flowchart of Guideline Development Process* (Appendix 10) outlines the stages of guideline development and involved three phases (Figure 2.2).

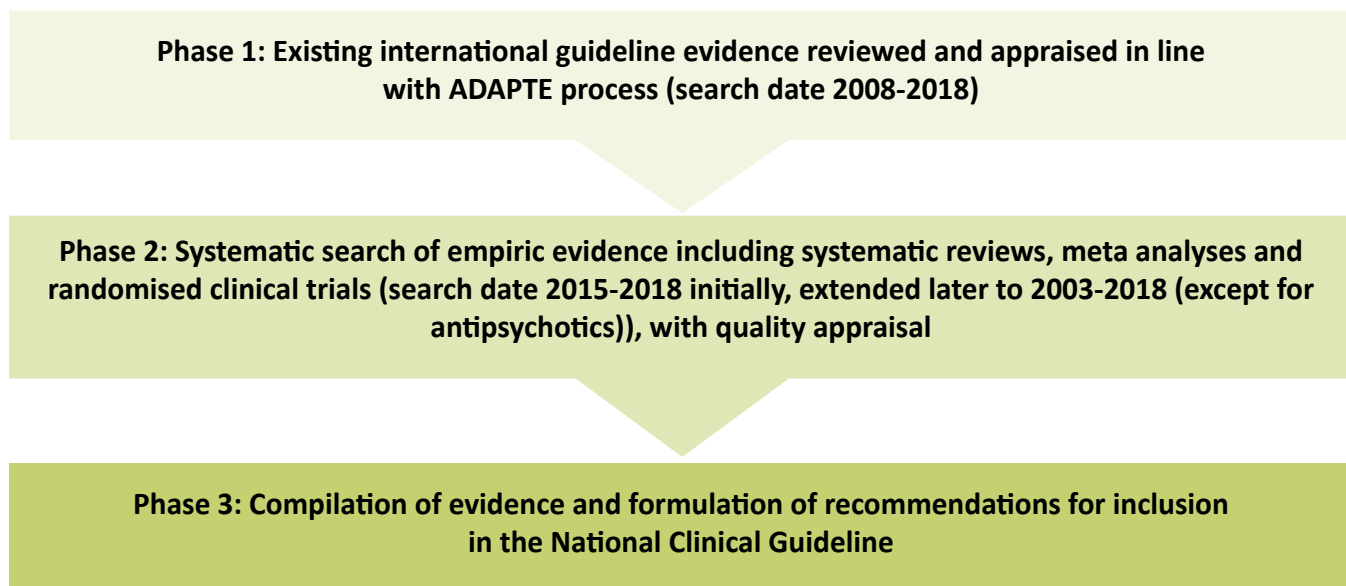


Figure 2.2: Phases of the evidence review process

The process of guideline development involved several steps:

Step 1: Formulate the key questions

Step 2: Search methodology

Step 3: Screen and appraise the evidence

Step 4: Develop and grade the recommendations

Step 1: Formulate the key questions

The first meeting of the GDG in December 2017 established the scope of the guideline and the overall work plan for 2018. At this meeting, the medication classes to be included were agreed, namely antipsychotics, acetylcholinesterase inhibitors and memantine, antidepressants, anticonvulsants, benzodiazepines and z-drugs, as these are the most common medications used in clinical practice in this context. The GDG then met in February 2018 to discuss the key questions for the literature review. It was agreed that broad focus would be:

- (1) What do existing guidelines recommend in terms of best practice with regard to psychotropic medication in people with dementia for the treatment of non-cognitive symptoms/BPSD? Where are there gaps or contradictions in the existing guidelines?
- (2) What does recent empiric evidence-including systematic reviews, meta-analyses and randomised controlled clinical trials, published on psychotropic medication use in people with dementia, state to support or contradict existing guidelines?

These were refined to specific healthcare questions, as presented in Table 2.5.

Table 2.5: Key healthcare questions

1	a) What is the <u>process</u> that needs to take place when considering the use of psychotropic medication in a person with dementia, to optimise safety and efficacy? b) When should pharmacological medication be commenced relative to non-pharmacological interventions?
2	If psychotropic medication is deemed necessary for the management of non-cognitive symptoms, what route of administration should be used?
3	What is the efficacy of antipsychotic medication for non-cognitive symptoms? (Which symptoms or behaviours best respond to antipsychotics?)
4	What are the risks of using an antipsychotic medication in the management of non-cognitive symptoms?
5	If antipsychotic medication is deemed necessary for the management of non-cognitive symptoms, which is the most appropriate choice of antipsychotic to use?
6	a) When should a review of a person with non-cognitive symptoms who has commenced antipsychotic medication occur? b) What is the process that needs to take place when tapering/withdrawing antipsychotic medication in the management of non-cognitive symptoms?
7	What is the evidence to support the use of acetylcholinesterase inhibitors and memantine in people with dementia in the management of non-cognitive symptoms?
8	What is the evidence to support the use of antidepressants in people with dementia in the management of non-cognitive symptoms?
9	What is the evidence to support the use of anticonvulsants in people with dementia in the management of non-cognitive symptoms?
10	What is the evidence to support the use of benzodiazepines in people with dementia in the management of non-cognitive symptoms?
11	What is the evidence to support the use of z-drugs in people with dementia in the management of non-cognitive symptoms?

In order to frame these questions, the PICOS framework was employed. Appendix 2 includes the population, intervention, comparator, outcomes, and setting for the searches performed (Appendix 2.1 to 2.4).

Step 2: Search methodology

The review was based on a framework by Arksey and O' Malley (2005) and employed the PRISMA frameworks (Appendix 2.5 PRISMA Framework for International Guideline Review; Appendix 2.6. PRISMA Framework for Empiric Evidence).

International guidelines search

A formal literature search was undertaken by a postdoctoral researcher with the necessary skills to identify applicable published guidelines between 1st January 2008 and 30th March 2018 (10-year span, as agreed by the Guideline Writing Group).

The writing group established a list of websites and databases to be searched for guidelines and other relevant content. The websites included:

- National Guideline Clearinghouse (www.guideline.gov)
- Guidelines International Network (www.g-i-n.net)
- Agency for Healthcare Research and Quality (AHRQ) (<https://www.ahrq.gov/>)
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)
- National Institute for Health and Clinical Excellence (www.nice.org.uk)

The search for guidelines included a hand search of international government sources, professional medical organisations, and specialised dementia services, as well as nongovernmental bodies (e.g. Alzheimer's Association, Alzheimer's Society), in conjunction with a search of associated databases (Appendix 2.3: Search Strategy for International Guidelines). The search strategy focused on developed countries, given the specific geographical, governance and healthcare system similarities to Ireland. The search utilised keywords "*dementia*", "*antipsychotics*", "*anticonvulsants*", "*antidepressants*", "*benzodiazepines*", "*acetylcholinesterase inhibitors*" and "*z-type medication*". Appropriate synonyms were adopted for each keyword (Appendix 2.3).

A search for existing guidelines was performed using the same keywords in Google search engine; the first 200 hits were screened for eligibility using the pre-defined inclusion/exclusion criteria.

Inclusion criteria:

Guidelines were included if they:

- were written in English
- focused on dementia (any type)
- included recommendations on non-cognitive and/or behavioural symptoms
- were developed for use within countries with a relevant healthcare system for the Irish context
- were published since 1st Jan 2008.

Empiric evidence search

The initial plan was to review empiric evidence since the end date of the search for the most recent guidelines (i.e. for APA 2016 and NHMRC 2016 guidelines); thus, the initial search period was set from 30th March 2015 to 30th March 2018. Of note, although the updated 2018 NICE guidelines on this topic were available in draft format for consultation at this time, they were not finalised at the time of our literature search.

The literature search used the same keywords as the international guideline review ("*dementia*", "*antipsychotics*", "*anticonvulsants*", "*antidepressants*", "*benzodiazepines*", "*acetylcholinesterase inhibitors*" and "*z-type medication*"), with the addition of limits to include only: "systematic review", "meta-analysis", "randomised clinical trial" and "nonrandomised clinical trial" and appropriate synonyms. The search was an extension of the search strategy used for the American Psychiatric College guidelines (conducted in 2015) and the Agency for Healthcare Research and Quality (AHRQ) review of Maglione et al. (2011) (Appendix 2.4: Search Strategy for Empiric Evidence). The search included PubMed, Medline, EBSCO, PsycINFO, Cochrane DARE (Database of Abstracts of Reviews of Effects), and Cochrane CENTRAL (Cochrane Central Register of Controlled Trials) databases.

Subsequently, the detailed review of existing guidelines revealed gaps in medication coverage compared to our planned guideline scope (i.e. most existing guidelines focused on antipsychotic medication only).

Thus, a second, more retrospective search was performed for all psychotropic medications except antipsychotics, based on literature published from 1st January 2003 to the 30th March 2018.

Inclusion criteria:

- randomised controlled trials (RCTs), Cochrane or systematic reviews, or meta-analyses;
- published in peer-reviewed journals;
- published in English;
- included adults with any type of dementia, of any severity, in any setting;
- focused on the treatment/management of non-cognitive symptoms;
- reported on pharmacological interventions alone or compared pharmacological interventions with non-pharmacological interventions;
- compared placebo or usual care with psychotropic medication (any classification of drug);
- reported on pharmacological interventions, including antipsychotics, antidepressants, cognitive enhancers, benzodiazepines and z-drugs, anticonvulsants;
- reported on outcomes or adverse effects in people with non-cognitive symptoms.

Evidence was excluded if it was:

- not focused on a population with dementia;
- not focused on psychotropic medications (any classification);
- not focused on non-cognitive symptoms (e.g. treating other mental health conditions or delirium);
- focused on cognitive symptoms with no reference to non-cognitive symptoms;
- solely focused on treatments other than pharmacological interventions, including non-pharmacological or alternative;
- focused on experimental therapies;
- low level evidence including case reports, editorials, and commentaries.

In addition, the bibliographic databases and reference lists of included articles were reviewed for additional studies. Irrelevant articles were excluded, and potentially eligible articles were categorised by classification of psychotropic drug.

Step 3: Screen and appraise the evidence

International guidelines screen and appraisal

The title and abstracts of guidelines were screened by the postdoctoral researcher. Following this, 31 guidelines that met the pre-defined inclusion criteria were read in full, and of these 21 were selected as being potentially eligible. These were independently reviewed in full by a second reviewer (GDG member), and following discussion, a final list of eight eligible guidelines was agreed by the two reviewers. Excluded guidelines at this stage did not focus on dementia or non-cognitive symptoms or psychotropic medications or were not actually guidelines despite using this term in the title and abstract. Earlier versions of guidelines that were replaced by a later version of the guideline were also excluded. In total, eight guidelines were finally eligible for inclusion. A full depiction of this process is presented in Appendix 2.5.

The eight guidelines were graded for methodological rigour according to the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE) II tool (Brouwers et al., 2010). This tool is used internationally and forms part of the ADAPTE process. Appraisal was performed independently by two reviewers. Differences of opinions were resolved by mutual consensus. The AGREE II overall scores for

included guidelines are included in Appendix 3.1 (Coverage within international guidelines of evidence related to key questions).

Ultimately, six guidelines were deemed to be of acceptable quality and relevance for inclusion in the review. Permission was granted from the guideline owners to reproduce their content, including the adaptations herein. These six guidelines represented a variety of geographical regions including: 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 Columbia (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).

Table 2.6: International guidelines adapted for this National Clinical Guideline

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

For details of which guideline informed each key question, please refer to Appendix 3.1. The relevant recommendations within these guidelines were mainly adapted rather than adopted, as indicated in the relevant sections and related evidence tables in Appendix 3.2. All final recommendations in this current guideline have a clear link to each relevant guideline recommendation, and to empiric evidence where relevant.

Empiric evidence screen and appraisal

The title and abstracts of retrieved articles in the empiric literature were reviewed by the postdoctoral researcher and screened with the inclusion/exclusion criteria. Following this, full text articles were read by two reviewers to determine those that met the inclusion criteria. The decision on which studies to include/exclude was performed independently. Disagreements between reviewers were resolved by an impartial third party.

The Assessment of Multiple Systematic Reviews (AMSTAR) 2 checklist (Shea et al., 2007) was employed at screening stage for the empiric evidence. Randomised controlled trials (RCTs) were appraised by two reviewers, using the methodology described by Hawker et al. (2002). This appraisal process is simple and is particularly suitable for appraising data across different settings and disciplines. Reviews required a rating of five or greater on the AMSTAR to be included, with RCTs requiring a score of 28/36 to be

included. Reviews that overlapped with the most recent and comprehensive review were excluded to avoid double entries.

Data extraction

International guidelines

Data extraction from the included guidelines was initially performed by the postdoctoral researcher, using a “recommendation matrix table”, and then checked by at least one other member of the Guideline Writing Group, and discussed by the whole Guideline Writing Group. This table contained key points from the reviewed guidelines, recorded verbatim, and their recorded strength of recommendation where available. The grading systems used by the original guidelines are presented in Appendix 9.2.

Empiric evidence

Data from systematic reviews, meta-analyses and randomised controlled trials (RCTs) were extracted using standardised extraction tables (Appendix 3.2 to 3.4), by two independent data extractors, who met to resolve any discrepancies.

Step 4: Develop and grade the recommendations

The draft guideline recommendations were developed by the Guideline Writing Group following the amassing of all relevant literature, and were discussed in very draft form in April 2018 and then in detail at a GDG meeting in June 2018, where pre-meeting emailed feedback from GDG members was collated to guide the discussions. Decisions about which recommendations from existing guidelines to adopt and/or adapt were based on GDG consensus. In cases where discrepancies existed between guideline recommendations, newer and more robust guidelines were given precedent, and the supporting evidence was reviewed to guide the recommendation wording. In cases where no recommendations were suitable or available, evidence from systematic reviews, meta-analyses and RCTs were used to develop a new recommendation. Finally, Good Practice Points were developed by the GDG to provide guidance on important aspects of psychotropic prescribing that had little existing evidence base but were agreed by GDG consensus.

Each recommendation was assigned a grade for quality of evidence and strength of recommendation by the GDG, using the GRADE system (Table 2.7 GRADE system - quality of evidence; Table 2.8 GRADE system - strength of recommendation) (Guyatt et al., 2011; Ryan and Hill, 2016). The quality of evidence grade reflected the overall level of evidence upon which the recommendation was 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 was primarily based on the quality of evidence, but did take other factors into account, as explained in each relevant section.

The draft guideline was progressed through GDG sub-group meetings in September-October 2018, and a full GDG meeting in November 2018. Members were asked to verify if any key documents, resources, bodies or organisations had been omitted. 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 in February 2019 (Appendix 4: Consultation report).

Table 2.7: GRADE system - quality of evidence (summarised from the GRADE handbook)

GRADE of quality of the evidence	Description of what this means
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Note: The quality of evidence assigned for each recommendation is based on overall appraisal of the evidence for the clinical question, rather than the rating of individual studies. The GRADE system takes into account the following when applying an evidence level: risk of bias in included studies; magnitude of effect, dose-response gradient, and consistency of effect between studies; imprecision of results; directness of the evidence to the recommendation in question; publication bias (and confounding effects in observational studies- not included in this evidence review).

Table 2.8: GRADE system - strength of recommendation (adapted from the GRADE handbook)

The strength of a recommendation reflects the extent to which the GDG is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa. GRADE specifies two categories of the strength of a recommendation, strong and weak (or conditional). The implications for clinicians are as follows:

Strong recommendation	Conditional recommendation
<p>Most individuals should receive the recommended course of action.</p> <p>Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.</p> <p>Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</p>	<p>Recognise that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences.</p> <p>(Would not usually be suitable as a quality criterion or performance indicator)*</p> <p>Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.</p>

**This sentence added to the GRADE wording for clarity by the GDG*

2.9 Consultation summary

2.9.1 People with dementia, carer, advocacy and other relevant groups

The GDG membership included a person with dementia and a family member of a person with dementia (two additional members had to withdraw for personal reasons early in the guideline development process), to ensure that guidelines were cognisant of relevant views and opinions of people with dementia and their families. In addition, members of the Guideline Writing Group met with the Dementia Carers' Campaign Network in July 2018 and the Eastern Branch of the Irish Dementia Working Group in Sept 2018 (both meetings were kindly facilitated by the Alzheimer Society of Ireland). This gave people living with dementia and carers a chance to provide input into and feedback on the draft recommendations as they were in development, including the language used.

2.9.2 National stakeholder review

The draft guideline was circulated to relevant organisations and individuals for comment from February 12th to March 14th 2019, accompanied by an invitation letter and a standardised feedback form. A full list of those invited to review this guideline is available (Appendix 4: Consultation report). A detailed log was recorded of all submissions received, and any amendments made following the national stakeholder review process and resulting amendments are also included in Appendix 4: Consultation report.

2.10 External review

The final draft guideline was submitted for international expert review. The GDG agreed on two international reviewers to provide feedback on the draft guideline: Professor Sube Banerjee and Professor Louise Allan. These reviewers were chosen based on their indepth knowledge of the subject area and guideline development processes (detailed in Appendix 4). The guideline was reviewed by the experts, between the 12th February 2019 and the 12th March 2019, informed by a standardised set of questions (Appendix 4). The GDG carefully considered the comments received from the experts and made amendments to the guideline as appropriate. These are included in Appendix 4.

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.

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 (Appendix 6). 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.

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. 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. As described in Appendix 8, 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.

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.

2.14 Summary budget impact analysis

Overview

A systematic literature review of economic evaluations examining the effectiveness of pharmacological interventions for the treatment of non-cognitive symptoms of dementia was undertaken (Appendix 5, Part A). A Budget Impact Analysis (BIA) was then performed of the 5-year cost and cost avoidance/reduction of implementing the National Clinical Guideline, from the health payer perspective. Please refer to Appendix 5, Part B, for full details.

Key findings relating to costs

Four key categories of additional resources were costed:

1. Direct implementation costs: The cost of additional staff required for a national implementation team to support guideline implementation (one coordinator, two national trainers and part-time administrative support), dissemination/awareness raising costs, and the cost of developing an online training programme.
2. Auditing and evaluation costs: The resource impact of auditing hospitals and residential units to monitor the implementation of the guideline, and for evaluation at the end of the implementation period.
3. Training attendance costs: The cost of local HSE staff attending train-the-trainer sessions.
4. 'New practice' costs: Time resource for comprehensive assessment, and multidisciplinary/decision-making meetings with the person with dementia/Decision Supporter when considering antipsychotic medication.

The total direct implementation cost over a 5-year cycle is €0.87m- this is an actual cost, necessary for successful implementation (includes direct implementation and evaluation costs). It is anticipated that the remaining resources (€5.7m) for local trainer training-up time, audit and assessment and discussion will be 'provided within usual service' and therefore costs will be borne by individual services.

Key findings relating to benefits

If we match the UK reduction in the overall prescribing of antipsychotic medications (best available estimate) of 48.42% following implementation of policy there (benefit expected from year 2 of our implementation), we estimate a cost avoidance of €22.7m over 5 years from reduced medication costs and from reduced health and social care costs related to psychotropic medication adverse events. In

the USA, there was a 33% reduction in antipsychotic prescribing in residential care following a national initiative (Gurwitz et al., 2017). Thus, a sensitivity analysis was performed with more conservative 30% and 20% reductions in prescribing, yielding a cost avoidance of €14.1m and €9.4m, respectively, over 5 years (see summary of sensitivity analysis results in Table 3.2 below). The net cost avoidance is thus between €2.8m and €16.2m. In reality, this cost avoidance may be lower, due to the exclusion of the unquantifiable costs of local education to support compliance with the recommendations, but this is offset by our assumption that no services were currently following “best practice”, whereas it is part of usual care in some services.

Conclusion

With the caveat that there was scant evidence to guide the modelling of cost avoidance, a reduction in healthcare costs is anticipated following more appropriate prescribing of psychotropic medications, linked to the expected associated reduced prescribing of these medications. The cost of providing non-pharmacological interventions was not within the scope of this BIA, but is likely to be significant, and this should be costed in the future.

Table 3.2: Total costs and costs avoided from guideline implementation over a five-year horizon: baseline and sensitivity analysis (SA)

		Baseline 48.42%	SA 1: 30%	SA 2: 20%
Direct costs	National Implementation¹	777,095.15	777,095.15	777,095.15
	Evaluation²	93,146.01	93,146.01	93,146.01
	<i>Sub-total</i>	870,241.16	870,241.16	870,241.16
Absorbed into usual practice	Audit³	159,230.16	159,230.16	159,230.16
	Local Training⁴	258,019.70	258,019.70	258,019.70
	Assessment⁵	5,285,809.69	5,285,809.69	5,285,809.69
	<i>Sub-total</i>	5,703,059.55	5,703,059.55	5,703,059.55
	Total Costs	6,573,300.71	6,573,300.71	6,573,300.71
	Cost Avoided⁶	22,741,003.09	14,095,663.07	9,397,108.72
	Net Cost Avoided⁷	16,167,702.38	7,522,362.36	2,823,808.01

¹ National implementation officer and 0.5FTE admin support in post for three years; two national trainers for two years; online learning development; GP/community pharmacist dissemination and awareness activities (see table 1.1 in Appendix 5).

² Evaluation will include two baseline projects, and two end of implementation projects (see table 2.1)

³ Auditing of hospitals and public residential units, beginning in year three, once all appropriate staff is trained (see table 3.1 in Appendix 5).

⁴ The cost of training in year one includes 25% of local trainer costs (for train-the-trainer sessions). Training in year two includes 75% of local trainer costs. (See table 3.1 in Appendix 5)

⁵ The total cost is calculated by adding together the cost of training, national staffing, audit and assessment.

⁶ Less people with dementia will be prescribed psychotropic medications: cost avoided per person is €892.39 is applied.

⁷ The potential cost saving is calculated by subtracting total costs from costs avoided.

3 National Clinical Guideline Recommendations

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*

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".

The BPS guidance (2015) gives useful additional information for assessing and understanding non-cognitive symptoms in a person with intellectual disabilities and dementia (page 64, 65).

<https://www.bps.org.uk/sites/bps.org.uk/files/Member%20Networks/Faculties/Intellectual%20Disabilities/Dementia%20and%20People%20with%20Learning%20Disabilities%20%282015%29.pdf>

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 assessment¹ 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).

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.

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.

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

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 identifiable² 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

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 GDG were in agreement that if a decision to commence psychotropic medication is made, 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 psychotropic medication should be stopped if not improving symptoms after a reasonable trial (using clinician’s judgement as to final dose tried and the duration of trial at this dose, based on initial symptoms, degree of distress, and side effects). The GDG also felt that, in general, there should be a trial of tapering or withdrawing psychotropic medication once symptom stability is reached (although this may not be possible with some depressive episodes where relapse likelihood is high), in conjunction with re-trialling non-pharmacological interventions to maintain symptom remission. A good practice point was formulated to reflect this consensus.

Good Practice Point 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.

3.1.4 Route of administration of psychotropic medications

If a decision is made that a person requires psychotropic medication, a question occasionally arises as to the best route of administration. A person with dementia may be receiving depot antipsychotics for a pre-existing and co-morbid primary mental health disorder. Such prescribing is outside the scope of this guideline.

One international guideline (NHMRC, 2016) stated as a Good Practice Point that where medication is deemed necessary for the treatment of non-cognitive symptoms, the oral route should be used first, with intramuscular preferred to intravenous in cases where the oral route was not suitable or contraindicated (Appendix 3.2.3). Of note, other guidelines, including the NICE guidelines (2018) did not make reference to the route of administration for psychotropic medications; the NICE guideline referred users to NICE medicine management guidelines.

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*

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 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.

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 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.

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**

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.

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.

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 well 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.

Recommendation 7

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.

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).

⁴ 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 symptoms⁵.

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**

⁵ Prescribing an antipsychotic for BPSD, other than risperidone for short-term treatment of persistent aggression in Alzheimer's dementia, is off-label.

Good Practice Point 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).

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 Supporter⁴.

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 Supporter⁴.

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.

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 medication⁶.

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.

⁶ 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.

3.3 Acetylcholinesterase inhibitors and memantine

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 bodies³, 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

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.

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 **carer 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 **carer 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 **carer 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 moderate⁷ 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.

⁷ 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.

3.4 Antidepressant medication

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.

3.4.1 Empiric evidence for the use of antidepressants in a person with dementia

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 trazodone 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 trazodone 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>).

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 dementia⁸, 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.

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 (Konovalov 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 over-sedation 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 episodes⁹.

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**

⁹ For maximum duration of use refer to the Summary of Product Characteristics (SmPC). The Medicine Management Programme guidance (2018) contains an Appendix with useful details on dosage and maximum duration for the benzodiazepines licenced in Ireland, for both anxiety and insomnia (<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxiety-insomnia/bzraguidancemmpfeb18.pdf>). Appendix D.

3.7 Z-drugs (hypnotics) and melatonin

The HSE's Medicines Management Programme (2018) has useful information on the non-pharmacological treatment of insomnia (Appendix B of that document: The Good Sleep Guide) (<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/bzra-for-anxiety-insomnia/bzraguidancemmpfeb18.pdf>). The MMP guidance (2018) recommends that "BZRA (benzodiazepines and z-drugs) should only be prescribed for a period of a few days to two weeks for insomnia".

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 regimen¹⁰ 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**

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.

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.

4 Appendices

Appendix 1: Guideline Development Group terms of reference

The members of the Guideline Development Group are listed in the introduction section.

Role:

- Approval of the terms of reference and project plan
- Ensure project is aligned with the objectives of the National Dementia Strategy
- Ensure the guidelines are developed in line with NCEC framework
- Provide governance, guidance and direction in order to attain the objectives of the project
- Keep the project scope under control in order to assure the attainment of outcomes and deliverables as outlined in the project plan
- Ensure strategies to address potential threats to the project's success have been identified and are regularly re-assessed
- Attend, participate and contribute at the pre-agreed meetings
- Use influence and authority to assist the project in achieving its outcomes
- Review and approve final project deliverables (no individual veto power, but dissent can be noted).

Responsibilities:

Individual GDG members have the following responsibilities:

- Understand the goals, objectives and desired outcomes of the project
- Understand and represent the interests of project stakeholders and facilitate knowledge transfer exchange between the project group and stakeholders
- Take a genuine interest in the project's outcomes and overall success
- Act on opportunities to communicate positively about the project
- Check that the project is aligned with the priorities of the National Dementia Strategy and follows the NCEC framework for development
- Actively participate in meetings through attendance, discussion, and review of minutes, papers and other documents
- Support open discussion and debate, and encourage fellow GDG members to voice their insights
- Attend regular meetings as required (4-5 over 1 year) and actively participate in the group's work.

External reviewers

Potential expert reviewers were selected based on having a particular expertise in dementia, psychotropic medication and/or policy and guideline development. A short list of potential reviewers was drawn up, across different countries, disciplines and genders, based on invited suggestions from GDG members.

From these, two final expert reviewers were selected.

Name	Affiliations/organisations
Prof. Sube Banerjee	Associate Dean for Strategy and Professor of Dementia, University of Sussex, UK
Prof. Louise Allan	Professor of Geriatric Medicine, University of Exeter

Prof. Sube Banerjee is an old age psychiatrist. His research focusses on quality of life in dementia, evaluation of new treatments and services, and the interface between policy, research and practice. He served as the UK Department of Health's senior professional advisor on dementia and led the development of the UK National Dementia Strategy. Prof. Banerjee wrote the 2009 report on antipsychotics in dementia for the Dept. of Health in the UK that led to the UK government pledging to reduce by two-thirds the use of antipsychotics for people with dementia by November 2011. He also has led several trials of pharmacologic and non-pharmacologic interventions for non-cognitive symptoms in dementia.

Prof. Louise Allan is a geriatrician with a specialist interest in the Neurology and Psychiatry of Old Age. Her research interests include the non-Alzheimer's dementias and the physical health of people with dementia. She is the Dementia lead for the Dementia and Related Disorders Section of the British Geriatrics Society. She was a member of the Guideline Committee for the NICE Dementia guideline (2018).

Conflict of interests: None

Appendix 2: Search strategy

Appendix 2.1: PICOS population, intervention, comparator, outcomes, setting for overall search strategy

Criteria	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> Age 18 years or older (adult) Dementia (any type) Cognitive impairment/cortical dementia/ frontal dementias/ cognition disorders/ Alzheimer’s disease/ memory loss/ cognition impairment/ memory problems/ vascular dementia/ Parkinson’s disease dementia/ senile/ senility/ poor cognition/ dementia Lewy bodies/ mixed dementias 	<ul style="list-style-type: none"> Age 17 years or younger (not adult context) Mental health disorders (only) Psychiatric disorders (only)
Intervention	<ul style="list-style-type: none"> Pharmacological interventions Any psychotropic medication Antipsychotics/ psychotics/antipsychiatry / antipsychotic agent / antipsychotic drug Benzodiazepines/ anxiolytics Z-drugs/Zolpidem/Zopiclone Anticonvulsants/sodium valproate/valproate Tranquiliser/ major tranquiliser Neuroleptic/ neuroleptic agent/ neuroleptic drug Antidepressant(s)/ selective serotonin reuptake inhibitors/ MAOI’s/tricyclic/non-tricyclic/ maleate Acetylcholinesterase inhibitor/memantine/ cognitive drugs/ anti-dementia drugs/ dementia drugs 	<ul style="list-style-type: none"> Not related to psychotropic drugs (i.e. alternative or experimental therapies) Non-pharmacological interventions only
Comparator	<ul style="list-style-type: none"> Comparison with other pharmacological interventions or placebo Comparison with non-pharmacological intervention(s) Usual care No comparator 	<ul style="list-style-type: none"> None
Outcomes	<ul style="list-style-type: none"> Any patient/ healthcare outcomes <ul style="list-style-type: none"> Morbidity Mortality Quality of life Satisfaction Cost and resource use Adverse events/efficacy 	<ul style="list-style-type: none"> Outcomes attributable to comorbid conditions Outcomes among healthcare providers/caregivers/staff
Setting	<ul style="list-style-type: none"> All settings 	<ul style="list-style-type: none"> None
Study Design	<ul style="list-style-type: none"> Guidelines Systematic reviews Meta analyses RCTs 	<ul style="list-style-type: none"> Case studies Case reports Opinion pieces Editorials Commentaries Conference abstracts Conference proceedings Thesis/dissertations Non-systematic reviews Letters with no primary data
Language	<ul style="list-style-type: none"> English 	<ul style="list-style-type: none"> Non English

Appendix 2.2: PICOS for key questions

- 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?
- 1b When should pharmacological medication be commenced relative to non-pharmacological interventions?
- 2 If psychotropic medication is deemed necessary for the management of non-cognitive symptoms, what route of administration should be used?

Criteria	Broad areas	Synonyms searched
Population	People with Dementia	Dementia [TI/AB] OR "Dementia [MH] OR "cortical dementia* OR frontal dementias OR cognition disorders OR Alzheimer's, Alzheimer's disease* OR memory loss OR cognition impairment OR memory problems OR vascular dementia OR Parkinson's dementia OR senile, senility OR poor cognition OR Dementia Lewy bodies OR Pick Disease of The Brain [MH]
Intervention	Psychotropic medication	Psychotropic* OR pharmacological intervention.
Comparator	No comparator or comparison with non-pharmacological intervention or other pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non medicinal
Outcomes	Clinical outcomes	"Behavioural and psychological symptoms" OR cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

- 3 What is the efficacy of antipsychotic medication for non-cognitive symptoms? Which symptoms or behaviours best respond to antipsychotics?
- 4 What are the risks of using an antipsychotic medication in the management of non-cognitive symptoms?
- 5 If antipsychotic medication is deemed necessary for the management of non-cognitive symptoms, which is the most appropriate choice of antipsychotic to use?
- 6a When should a review of a person with non-cognitive symptoms who has commenced antipsychotic medication occur?
- 6b What is the process that needs to take place when tapering/withdrawing antipsychotic medication in the management of non-cognitive symptoms?

Criteria	Broad areas	Synonyms searched
Population	People with Dementia	Dementia [TI/AB] OR "Dementia [MH] OR "cortical dementia* OR frontal dementias OR cognition disorders OR Alzheimer's, Alzheimer's disease* OR memory loss OR cognition impairment OR memory problems OR vascular dementia OR Parkinson's dementia OR senile, senility OR poor cognition OR Dementia Lewy bodies OR Pick Disease of The Brain [MH].
Intervention	Antipsychotic medication	Psychotropic* OR anti-psychotics OR antipsychotics OR pharmacological interventions OR psychotics OR antipsychiatry OR psychiatric OR psychiatry OR antipsychotic agent OR antipsychotic drug OR major tranquilizer OR major tranquilliser OR major tranquillizer OR neuroleptic OR neuroleptic agent OR neuroleptic drug OR chlorpromazine OR Thorazine OR clozapine OR Clozaril OR diphenylbutyl piperidine OR fluphenazine OR Haldol OR haloperidol OR loxapine OR Loxitane OR Moban OR molindone OR prochlorperazine OR Mellaril OR thioridazine OR Navane OR thiothixene OR antianxiety agent OR ataractic OR ataractic agent OR ataractic drug OR tranquilizer OR tranquilliser OR tranquillizer OR Eskalith OR Lithane OR lithium carbonate OR Lithonate
Comparator	No comparator or comparison with non-pharmacological intervention or other pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non medicinal
Outcomes	Clinical outcomes	"Behavioural and psychological symptoms" OR cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

7 What is the evidence to support the use of acetylcholinesterase inhibitors and memantine in people with dementia in the management of non-cognitive symptoms?

Criteria	Broad Areas	Synonyms Searched
Population	People with Dementia	See above
Intervention	Use of cognitive enhancing drugs	Anti-dementia OR anti-dementia drugs OR anti-dem* OR cognitive drugs OR cognition drugs OR cognition enhancing OR enhancing drugs OR memory drugs OR enhancing cognition medication OR donepezil OR galantamine OR rivastigmine OR memantine
Comparator	No comparator or comparison with non-pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non-pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non-medicinal
Outcomes	Clinical outcomes	Cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

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

Criteria	Broad Areas	Synonyms Searched
Population	People with Dementia	See above
Intervention	Antidepressant drug	Antidepressant OR anti-depressant* OR anti-depre* OR Medication OR medicinal drug OR medicine OR MAOI OR monoamine oxidase inhibitor OR nefazodone OR Serzone OR nontricyclic OR nontricyclic antidepressant OR nontricyclic antidepressant drug OR nontricyclic drug OR Edronax OR reboxetine OR selective-serotonin reuptake inhibitor OR SSRI OR tricyclic OR tricyclic antidepressant OR tricyclic antidepressant drug OR maleate
Comparator	No comparator or comparison with non-pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non-pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non-medicinal
Outcomes	Clinical outcomes	Cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

9 What is the evidence to support the use of anticonvulsants in people with dementia in the management of non-cognitive symptoms?

Criteria	Broad Areas	Synonyms Searched
Population	People with Dementia	See above
Intervention	Anticonvulsant medication	Anticonvulsant drug OR anticonvulsants OR "convulsants" OR antiepileptic OR antiepileptic drug OR Emeside OR ethosuximide OR Zarontin OR gabapentin OR Neurontin OR hydantoin medicament OR medication OR medicinal drug OR mephenytoin OR Mesantoin OR Mebaral OR mephobarbital OR Gemonil OR metharbital OR Milontin OR phensuximide OR Mysoline OR primidone OR Depokene OR Valproic Acid OR valproic acid
Comparator	No comparator or comparison with non-pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non-pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non-medicinal
Outcomes	Clinical outcomes	Cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

- 10 What is the evidence to support the use of benzodiazepines in people with dementia in the management of non-cognitive symptoms?
- 11 What is the evidence to support the use of z-drugs in people with dementia in the management of non-cognitive symptoms?

Criteria	Broad Areas	Synonyms Searched
Population	People with Dementia	See above
Intervention	Benzodiazepine drugs	Benzodiazepines OR benzo's OR benzodiazepines OR alprazolam OR Xanax OR chlordiazepoxide OR Libritabs OR Librium OR diazepam OR Valium OR estazolam OR ProSom OR Ativan OR lorazepam OR midazolam OR Versed OR antianxiety drug OR anxiolytic OR anxiolytic drug OR minor tranquilizer OR minor tranquilliser OR minor tranquillizer OR muscle relaxant OR nitrazepam OR Restoril OR temazepam OR Halcion OR triazolam OR Zolpidem OR zopiclone OR z type OR z type medications
Comparator	No comparator or comparison with non-pharmacological intervention or placebo	Pharmacological OR medicinal OR medication OR non-pharmacological OR non-pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non-medicinal
Outcomes	Clinical outcomes	Cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy

Appendix 2.3: Search Strategy for international guidelines

Websites searched 30/03/2018

Resource name	URL	Category/Sub-category	Records
The Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/	Guidelines	500
Alzheimer's Association	https://www.alz.org/health-care-professionals/clinical-guidelines-dementia-care.asp	Guidelines/ Organisation	696
Australian National Health and Medical Research Council (NHMRC) Guidelines & Publications	www.nhmrc.gov.au/guidelines-publications	Guidelines and technology assessments	3
Canadian Agency for Drugs and Technologies in Health	www.CADTH.ca	Guidelines and technology assessments	3
Cochrane Dementia and Cognitive Improvement Group's	http://dementia.cochrane.org/	Guidelines and reviews	25
CMA Infobase Clinical Practice Guidelines Database (CPGs) (Canada)	www.cma.ca/En/Pages/clinical-practice-guidelines.aspx	Guidelines and technology assessments	17
Drugs@FDA (US Food and Drug Administration (FDA) database of approved drug products.)	www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm	Guidelines and technology assessments	2
Evidence Search (UK)	www.evidence.nhs.uk	Guidelines and technology assessments	3,688
National Guideline Clearinghouse (NGC) (US)	www.guideline.gov	Guidelines and technology assessments	22
National Health Service (NHS) (UK)	https://www.evidence.nhs.uk/	Guidelines	210
National Institute for Health and Care Excellence (NICE) Guidance (UK)	www.nice.org.uk/Guidance	Guidelines and technology assessments	260
New Zealand Guidelines Group (NZGG)	www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group	Guidelines and technology assessments	90
The Scottish Intercollegiate Guidelines Network (SIGN)	http://sign.ac.uk/	Guidelines	5
Registered Nurses Association of Ontario (RNAO)	http://rnao.ca/	Guidelines/ Organisational	37
Results following removal of duplicates, publication 2003-2018 and non-applicable content			37

Google searched 30/03/2018

Search engine	Search term	Date of search	Screened	Outputs
Google	Advanced Search All these words: "dementia" OR "Alzheimer's" AND this exact word or phrase: "management in adults" "guideline" Limited to: English language	30/03/2018	First 200 hits screened	First screen: 125 disregarded as not relevant e.g. Dementia: Diagnosis and Management in General Practice (exclude – not a national guideline)
				Clinical Practice Guidelines for Management of Dementia (excluded as not focussed on psychotropic medication but on diagnosing and assessment)
				The Irish National Dementia Strategy (2014) (excluded as it is a strategy not a guideline)
				understandtogether.ie (excluded as website not a guideline)
				Considerable repetition of guidelines particularly NICE
				Second screen: 70 disregarded as not guidelines
				Included: 5

Additional database searches for existing guidelines (PubMed, EBSCO*, CINAHL on 30th March 2018)

Search	PubMed	CINAHL	EBSCO*	Total
1. exp Dementia/	185,852	49,148	401,477	
2. (dementia or dementias or alzheimer* or Alzheimers or Alzheimer disease or Dementia [tiab] or "Dementia [MH] or "cortical dementia* or frontal dementias or cognition disorders or Alzheimer's, Alzheimer's disease* or memory loss or cognition impairment or memory problems or vascular dementia or Parkinson's dementia or senile, senility or poor cognition or Lewy bodies dementia or Pick Disease of The Brain [MH]).tw.	148,120	89,410	788,591	
3. 1 or 2	148,120	49,148	401,477	
4. Antipsychotics	125,154	14,860	159,547	
5. Risperidone/	9,397	2,579	28,698	
6. (aripiprazole or abilify or asenapine or saphris or clozapine or clozaril or lurasidone or latuda or olanzapine or zyprexa or paliperidone or invega or quetiapine or seroquel or risperidone or risperidal or ziprasidone or zeldox or anti-psychotics or antipsychotics pharmacological interventions psychotic antipsychiatry psychiatric psychiatry or antipsychotic agent or antipsychotic drug or major tranquilizer or major tranquilliser or major tranquilizer or neuroleptic or neuroleptic agent or neuroleptic drug or chlorpromazine or thiorazine or clozapine or clozaril or diphenylbutyl piperidine or fluphenazine or haldol or haloperidol or loxapine or loxitane or moban or molindone or prochlorperazine or mellaril or thioridazine or navane or thiothixene or antianxiety agent or ataractic or ataractic agent or ataractic drug or tranquilizer or tranquilliser or tranquilizer or eskalith or lithane or lithium carbonate or lithonate).tw.	235,232	23,013	261,829	

Search (continued)	PubMed	CINAHL	EBSCO*	Total
7. (atypical adj3 antipsychotic*).tw.	10,514	2,113	28,673	
8. (anticonvulsant drug or anticonvulsants or "convulsants" or antiepileptic or antiepileptic drug or emeside or ethosuximide or zaronin or gabapentin or neurontin or hydantoin medicament or medication or medicinal drug or mephenytoin or mesantoin or mebaral or mephobarbital or gemonil or metharbital or milontin or phensuximide or mysoline or primidone or depokene or valproic acid or valproic acid or antidepressant or anti-depressant* or anti-depre* or medication or medicinal drug or medicine or maoi or monoamine oxidase inhibitor or nefazodone or serzone or nontricyclic or nontricyclic antidepressant or nontricyclic antidepressant drug or nontricyclic drug or edronax or reboxetine or selective-serotonin reuptake inhibitor or ssri or tricyclic or tricyclic antidepressant or tricyclic antidepressant drug or maleate).tw.	6,130,350	302,622	6,781,758	
9. 4 or 5 or 6 or 7	1,011,321	128,685	3,641,777	
10. (benzodiazepines or benzo's or benzodiazepines or alprazolam or xanax or chlordiazepoxide or libritabs or librium or diazepam or valium or estazolam or prosom or ativan or lorazepam or midazolam or versed or antianxiety drug or anxiolytic or anxiolytic drug or minor tranquilizer or minor tranquilliser or minor tranquillizer or muscle relaxant or nitrazepam or restoril or temazepam or halcion or triazolam or anti-dementia or antidementia drugs or anti-dem* or cognitive drugs or cognition drugs or cognition enhancing or enhancing drugs or memory drugs or enhancing cognition medication). tw.	124,260	20,124	244,849	
11. exp Loxapine/	785	60	1,081	
12. (haloperidol or haldol or loxapine or loxapac or xylac).tw.	22,493	1,596	41,800	
13. 10 or 11 or 12	146,769	9,015	137,061	
14. antipsychotic agents/ or chlorpromazine/ or flupenthixol/ or fluphenazine/ or methotrimeprazine/ or perazine/ or perphenazine/ or pimozide/ or thiothixene/ or trifluoperazine/	124,493	12,285	149,184	
15. (antipsychotic or antipsychotics or chlorpromazine or largactil or fluphenazine or modocate or moditen or methotrimeprazine or nozinan or pericyazine or trilafor or pipotiazine or piportil or thioperazine or stelazine or flupentixol or fluanxol or thiothixene or navane or zuclopenthixol or clopixon or pimozide or orap).tw.	527,945	15,236	190,173	
16. 14 or 15	5,279,81	15,260	196,999	
17. (amisulpride or solian or blonanserin or lonasen or carpipramine or prazinil or clocapramine or clofekton or clotiapine or entumine or iloperidone or fanapt or fanapta or zomaril or mosapramine or cremin or perospirone or lullan or remoxipride or roxiam or sertindole or serdolect or sulphiride or sulphirid or eglonyl or zotepine or nipolept).tw.	8,565	388	16,076	
18. practice guideline/	130,650	223,976	2,343,284	

Search (continued)	PubMed	CINAHL	EBSCO*	Total
19. Critical Pathways/	47,528	1,114	27,129	
20. Clinical Protocols/	194,801	3,962	90,410	
21. (clinical pathway* or consensus or directive or directives or guideline* or protocol*).tw.	1,026,869	258,299	2,921,031	
22. ((standard or standards) adj3 (care or practice*)).tw.	1,067,152	765,595	11,551,105	
23. 17 or 18 or 19 or 20 or 21	2,180,990	1,248,271	23,530,718	
24. limit 22 to yr="2003 -Current"	727,263	641,044	8,627,295	
25. limit 23 to animals	224,439	102,000	108,041	
26. limit 23 to (animals and humans)	1,756,436	11,760	17,439	
27. 23 not 26	424,554	191	47,737	
28. limit 23 to (animals and humans)	399,763	191	38,643	
29. 8 or 12 or 15 or 16	5,842,673	312,266	6,827,248	
30. 3 and 28 and 29	2,041	341	2,527	4,909

*EBSCO database search included PsychInfo, PsychArticles, SociIndex

Appendix 2.4: Search Strategy for empiric evidence**EBSCO*, PubMed, CINAHL - conducted on the 30/03/2018**

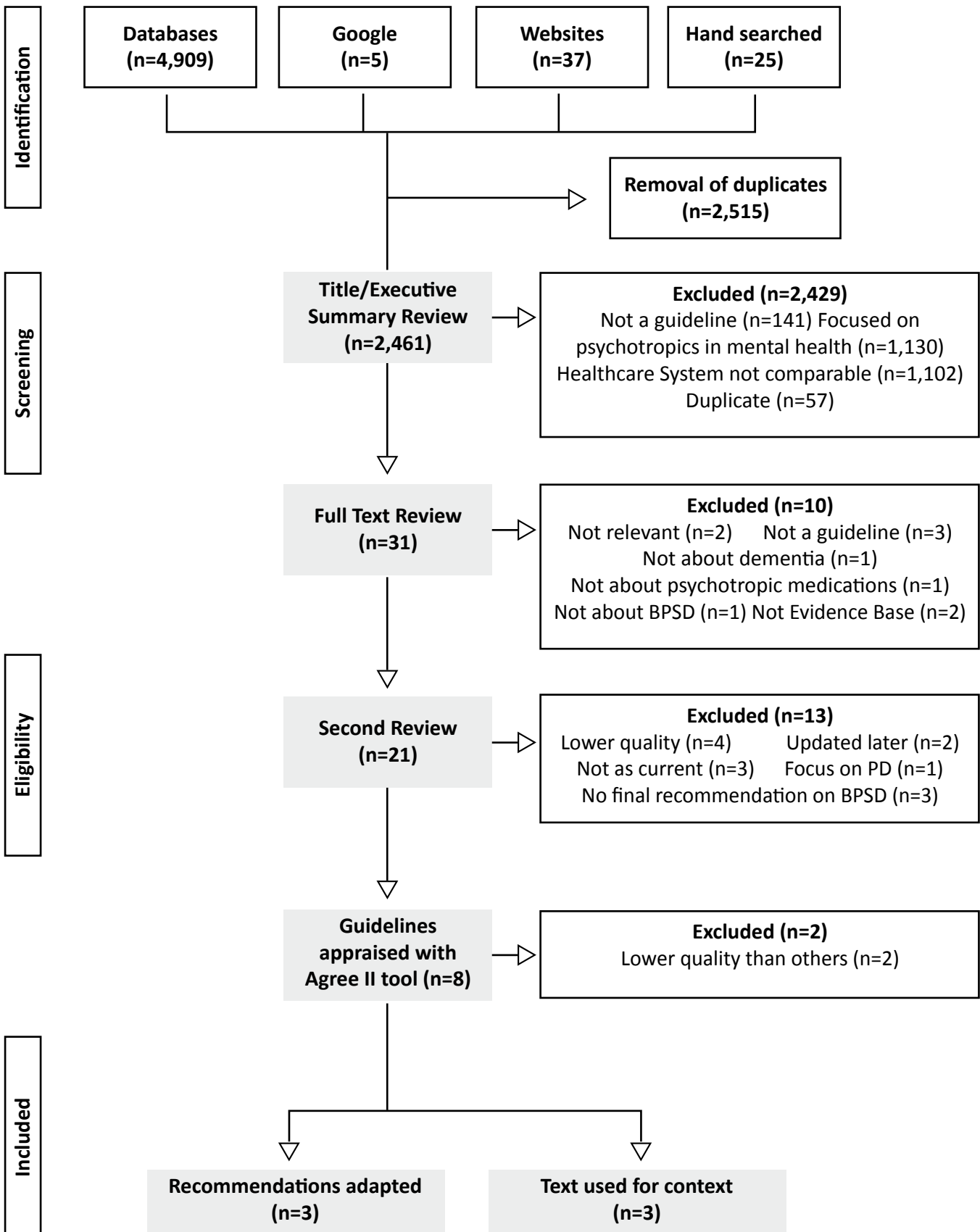
S1.	Dementia [TI/AB] OR "Dementia [MH] OR "cortical dementia* OR frontal dementias OR cognition disorders OR Alzheimer's, Alzheimer's disease* OR memory loss OR cognition impairment OR memory problems OR vascular dementia OR Parkinson's dementia OR senile, senility OR poor cognition OR Dementia Lewy Bodies OR Pick Disease of The Brain [MH]	1,248,434
S2.	psychotropic* OR anti-psychotics OR antipsychotics OR pharmacological interventions OR psychotics OR antipsychiatry OR psychiatric OR psychiatry OR antipsychotic agent OR antipsychotic drug OR major tranquilizer OR major tranquilliser OR major tranquillizer OR neuroleptic OR neuroleptic agent OR neuroleptic drug OR chlorpromazine OR Thorazine OR clozapine OR Clozaril OR diphenylbutyl piperidine OR fluphenazine OR Haldol OR haloperidol OR loxapine OR Loxitane OR Moban OR molindone OR prochlorperazine OR Mellaril OR thioridazine OR Navane OR thiothixene OR antianxiety agent OR ataractic OR ataractic agent OR ataractic drug OR tranquilizer OR tranquilliser OR tranquillizer OR Eskalith OR Lithane OR lithium carbonate OR Lithonate.	2,600,281
S3.	S1 AND S2	64,024
S4.	pharmacological OR medicinal OR medication OR non-pharmacological OR non pharmacy OR natural OR cognitive therapy OR behavioural therapy OR non medicina	5,389,490
S5.	(behavioural and psychological symptoms of dementia) OR (cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy)	33,520,351
S6.	S3 and S5	61,384
S7.	S6 Limiters - Published Date: 20030101-20181231	49,339
S8.	S7 Limiters - Published Date: 20030101-20181231; Narrow by Language: - English Search modes - Boolean/Phrase	47,970
S9.	S9 and S6 Limiters - Published Date: 20030101-20181231; Narrow by Language: - English Search modes - Boolean/Phrase	3,043
S10.	systematic review or meta-analysis or randomized controlled trial Limiters - Published Date: 20030101-20181231; Search modes - Boolean/Phrase	1,012,235
S11.	(systematic review or meta-analysis or randomized controlled trial) AND S9 Search modes - Boolean/Phrase	1,247
S12.	S11 AND S4 Search modes - Boolean/Phrase	6,893

*EBSCO database search included PsychInfo, PsychArticles, SociolIndex

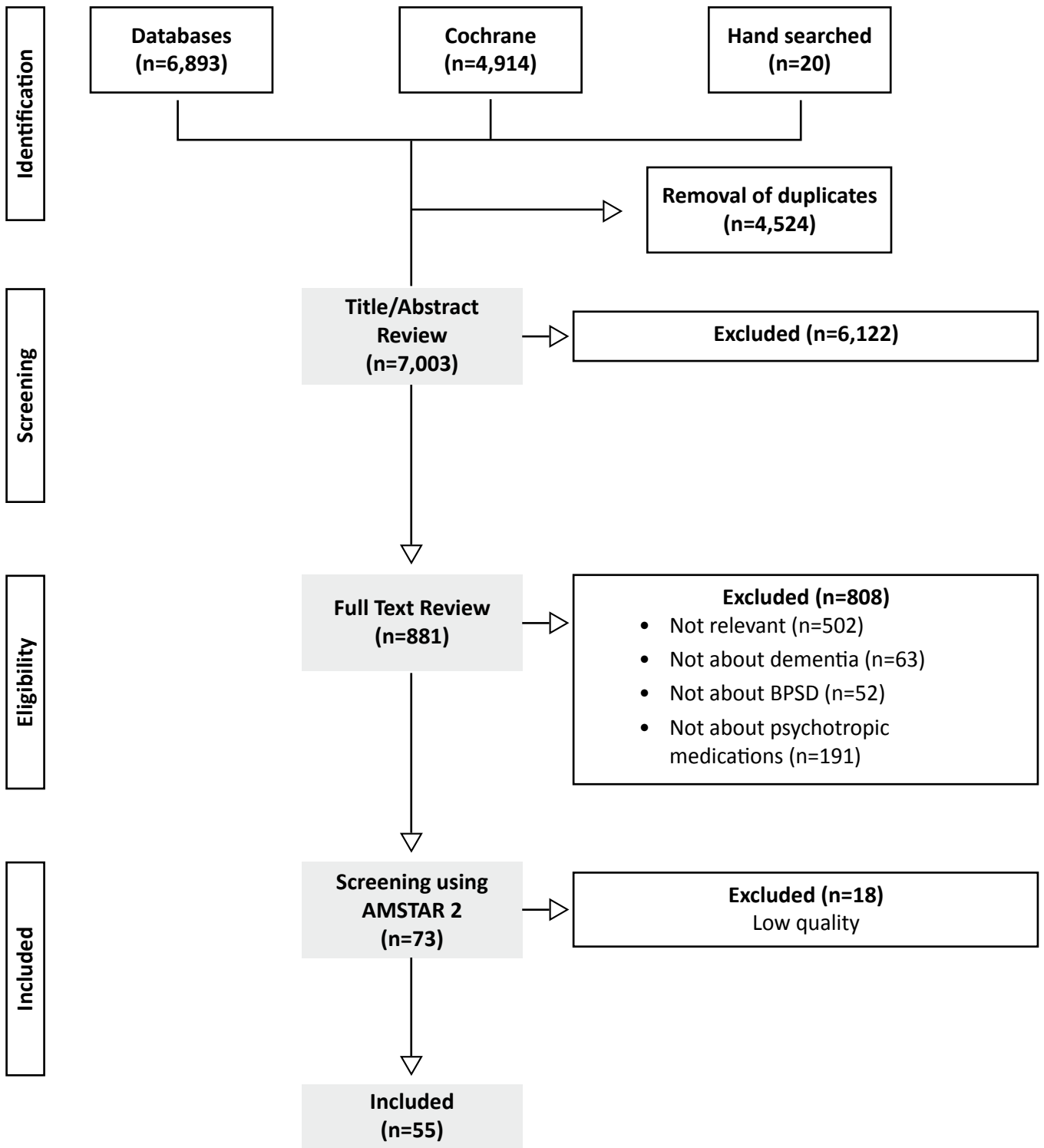
Cochrane database search conducted on the 30/03/2018

#1.	Dementia OR "Dementia" OR "cortical dementia*" OR frontal dementias OR cognition disorders OR Alzheimer's, Alzheimer's disease* OR memory loss OR cognition impairment OR memory problems OR vascular dementia OR Parkinson's dementia OR senile, senility OR poor cognition OR Dementia Lewy Bodies	21,166
#2.	Systematic review or meta-analysis or randomized controlled trial	742,248
#3.	psychotropic* OR anti-psychotics OR antipsychotics OR pharmacological interventions OR psychotics OR antipsychiatry OR psychiatric OR psychiatry OR antipsychotic agent OR antipsychotic drug OR major tranquilizer OR major tranquilliser OR major tranquillizer OR neuroleptic OR neuroleptic agent OR neuroleptic drug OR chlorpromazine OR Thorazine OR clozapine OR Clozaril OR diphenylbutyl piperidine OR fluphenazine OR Haldol OR haloperidol OR loxapine OR Loxitane OR Moban OR molindone OR prochlorperazine OR Mellaril OR thioridazine OR Navane OR thiothixene OR antianxiety agent OR ataractic OR ataractic agent OR ataractic drug OR tranquilizer OR tranquilliser OR tranquillizer OR Eskalith OR Lithane OR lithium carbonate OR Lithonate.	60,915
#4.	(behavioural and psychological symptoms of dementia) OR (cognitive functional OR behavioural ability OR quality of life OR symptoms OR side effects OR over-prescribing OR under-prescribing OR adverse effects (including hospital admission) OR behaviours OR cognition OR social OR physical OR quality of life OR behavioural OR impact OR function OR mental OR capacity OR effect OR efficacy)	498
#5.	#1 AND #2 AND #3	7,064
#6.	systematic review or meta-analysis or randomized controlled trial	742,258
#7.	#5 AND #6	7,064
#8.	#7 Limiter: English language	6,045
#9.	#8 Limiter: Publication 01/01/2003 to 30/03/2018	4,914

Appendix 2.5: PRISMA framework for international guideline review



Appendix 2.6: PRISMA framework for empiric evidence



Appendix 3: Evidence tables

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

Clinical Guideline	NICE	National Health Medical Research Council	American Psychiatric Association	Ministry of Health British Columbia	American Medical Directors Association	British Psychological Society (Intellectual disability only)
Year	2018	2016	2016	2012	2013	2015
Country	UK	Australia	USA	Canada	USA	UK
AGREE II score* (max 7)	6.5	6	5.5	4.5	4.5	4
Psychotropic prescribing general principles	✓	✓	✓			
Psychotropic route of administration		✓				
Efficacy of antipsychotics for non-cognitive symptoms	✓	✓	✓	✓		
Risks of antipsychotics for non-cognitive symptoms	✓	✓	✓			
Choice of antipsychotic for non-cognitive symptoms		✓	✓			
Review and tapering of antipsychotics in non-cognitive symptoms	✓		✓			
Acetylcholinesterase inhibitors and memantine for non-cognitive symptoms**						✓
Antidepressants for non-cognitive symptoms	✓	✓				
Anticonvulsants for non-cognitive symptoms	✓					✓
Benzodiazepines for non-cognitive symptoms**						
Hypnotics/ z-drugs for non-cognitive symptoms	✓					

* 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?		
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
APA 2016	<p>APA recommends that patients with dementia be assessed for the type, frequency, severity, pattern, and timing of symptoms.</p> <p>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.</p> <p>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.</p>	<p>1C= low evidence, but strong rec.</p> <p>1C= low evidence, but strong rec.</p> <p>1C= low evidence, but strong rec.</p>	<p>Adapted as recommendation 1 (plus detail in footnote)</p> <p>Adapted as recommendation 1 (plus detail in footnote)</p> <p>Adapted as GPP (for psychotropic medication)</p>
NICE 2018	<p>Before starting non-pharmacological or pharmacological treatment for distress in people living with dementia, conduct a structured assessment to:</p> <ul style="list-style-type: none"> • explore possible reasons for the person’s distress and • check for and address clinical or environmental causes (for example pain, delirium or inappropriate care) 	Not stated but wording is strong	Adapted as recommendation 1

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?		
Guideline	Recommendation	Strength	Adapted or adopted by GDG
APA 2016	APA recommends reviewing the clinical response to nonpharmacological interventions prior to nonemergency use of antipsychotic medication to treat agitation or psychosis	1C= low evidence, but strong rec.	Adapted as recommendation 2
NHMRC 2016	<p>People with dementia who develop BPSD should usually be treated using non-pharmacological approaches in the first instance.</p> <p>If pharmacological management is used, this should complement, not replace, non-pharmacological approaches.</p> <p>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).</p>	<p>Practice Point</p> <p>Practice Point</p> <p>Practice Point</p>	<p>Adapted as recommendation 2</p> <p>Adapted as recommendation 2</p>
NICE 2018	<p>As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.</p> <p>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.</p> <p>Only offer <u>antipsychotics</u> for people living with dementia who are either:</p> <ul style="list-style-type: none"> at risk of harming themselves or others or experiencing agitation, hallucinations or delusions that are causing them severe distress. 	<p>Not stated but strong wording</p> <p>Not stated but strong wording</p> <p>Not stated but strong wording</p>	<p>Adapted as recommendation 2</p> <p>Not used</p> <p>Adapted as recommendation 2</p>
Systematic Reviews	Conclusions		GRADE level of evidence
Jutkowitz et al., 2016	<i>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.</i>		Low
Abraha et al., 2017	<i>Music therapy and behavioural management techniques were effective for reducing BPSD.</i>		Low
Dyer et al., 2017	<i>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).</i>		Moderate
van der Steen et al., 2018	<i>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.</i>		Moderate (for depression, behaviour, agitation, aggression)
RCT	Conclusions		GRADE level of evidence
Pieper et al., 2016	<i>Behavioural management training for staff resulted in improved agitation and neuropsychiatric symptoms and less antidepressant medication use.</i>		Moderate

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)

Key Question 2			
What route of administration should be used if psychotropic medication is deemed necessary for the management of BPSD?			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
NHMRC 2016	If medications are necessary for the control of violence, aggression and extreme agitation in people with dementia, oral medication should be offered before parenteral medication.	Practice point	Adapted as GPP
	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.	Practice point	Adapted as GPP
	Intravenous administration should be used only in exceptional circumstances. Vital signs should 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.	Consensus Based Recommendation	Not used
	If parenteral medication is necessary for the control of violence, aggression and extreme agitation in people with dementia, olanzapine or lorazepam are preferred.	Consensus Based Recommendation	Not used
	Wherever possible, a single agent should be used in preference to a combination.	Consensus Based Recommendation	Adapted as GPP

Appendix 3.2.4: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 3

Key Question 3			
What is the efficacy of antipsychotic medication for non-cognitive symptoms (and which symptoms or behaviours best respond to antipsychotics)?			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
APA 2016	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.	1B= moderate evidence, and strong rec.	Adapted as Recommendation 3
NICE 2018	Only offer antipsychotics for people living with dementia who are either: <ul style="list-style-type: none"> • at risk of harming themselves or others or • experiencing <u>agitation, hallucinations or delusions</u> that are causing them severe distress. 	Not stated	Adapted as Recommendation 3
NHMRC 2016	People with dementia and severe BPSD (i.e. <u>psychosis and/or agitation/aggression</u>) causing significant distress to themselves or others , may be offered treatment with an antipsychotic.	Evidence Based Recommendation (conditional)	Adapted as Recommendation 3
MHBC 2012	Antipsychotic medications are indicated only if <u>aggression, agitation or psychotic symptoms</u> cause severe distress or an immediate risk of harm to the resident or others	Strong	Adapted as Recommendation 3
Systematic Review	Conclusions		GRADE level of evidence
Tampi et al., 2016	Antipsychotics demonstrated <u>modest</u> 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.		High

Appendix 3.2.5: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 7

<p>Key Question 4</p> <p>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)?</p> <p>b) What discussion should take place with a person with dementia or their family about risks?</p>			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
NICE 2018	Before starting antipsychotics, discuss the benefits and harms with the person and their family members or carers (as appropriate).	Not stated but wording implies strong.	Adapted as Recommendation 7
	Consider using a decision aid to support this discussion.	Conditional	Not used
	Be aware that for people with dementia with Lewy bodies or Parkinson’s disease dementia, antipsychotics can worsen the motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions .	Not stated	Adapted as Recommendation 5
NHMRC 2016	People with AD, VaD or mixed dementias with <u>mild-moderate BPSD</u> should not usually be prescribed antipsychotic medications due to increased risk of cerebrovascular adverse events and death .	Evidence Based Recommendation (strong)	Adapted as Recommendation 4
	As far as possible, antipsychotics should be avoided in people with Dementia with Lewy bodies due to the risk of severe untoward reactions, particularly extrapyramidal side effects .	Practice Point	Adapted as Recommendation 5
	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”	Evidence Based Recommendation (strong)	Adapted as Recommendation 7
APA 2016	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.	1B = moderate evidence, and strong rec.	Adapted as Recommendation 7

Appendix 3.2.6: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendation 9

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?			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
NHMRC 2016	The choice of antipsychotic should be made after an individual risk–benefit analysis.	EBR (strong)	Not used - see text
	(Risperidone has the strongest evidence for treating psychosis. Risperidone and olanzapine have the strongest evidence for treating agitation/aggression, with weaker evidence for aripiprazole).	EBR	Not used - see text
	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.	Practice Point	Adapted as recommendation 9
APA 2016	In the absence of delirium , if non-emergency antipsychotic treatment indicated, HALOPERIDOL should not be used as a first-line agent .	1B= moderate evidence, and strong rec.	Not used - see text
Systematic Review	Summary		GRADE level of evidence
Holmes et al. 2015	Atypical antipsychotics have the strongest evidence base, although these benefits are moderate.		High
Preuss et al. 2016	Atypical antipsychotics (SGA) have the strongest evidence base, although their benefits are moderate at best.		High
Hsu et al. 2017	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)		High
Kales et al. 2015	Olanzapine and risperidone were more efficacious than quetiapine or placebo, but quetiapine and placebo were better tolerated.		High
Desmarais 2016	Quetiapine failed to significantly reduce psychotic symptoms when compared to placebo.		High
El-Saifi et al. 2016	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.		Low
Meta-Analysis	Summary		GRADE level of evidence
Farlow et al. 2017	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.		High
Rao et al. 2016	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.		High

Appendix 3.2.7: Matrix table for evidence from guidelines and systematic empiric literature pertaining to recommendations 10 and 11

Key Question 6	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?		
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
<p>NICE 2018</p>	<p>When using antipsychotics</p> <ul style="list-style-type: none"> 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. <p>Stop treatment with antipsychotics if:</p> <ul style="list-style-type: none"> 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). 	<p>Not stated but wording implies strong</p>	<p>Adapted as recommendation 10</p> <p>Adapted as recommendation 11</p>
<p>APA 2016</p>	<p>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.</p> <p>APA recommends that in patients with dementia with agitation or psychosis, if there is <u>no clinically significant response</u> after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn.</p> <p>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.</p> <p>APA recommends that in patients with dementia who show <u>adequate response</u> 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.</p> <p>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.</p>	<p>1C= weak evidence, and strong rec.</p> <p>1B= moderate evidence, and strong rec.</p> <p>1C= weak evidence, and strong rec.</p> <p>1C= weak evidence, and strong rec.</p> <p>1B= moderate evidence, and strong rec.</p>	<p>Adapted as recommendation 11</p> <p>Adapted as recommendation 11</p> <p>Adapted as recommendation 10</p> <p>Adapted as recommendation 10</p> <p>Adapted as recommendation 12</p>

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?			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
NHMRC 2016	People with dementia who experience agitation <i>should</i> 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.	EBR (strong)	Adapted (as good practice point)
	Antidepressant medications with anticholinergic effects (e.g., tricyclic antidepressants) should be avoided because they may adversely affect cognition.	PP	Not included
	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 <i>should</i> be treated in the usual way.	EBR (strong)	Adopted as recommendation 17
NICE 2018	For people living with mild to moderate dementia who have mild to moderate depression and/or anxiety, consider psychological treatments.	Conditional	Adopted as recommendation 17
	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.	Not stated; but strong wording	Adopted as recommendation 17

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?			
Guideline	Recommendation	Strength of recommendation	Adapted or adopted by GDG
NICE 2018	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.	Not stated but wording implies Conditional	Adopted as recommendation 19
	Do not offer melatonin to manage insomnia in people living with Alzheimer's disease.	Not stated but wording implies Strong	Adopted as recommendation 20

Appendix 3.3: Detailed evidence from literature review of acetylcholinesterase inhibitors and memantine for non-cognitive symptoms in a person with dementia

Systematic reviews of acetylcholinesterase Inhibitors and Memantine

Source	Country	Studies	Drug	Dementia type	Recommended for use?	Key findings
Birk and Harvey 2018	UK	30 studies	Donepezil	AD	No	No difference for behavioural symptoms or quality of life. Participants on donepezil were more likely to experience adverse events (OR 1.6) or to withdraw from the trial before the end.
Hansen et al. 2008	USA	26 studies	Donepezil, Galantamine, Rivastigmine	AD	Evidence not clear	Indirect comparisons favoured donepezil over galantamine with regard to behaviour. Across trials, the incidence of adverse events was generally lowest for donepezil and highest for rivastigmine.
Rodda et al. 2009	UK	14 studies	9 Donepezil, 3 Galantamine 2 Rivastigmine	AD	Yes in absence of alternatives	The evidence regarding the efficacy of cholinesterase inhibitors in BPSD is limited, in part due to methodological considerations. In the absence of alternative safe and effective management options, their use is an appropriate pharmacological strategy for the management of BPSD in Alzheimer's disease.
Ballard et al. 2011	UK	2 for donepezil 2 for rivastigmine 2 for memantine	Donepezil, Rivastigmine and Memantine	DLB PDD	Evidence not clear	Modest but significant benefit conferred by AChEI treatment in people with DLB and PDD who are experiencing neuropsychiatric symptoms. Contradictions remain around the specific effects of ChEIs: two key studies reported different effects. It therefore remains difficult to make any interpretations beyond the reported benefit to the four main neuropsychiatric symptoms within the NPI.
McShane et al. 2006(Cochrane Review)	UK	12 trials	Memantine	AD	Evidence not clear	In moderate-severe AD, there is a (very) small beneficial effect at 6 months on behaviour (NB: NPI change only 2.76), but no effect on behaviour in mild-moderate AD. In mild-moderate vascular dementia, there is a small beneficial effect on behaviour. Overall, patients taking memantine were slightly less likely to develop agitation (OR 0.78; 95% CI 0.61-0.99) but no data on prevalent agitation .
Maidment et al. 2008	UK	6 RCTs (5 in meta-analysis)	Memantine	AD	Evidence not clear	In 1750 patients, memantine decreased NPI scores (mean difference -1.99 (95% CI -0.08 to -3.91) – NB not clinically significant . Authors' conclusion: Memantine may have a role in managing BPSD, but a number of limitations with the current data; effect size was relatively small, and whether memantine produces significant clinical benefit is not clear. [Note overlap with Cochrane review, but meta-analysis useful]
Gauthier et al. 2008	Canada	Pooled analysis from 6 RCTs	Memantine	AD	Yes	In 1,826 patients with moderate to severe AD, at 12 and 24/28 weeks, "any improvement" in NPI total score was more likely with memantine (p = 0.001 and p = 0.008). Authors' conclusion: "Memantine is effective in treating and preventing the behavioural symptoms of moderate to severe AD". [Maidment and Gauthier's included studies were the same, except Bakchine et al. (2005) not in Maidment's meta-analysis; but conclusions quite different, based on different choice of outcome change in NPI].
Wilcock et al. 2008	UK	Pooled analysis from 3 RCTs	Memantine	AD	n/a	Memantine treatment provided benefits for agitation/aggression. (55.3% vs. 43.1% improved at week 12, p = .011; 61.0% vs. 45.0% at week 24/28, p < .001). [Note overlap with Maidment and Gauthier]
Schneider et al. 2011	UK	6 (industry sponsored meta-analyses)	Memantine	AD	n/a	In mild AD (n=431), mean difference NPI was -0.17 (95% CI, -1.60 to 1.26). In moderate AD (n=697), mean difference was 0.25 (95% CI, -1.48 to 1.9). Authors' conclusions related more to cognition, but the lack of effect is obvious from the NPI results. [Note overlap with Maidment and Gauthier]
Gauthier et al. 2013	Canada	RCTs observational studies	Combination AChEI and memantine	AD	Yes, but not specifically for BPSD	In patients with moderate-to-severe AD, combination treatment with memantine and the ChEI donepezil has produced significant benefits in cognition, function, behaviour, global outcome, and care dependency, compared with donepezil treatment alone. Data from long-term observational studies support these findings. (Pharma sponsored review)

Individual trial	Country	Intervention	Drug	Type of dementia	Sample	Outcome measure	Duration	Effect	Systematic reviews including this study
Acetylcholinesterase Inhibitors									
Alzheimer's disease [AD]									
Black et al. 2007	Canada	RCT	Donepezil	Severe AD	Donepezil (n = 176) or placebo (n = 167)	Neuropsychiatric Inventory (NPI)	24 weeks	N/S	Rodda et al. 2009 Birk and Harvey 2018
Howard et al. 2007	UK	RCT	Donepezil	AD	272 patients	Cohen-Mansfield Agitation Inventory (CMAI)	12 weeks	N/S	Rodda et al. 2009
Holmes et al. 2004	UK	RCT	Donepezil	Mild to moderate AD	34 patients	NPI	12 weeks	[+]	Rodda et al. 2009
Selzer et al. 2004	USA	RCT	Donepezil	Early stage AD	Donepezil (n = 96), placebo (n = 57)	Apathy Scale	24 weeks	[+]	Rodda et al. 2009
Courtney et al. 2004	UK	RCT	Donepezil	Mild to moderate AD	565 community-resident patients	Bristol activities of daily living scale (BADLS)	12 weeks	N/S	Hansen et al. 2008 Rodda et al. 2009
Gauthier et al. 2002	Canada	RCT	Donepezil	Moderate to severe AD	290	NPI	24 weeks	[+]	Rodda et al. 2009
Feldman et al. 2001	Canada	RCT	Donepezil	Moderate to severe AD	290 patients with AD	Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+), NPI	24 weeks	[+]	Hansen et al. 2008 Birk and Harvey 2018
Tariot et al. 2000	USA	RCT	Galantamine	AD	978 patients with mild to moderate AD	NPI	5 months	[+]	Hansen et al. 2008
Rockwood et al. 2001	43 centres USA, Canada, UK, South Africa, Australia, and New Zealand	RCT	Galantamine	AD	Patients with probable Alzheimer's disease (n=386; 171 women)	ADAS/11	3 months	N/S	Hansen et al. 2008
Brodsky et al. 2005	Australia	RCT	Galantamine	AD	971 patients	ADAS/11, NPI	6 months	N/S	Hansen et al. 2008 Rodda et al. 2009
Ballard et al., 2005	UK	RCT	Rivastigmine	AD	93 patients (25 rivastigmine, 26 quetiapine, 29 placebo)	CMAI	26 weeks	N/S	Rodda et al. 2009

N/S=not significant, N/A=not applicable, N/R= not reported, RCT=randomised clinical trial, (+) = positive effect in favour of mentioned drug

Individual trial	Country	Intervention	Drug	Type of dementia	Sample	Outcome measure	Duration	Effect	Systematic reviews including this study
Acetylcholinesterase inhibitors									
Dementia Lewy bodies [DLB]									
Manabe et al. 2016	Japan	Open-label trial	Donepezil	DLB	24	NPI	N/R	[+]	N/A. GRADE quality: very low
Mori et al. 2012	Japan	RCT	Donepezil	DLB	140	NPI	12 weeks	[+]	Ballard et al. 2013
McKeith et al. 2000	UK, Spain, and Italy	RCT	Rivastigmine	DLB	120	cognitive assessment system and neuropsychological tests	20 weeks	[+]	Ballard et al. 2013
Parkinson's disease dementia [PDD]									
Dubois et al. 2012	France	RCT	Donepezil	PDD	550	ADAS-cog	24 weeks	N/S	Ballard et al. 2013
Emre et al. 2004	Turkey	RCT	Rivastigmine	PDD	410	NPI	24 weeks	[+]	Ballard et al. 2013
Vascular dementia [VaD]									
Auchus et al. 2007	USA	RCT	Galantamine	VaD	788 patients with probable VaD	NPI	26 weeks	N/S	N/A. GRADE quality: moderate (large sample but secondary outcome measure- very little details)
Mixed Dementia									
Tariot et al. 2001	USA	RCT	Donepezil	AD, or AD with cerebrovascular diseased	208 NH residents	Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)	24 weeks	[+]	Hansen et al. 2008 Birk and Harvey 2018
Erkinjuntti et al. 2008	Finland	RCT	Galantamine	AD with cerebrovascular disease	285	ADAS-cog/11 (primary outcome) NPI (secondary outcome)	6 months	N/S	N/A. GRADE quality: low (Pharmaceutical company funded; retrospective subgroup analysis; not powered for this outcome)

N/S=not significant, N/A=not applicable, N/R= not reported, RCT=randomised clinical trial, (+) = positive effect in favour of mentioned drug

Individual trial	Country	Intervention	Drug	Type of dementia	Sample	Outcome measure	Duration	Effect	Systematic reviews including this study
Memantine									
Alzheimer's disease [AD]									
Fox et al. 2012	UK	RCT	Memantine	AD	149 people with mod to severe agitation	CMAI (primary outcome) NPI (secondary outcome)	12 weeks	N/S on CMAI [+] NPI	N/A (hand search) GRADE quality moderate: study entry had minor issues; sample had high symptom level and placebo group responded a lot.
Porsteinsson et al. 2008	USA	RCT	Memantine	AD	433 with probable AD	NPI	24 weeks	N/S	Maidment et al. 2008 Gauthier et al. 2008 Schneider et al. 2011
Peskind et al. 2006	USA	RCT	Memantine	AD	403	NPI	24 weeks	[+]	McShane et al. 2006
Tariot et al. 2004	USA	RCT	Memantine	AD	322	NPI	24 weeks	[+]	Maidment et al. 2008 Gauthier et al. 2008
Reisberg et al. 2003	USA	RCT	Memantine	AD	181	Measures of cognition, function, and behaviour	28 weeks	[+] on behaviour	Schneider et al. 2011
Vascular dementia [VaD]									
Orogogoz et al. 2002	France	RCT	Memantine	VaD	321 patients	Nurses Observation Scale for Geriatric Patients (NOSGP)	28 weeks	[+]	McShane et al. 2006
Dementia Lewy bodies [DLB] or Parkinson's disease dementia [PDD]									
Emre et al. 2010	Turkey	RCT	Memantine	Mild to moderate PDD or DLB	159	No primary endpoint was defined. NPI	24 weeks	DLB [+] at 12 weeks PDD N/S	N/A (hand search) GRADE quality: moderate Pharma funded; not focussed on BPSD; effect in DLB but not PDD lessens the value of the + result
Aarsland et al. 2009	Norway, Sweden, UK	RCT	Memantine	PDD or DLB	72	Clinical global impression of change (CGIC)	24 weeks	[+] on both	Ballard et al. 2013

N/S=not significant, N/A=not applicable, N/R= not reported, RCT=randomised clinical trial, (+) = positive effect in favour of mentioned drug

Appendix 3.4: Detailed evidence from literature review of antidepressants for non-cognitive symptoms in a person with dementia

Systematic Reviews

Source	Country	Studies	Drug	Studies	Dementia type	Sample size	Recommended for use?	Key findings
Dyer et al. 2017	Australia	Systematic review	Any antidepressant	1 study	All	44	No	Global BPSD outcomes: Standard mean difference -0.25 (95%CI -0.85 to 0.35). Rated as very low quality evidence
Harrison et al. 2016	Australia	Systematic review	Any antidepressant	13 study	All	3,225	Evidence not clear	Antidepressants had mixed results , with positive effects for apathy shown only for agomelatine, while stimulants, analgesics, and oxytocin study results were inconclusive.
Henry et al. 2011	USA	Systematic review	Any antidepressant	19 trials	All	1,150	Yes	Out of 19 trials, eight trials using an SSRI and three trials using trazodone showed benefit in the treatment of BPSD
Nelson and Devanand, 2011	USA	Systematic review	Any antidepressant	7 randomised controlled trials	All	330	Evidence not clear	No statistically significant difference between the treatment and placebo groups in depression scores (n=5); beneficial effect of an antidepressant on global ratings (n=2)
Thompson et al. 2007	USA	Meta-analysis	Any antidepressant	5 studies	AD	165	Yes	Antidepressant for depression in AD is efficacious, being superior to placebo for both treatment response (OR 2.32; 95% CI 1.04 to 5.16) and remission (OR 2.75; 1.13 to 6.65)
Preuss et al. 2016	Germany	Systematic review	Citalopram	13 studies	All	Not stated	Evidence not clear	Antidepressants have shown limited benefit for depression in dementia. Antidepressants can reduce agitation and psychosis and are generally well tolerated.
van de Glind 2013	The Netherlands	Scoping review of systematic reviews	Any antidepressant	4 studies	All	Not stated	Evidence not clear	Two reviews found that antidepressants can be effective in the treatment of BPSD; one found no effect of trazodone. Only 1 review showed weak support for antidepressants being effective in patients with depression and dementia.
Seitz et al. 2011	Canada	Systematic review	SSRI's, Sertraline, Citalopram	9 trials	All	692	Evidence not clear	The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies . Both SSRIs and trazodone appear to be tolerated reasonably well.
Young et al. 2018	USA	Systematic review	SSRI	Not reported	All	Not stated	Evidence not clear	Small number of studies reported improvement in behavioural symptoms with SSRIs
Sepehry et al. 2012	Canada	Systematic review	SSRI	5 studies	AD	621	No	Current evidence does not support the efficacy of SSRI treatment for symptoms of comorbid depression in AD.

Individual trial	Country	Intervention	Drug	Type of dementia	Sample	Outcome measure	Duration	Effect	Systematic reviews including this study
Pollock et al. 2007	Canada	RCT	Citalopram (C) versus Risperidone	All	103 (hospitalised)	NBRS	12 week	C+ only	Henry et al. 2011/Seitz et al. 2011
Weintraub 2010	USA	RCT	Sertraline	AD	131		24 week	N/S	Henry et al. 2011/Sepehry et al. 2012
Banerjee et al. 2011 HTA-SADD	UK	RCT	Sertraline, Mirtazapine, placebo	AD	326	CSDD	39 week	N/S	Sepehry et al. 2012
Lyketos 2003 DIADS	USA	RCT	Sertraline	AD	44	CSDD, HDRS	12 week	+	Henry et al. 2011/Preuss et al. 2016/Sepehry et al. 2012/Nelson and Devanand, 2011

N/S=not significant to warrant recommending use; +=positive effect in favour of antidepressant; RCT=randomised clinical trial; SSRI=selective serotonin reuptake inhibitor; CSDD=Corneil Scale for Depression in Dementia; HDRS = Hamilton Depression Rating Scale; NBRS = Neurobehavioural Rating Scale

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 4: Consultation report

As part of the guideline development process, the draft guideline was circulated to the following key stakeholders for feedback, (Table 4.1). Circulation was mainly by direct email invitation, or via email cascades within groups/organisations. In addition, the draft guideline and consultation form were hosted on the Understand Together website (<https://www.understandtogether.ie/>) for review by the general public.

Appendix 4.1: List of individuals and organisations specifically invited to provide feedback

HSE Clinical Programmes, divisions and offices

Office of Nursing and Midwifery Services Director
Nursing Midwifery Planning & Development Unit
National Clinical Programme Older Persons
National Clinical Programme Neurology
National Clinical Programme Palliative Care
Acute Operations /relevant hospital groups
HSE National Clinical Advisor and Group Lead for Mental Health
HSE National Clinical Advisor and Group Lead for Primary Care
Social Care (including Disability Services/Community Healthcare Organisations)
Medicines Management Programme
National Quality Improvement Team
National Safeguarding Office

intellectual disability service providers

Cope Foundation
St. John of God Hospital
Wexford ID services
Aras Attracta residential service
Daughters of Charity, Dublin Services

Other Groups and individuals

Health Information and Quality Authority
nursing homes Ireland
Prof. Kate Irwing, DCU
Prof. Carmel Hughes, QUB

National groups

National Dementia Strategy Implementation Monitoring Group
Pharmaceutical Society of Ireland
Irish Institute of Pharmacy
Irish Medication Safety Network
Irish Pharmacy Union

Professional groups

Faculty of Psychiatry of Old Age
Irish College of General Practice Quality in Practice committee
Hospital Pharmacists Association of Ireland
Irish Society for Physicians in Geriatric Medicine
Candidate Advanced Nurse Practitioners in Older Persons Care network

Patient and Advocacy Groups

Alzheimer Society of Ireland (including the Irish Dementia Working Group and Dementia Carers Network)
Sage Advocacy (National Advocacy group)
Dementia Research Education and Advocacy in Motion (DREAM)
Family Carers Ireland
Carers Alliance
Patients Association of Ireland
Age Action Ireland
National Federation of Voluntary Bodies

The consultation period opened on 14th February 2019 and ended on 12th March 2019. A standard invitation letter and feedback form was used (attached at end of this Appendix). The feedback form asked for comments about user friendliness, the content and the implementation plan outlined in the draft guideline. The stakeholders were also asked to provide any additional feedback.

External review

International external reviewers were asked to provide feedback based on the questions outlined below (reviewer details and rationale for selection are given in Appendix 1). The external reviewers were also asked to provide any additional feedback.

1. Has the appropriate evidence been identified and reviewed in line with the scope and clinical questions posed by this guideline?
2. Are there specific links between decisions and the available scientific evidence?
3. Have the risks and potential harms of recommendations been fully considered in the context of clinical practice?
4. Is the guideline clearly written, user friendly and allows for individual clinician decisions?
5. Is the guideline suitable for routine use as intended (in so far as you are able to comment on the Irish situation)?
6. Are there relevant international or well referenced guidelines (recommendations) on the same topic that these guidelines are in conflict with, and if yes are the reasons for this justified in the guidelines?

Stakeholder feedback was received from 24 groups and individuals in total, as well as the two international reviewers. A masterfile with all feedback was compiled. A summary of the feedback was then generated, reducing duplicative comments to a single item. This was reviewed by the GDG at a “post-consultation” meeting in March 2019 and amendments or clarifications were made where appropriate. The feedback received and response of the GDG is available to review in the following table (Table 4.2). Comments from the international reviewers are denoted as such in the table.

The GDG would like to acknowledge the time and effort of the stakeholders who provided feedback, and in particular the expert reviewers. The GDG would also like to thank the Decision Support Unit and the HSE Health and Social Care Professional Office for their advice on specific language and wording in relevant sections. The following pages contain the invitation letter and consultation form.

Appendix 4.2: Feedback received and resulting action

Feedback	GDG comment and/or incorporation of feedback:
<p>Is the draft guideline easy to read?</p> <p>Most comments were that the guideline was easy to understand and read.</p> <p>However, several commented on its length, suggesting more use of summaries, algorithms and illustrations, hyperlinks, and more content in appendices.</p> <p>In contrast, some requested the Glossary of terms and abbreviations list be at the start, not in an appendix.</p> <p>It was suggested that abbreviations be limited to facilitate users “dipping in and out” to the document.</p> <p>One expert reviewer commented that the inclusion in each section of the committee’s decision making is particularly accessible</p>	<p>Noted by the GDG.</p> <p>A guideline summary and decision aid for clinicians is being developed. Training in the guideline will use key-points and other brief content tools.</p> <p>These were moved to the start of the document.</p> <p>Many abbreviations were removed.</p> <p>Noted by the GDG.</p>

<p>Do the recommendations cover the stated scope of the draft guideline?</p> <p>The majority replied in the affirmative.</p> <p>One group questioned the guideline being not specifically for intellectual disability settings without a rationale for this.</p> <p>This group also questioned the guideline not addressing the risk of restraint and deprivation of liberty.</p>	<p>Noted by the GDG.</p> <p>Text altered to clarify that dementia in ID was within scope, just that evidence not based in this population so needs some care extrapolating.</p> <p>These were not within the scope of the guideline.</p> <p>Restraint is dealt with in existing standards (e.g. HIQA Standards for Residential Care Settings for Older People) and the forthcoming the Bill for Deprivation of Liberty will provide national legislation in this regard.</p>
<p>Has the appropriate evidence (guidelines and empiric evidence) been identified and reviewed in line with the scope and clinical questions posed by this guideline? (Question for expert reviewers only)</p> <p>Both expert reviewers replied in the affirmative. E.g. “this is a well-argued and comprehensive guideline that has been carefully developed. The authors were set a tough task by having to tackle the use of all psychotropic drugs in dementia”.</p> <p>Both reviewers commented that the large majority of the guideline focusses on the drug treatment of BPSD, so that the title should reflect this.</p>	<p>Noted by the GDG.</p> <p>Discussed by the GDG, and title reworded to better reflect the final scope (note term BPSD replaced by “non-cognitive symptoms”- see later)</p>
<p>Do the recommendations clearly link to the evidence presented?</p> <p>The majority replied in the affirmative.</p> <p>Both expert reviewers replied in the affirmative. One commented that “this is carefully done and well-articulated”.</p> <p>The other expert reviewer requested that the link between the evidence and the 12 week recommendation for review of antipsychotics (recommendation 10) needs to be more clearly argued.</p> <p>One group highlighted a potential mismatch between recommendations/GPP and the SmPC for some medications.</p>	<p>Noted by the GDG.</p> <p>Discussed by the GDG. Text added just before recommendation to summarise the evidence for timing of review.</p> <p>Discussed by the GDG and content referring the reader to the SmPC for off-label prescribing was removed (as most use is off-label)</p>
<p>Are there relevant international guidelines (recommendations) that these guidelines are in conflict with, and if so are the reasons for this justified? (Question for expert reviewers only)</p> <p>One reviewer felt there were no conflicts.</p> <p>The other stated that the guideline is in line with other guidelines in all important aspects and that where there are minor deviations then these are well justified.</p>	<p>Noted by GDG.</p>

<p>Does the guideline allow for individual clinician decisions? (Question for expert reviewers only)</p> <p>Both expert reviewers replied in the affirmative.</p> <p>One reviewer commented that it will always be the case that clinician decisions will be made that are not in line with a guideline, when it is imperative that the reasoning behind this and the sharing of that information (with patient and family) is documented. The reviewer felt this was in line with the approach advocated in the guideline.</p>	<p>Noted by GDG.</p>
<p>Does the draft guideline consider the views and needs of specific population groups?</p> <p>While most replied in the affirmative to this question, there were a few concerns:</p> <p>One group felt that the language could be clearer, and more person centred; one individual felt the guideline was over bio-medical in its approach; another group was not confident that we considered the view of people with dementia sufficiently in development. These comments mainly related to the use of the term BPSD.</p> <p>One group felt that there was insufficient consideration of the use of antipsychotics for people with learning disabilities and dementia.</p> <p>Three groups requested more emphasis on the guideline applying in all settings, to avoid this being overlooked or misunderstood; another requested clarity as to whether the guideline would apply in private hospitals, private residential settings and private nursing homes (if not, it would create a two tier system).</p> <p>One group felt it did not cover those who have “severe agitation or ongoing and enduring mental health problems”.</p>	<p>The GDG discussed this at length, and ultimately replaced “BPSD” with “non-cognitive” symptoms (the major focus of the comments); and some additional sentences were rephrased. The Alzheimer Society of Ireland rep. on the GDG provided extra text for the introduction; the GDG incorporated other text from another commenter.</p> <p>The ID subgroup were satisfied the guideline provided sufficient guidance given the dearth of evidence and noted the reference to a specific guidance document from the UK for the users.</p> <p>The GDG itemised the settings where the guideline applies for greater clarity in the scope section. The guideline applies in private services, and these will be included in training and education and awareness raising, noting that adoption of the guideline is however voluntary in these services.</p> <p>The prescribing for mental health illness was outside the scope of the guideline.</p>
<p>Does the draft guideline consider gaps in the current evidence?</p> <p>The majority replied in the affirmative and no comments to the contrary were received.</p>	<p>Noted by the GDG.</p>

<p>Do any recommendations change current practice substantially?</p> <p>The majority felt they did.</p> <p>One group highlighted that ‘non-pharmacological first’ is not always the current practice in acute care settings.</p> <p>Another believed current practice can be adhoc and the guideline would ensure a structure to inform best practice for all HCPs.</p> <p>One group had concerns surrounding changed practice re. deprescribing on people already taking these medications.</p> <p>[Another comment relating to this: “For admissions on long-term antipsychotics, benzodiazepines etc, I think this could give an inaccurate picture. Are we really looking at new prescriptions, or prescriptions within this care setting?”]</p>	<p>Noted by the GDG.</p> <p>Noted by the GDG.</p> <p>Clarification sentence inserted that the focus of the guideline was newly prescribed medications rather than long-term medications. Some guidance now provided on long-term medication discontinuation if felt to be appropriate by the clinician.</p>
<p>If so, do you consider that the reasons given in the draft guideline explain why the change is necessary?</p> <p>All who answered this item answered in the affirmative.</p> <p>One group suggested that the guideline needs to be put in context for the user with regards to medication management guidelines.</p>	<p>Reference to two relevant Irish medication management guidelines were added to the scope section for users’ reference (medication management is specifically outside the scope).</p>
<p>Are the recommendations likely to be acceptable and applicable in the target settings (acute hospital, residential care, community)? (Question for expert reviewers only)</p> <p>Both expert reviewers replied in the affirmative. One added “two small caveats”:</p> <ul style="list-style-type: none"> Request for further clarity about who is a suitably qualified and trained HCP to make the decision to prescribe- will vary from drug to drug and situation to situation. Particularly for antipsychotics, that there should be a strong clear simple statement of the absolute expectation that the prescriber should consult the patient (given capacity) and their family carers and inform them of the potential risks of antipsychotics and to agree with them the need for the control of the behaviour is such that the risks are acceptable. The use of the qualifier ‘(where appropriate)’ would therefore benefit from operationalisation. 	<p>Additional text added to clarify this (i.e. a nurse or doctor) but GDG did not want to specify type of doctor, as local context will dictate.</p> <p>Recommendation for antipsychotic medication (Rec. 7) was absolute.</p> <p>It was the GPP (2) on psychotropic medications which said ‘where appropriate’.</p> <p>As suggested by the reviewer, this GPP was reworded to ‘where possible’ – i.e. it is always appropriate, but not always possible.</p>

<p>Is the guideline suitable for routine use as intended (in so far as you are able to comment on the Irish situation)? (Question for expert reviewers only)</p> <p>One expert reviewer replied in the affirmative.</p> <p>The other commented that given that there appears to be a particular issue in Irish general hospitals, it might be useful to provide specific guidance on the use of antipsychotics in hospital that covers issues of delirium, post-operative care, and the management of behavioural disturbance at night. The need for alternate formulation and treatment (e.g. pain, infection) and consultation with family should still apply where possible but it may be helpful to instruct hospitals to generate standard procedures and to carry out regular audits of adherence.</p>	<p>Noted by the GDG. The NDO is developing delirium/dementia pathways for acute hospitals, to support use of the in-existence delirium algorithms for use in the Emergency Department and in general wards (the latter two developed by the NCP Older Persons).</p> <p>These pathways will synergise well with this guideline. The INAD acute hospital dementia audit in 2019 will establish current practice in acute hospitals this year and is planned to be repeated in 2021/2022 post pathway development (pending funding).</p>
<p>Which areas do you think may be difficult to put into practice? Please explain why.</p> <p>Many specified the difficulty of changing practice and cultures.</p> <p>Most highlighted the lack of time (to read the guideline; for initial assessment; to inform patient re. side effects; to review medication; for extra documentation of rationale and discussions); one group expressed concern that more referrals would result for psychiatry services if GPs don't have time/ contract to comply.</p> <p>Other specific comments included:</p> <p>"The time lines for discontinuation of antipsychotics would be challenging for secondary services"</p> <p>"Who will monitor if the guidelines are being implemented?"</p> <p>"Difficulties in making GPs aware of the guidelines"</p> <p>Difficult in the "large numbers already on long term medications"</p> <p>"Perceptions of what constitutes mild, moderate or severe BPSD by different practitioners may lead to issues</p>	<p>Noted by the GDG. The implementation will include awareness raising of the risks of psychotropic medications and hence benefit of the guideline, guideline champions, local implementation teams and audit, all designed to promote the use of the guideline despite time challenges.</p> <p>This will be targeted in training for acute care settings.</p> <p>Implementation, and monitoring and audit sections deal with this question.</p> <p>Implementation plan specifically targets GPs.</p> <p>See earlier reply - the guideline focus is on new prescriptions.</p> <p>Can be included in local training.</p>

<p>What would help users to implement the guideline?</p> <p>Almost all said training of HCPs (GPs, nursing home staff, any relevant HCP, especially in acute hospitals/ mental health settings), using education programme; HSELand; ICGP courses; workshops</p> <p>Practice guidelines which details specifically how the process of care should be in different settings.</p> <p>Algorithms; Flow charts (eg promote ‘start low go low’)</p> <p>Training in behavioural management techniques</p> <p>Template/ summary: for GPs specifically...and HCPs- easy to read & laminated</p> <p>Toolkit; Audit tools; Key performance indicators</p> <p>Checklists (many suggested these) - but one group specifically advised caution regarding checklists which may replace critical thinking and clinical decision making.</p> <p>Information leaflet/guide: for PwD and their families and carers; include perceived problematic behaviours such as walking about, potential non-pharmacological approaches. To be made available in relevant settings/ on relevant websites.</p> <p>Information guide for GPs and pharmacists.</p> <p>Computer system reminders for GPs when review is due/ pharmacies dispensing meds.</p> <p>“GP practices must have referral pathways and information on local sources of supports”.</p> <p>Champion in each area to cascade down the details behind the recommendations- in practice.</p> <p>Procedure for observation of behaviour triggers as part of comprehensive assessment.</p> <p>Social history and life story tools such as ‘This is Me.’</p> <p>List of psychosocial responses that may address responsive behaviours.</p> <p>An evaluation phase in implementation would support the guideline and provide evidence.</p> <p>Additional pharmacy resources for inpatients, ANP-led clinics, community geriatricians.</p> <p>Enhanced GP contract to support primary care particularly for care home patients.</p>	<p>Noted by GDG and incorporated in implementation plan.</p> <p>Guideline can be added to locally if necessary.</p> <p>Clinical algorithm being developed by GDG. Noted by GDG.</p> <p>Summary being developed.</p> <p>Toolkit being developed.</p> <p>Checklist not planned to be part of toolkit.</p> <p>Patient information leaflet developed – will be on Understand Together and Alzheimer Society of Ireland websites.</p> <p>Implementation plan includes infographics for pharmacist and GPs.</p> <p>Can be explored as part of ICT linkage (see implementation plan).</p> <p>The “Dementia Pathways” resource (website) will be highlighted within implementation programme.</p> <p>Champions are part of implementation plan.</p> <p>Noted by GDG.</p> <p>Guidance document on non-pharmacological interventions being developed by NDO.</p> <p>Evaluation included in monitoring plan and BIA.</p> <p>Noted by GDG - Implementation programme will leverage all current and future resources as possible.</p> <p>Noted by GDG- can be revisited during implementation if GP contract being re-drawn at that time.</p>
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<p>General comments e.g. overall layout, usefulness, ease of use of guidelines</p> <p>Request to use ‘for the person with dementia’ not “in” a person with dementia.</p> <p>Need to define the severity of BPSD (one stakeholder and one expert reviewer)</p> <p>“The use of the term BPSD should be replaced by other terms favoured by people with dementia themselves that reflect the complex nature of responsive behaviour”</p> <p>The fear of being over-prescribed medications because of behaviours, instead of non-pharmacological interventions, was a real fear for people with dementia.</p> <p>Stronger focus on the rights of PwD in relation to high risk medicines required.</p> <p>More reference to ‘advocates’ in the guideline.</p> <p>“The recommendations imply that non-pharmacological treatments are readily available to all people with dementia and BPSD nationwide”</p> <p>“Recommendations are worded strongly in the negative in instances where there is little/no evidence, e.g. anticonvulsants and melatonin”</p> <p>“Healthcare professionals is used throughout – are some people working with people with dementia better described by the term health and social care professionals? Or because that’s used for non-medical/ nursing/pharmacy professions like SLT, physio etc. is that confusing?”</p> <p>“As severe BPSD is quite subjective it would be easy to be at conflict with formal caregivers as to what symptoms should be treated”.</p> <p>“Lack of evidence for psychotropics in severe BPSD is because difficult to perform RCTs in this patient population; but there is anecdotal evidence. Clinicians experienced in the management of dementia may therefore have to consider using these medications despite little evidence”</p> <p>Suggestion to include that patients with dementia may need antipsychotics for other reasons...</p> <p>Suggestion to include as a recommendation that sub sets of Dementia should be diagnosed</p> <p>“Except for antipsychotics, guideline does not include review, tapering, stopping, monitoring after tapering etc for other psychotropics”. Suggestion to add a recommendation or good practice.</p>	<p>Wording of this sentence since changed.</p> <p>Definition amended as per detail of this comment.</p> <p>See earlier response- term changed.</p> <p>Noted by the GDG.</p> <p>Issue of rights added to introduction.</p> <p>Reference added.</p> <p>Noted by GDG (sentence added in implementation section to highlight need for these).</p> <p>GDG reviewed strength of these recommendations; no changes made based on this comment.</p> <p>Best wording later clarified with the HSE HSCP office and now used throughout the guideline.</p> <p>Noted by GDG.</p> <p>Noted by GDG. Although GDG agrees with this statement, recommendations have to be based on evidence. Supporting text does state where there is evidence of little/no effect versus where there is little/ no evidence.</p> <p>Sentence added to this effect.</p> <p>This is outside the scope of the guideline.</p> <p>Discussed by GDG- GPP (number 3) added to this effect.</p>
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<p>“Would it be possible to phrase one or two of the recommendations/GPP to mention supporting the workforce to deliver psychosocial and environmental interventions to minimise the need for medication?”</p> <p>“HCPs are strongly advised to contact a specialist team with experience in treating people with PDD/DLB for direct advice on an individual patient with PDD and DLB who has distressing psychosis.” Request that this is a GPP.</p> <p>“Should palliative care be mentioned also?”</p> <p>One individual stated that there are certain times when an antipsychotic is needed to provide relief for the PwD and feels this is a forgotten aspect in the debate.</p> <p>One group noted that there is no specific funding model for the provision of additional or one-to-one person centered care for persons that may benefit from additional non-pharmacological interventions in a residential setting.</p>	<p>Recommendation 2 and supporting text deals with this in detail; implementation plan includes plans for better psychosocial and environmental interventions, even though outside the scope of the guideline. NDO guidance document for non-pharmacological interventions also in development.</p> <p>Discussed by GDG- GPP added to this effect.</p> <p>NCP Palliative Care have reviewed the NCG and are happy with content- see table 2.3 also.</p> <p>Noted by GDG.</p> <p>Noted by GDG. Comment added to implementation plan to highlight challenges to implementation.</p>
<p>Recommendation 1:</p> <p>“Should be a link to the Comprehensive Geriatric assessment?”</p> <p>Need to state that CA may involve a MDT approach.</p> <p>One expert reviewer requested a specific reference to delirium as a potential cause of BPSD in the footnote.</p>	<p>Discussed by GDG- a comprehensive geriatric assessment is a different thing, so not appropriate to link.</p> <p>MDT involvement added to text.</p> <p>Delirium added to this list.</p>
<p>GPP on rapid tranquilisation:</p> <p>“Recommendation should be directed at the institution as well – to develop a protocol and ensure staff have access to it and information/training”.</p> <p>“On this page it says ‘in accordance with the SmPC’ – rapid tranquilisation practice is generally not in line with the SmPCs of the products which are often old and avoid these indications- remove this from this section”</p>	<p>Discussed by GDG- felt to not be appropriate to ‘promote’ a risky practice (outside of acute settings, where these protocols already exist).</p> <p>This GPP removed by GDG.</p>
<p>Recommendation 6:</p> <p>Request to specify ‘when non-pharma therapies are ineffective’</p>	<p>Discussed by GDG- for severe non-cognitive symptoms, causing severe distress, or an identifiable risk of harm to the person and/or others, it may not be appropriate to try non-pharmacological therapies first, so no change made to wording.</p>
<p>GPP 6 (behaviours unresponsive to antipsychotics):</p> <p>Expert reviewer comment that these behaviours have been less subject to RCTs or are of lower frequency and so are less well captured by portmanteau RCTs. Thus, it might be better to say there is ‘no evidence that they are effective’.</p>	<p>Discussed by GDG – wording revised to reflect this.</p>

<p>Recommendation 8:</p> <p>“Can the information explaining the efficacy and safety of atypicals overall and in comparison to each other be included in any summary document? Or can recommendation have additional text re. which atypicals might be considered and which shouldn’t? “</p> <p>Expert reviewer suggested possibly adding a final sentence: “Prescribers should be aware that if they prescribe an antipsychotic other than risperidone for BPSD, and if they prescribe risperidone for a BPSD that is not aggression, they are doing so off-label.”</p>	<p>Discussed by GDG- felt to be not suitable for recommendation itself; will be included in summary document.</p> <p>Discussed by GDG – added as footnote.</p>
<p>Recommendation 15/16:</p> <p>“What about anticholinesterases and mixed dementia/ unclear aetiology?”</p> <p>“Could clinical judgement be included for use of AChEI / Memantine in VD?”</p> <p>Footnote: Expert reviewer comment that actually NICE 2018 states that memantine should be considered in addition to AChEIs in moderate disease and should be offered in addition to AChEIs in severe disease.</p>	<p>Discussed by GDG- very limited evidence in mixed dementias, so hard to make recommendation. Additional text inserted for guidance in the text.</p> <p>Recommendation 15 states that anticholinesterases should not be used for VaD (and evidence presented to support this). The evidence for memantine in VaD is also presented.</p> <p>Footnote wording changed to clarify that this refers to monotherapy, not add-on therapy.</p>
<p>Recommendation 17:</p> <p>“Motivational and affective disturbances may arise in dementia but not indicate a biological depression (which would be amenable to antidepressant medication) therefore, clinical judgement based on the history of mood disturbance and current clinical picture is required when considering anti-depressant use in dementia “</p> <p>“Maybe if we looked at diagnosis of a depressive episode which is very different from someone being sad/ low/apathetic in the context of BPSD in dementia”.</p> <p>Await further evidence re benefits of SSRIs -Sertraline / Citalopram in reducing symptoms of BPSD and in particular in agitation /psychosis in dementia (as an alternative to anti-psychotic use)”</p> <p>One comment was that if the recommendation is read in isolation, it’s not clear that the reason not to use antidepressant in depression is because it lacks effect. Asked to consider placing in the recommendation.</p> <p>One comment on choice of antidepressant – “there is evidence reviewed but doesn’t make into a recommendation”.</p>	<p>Noted by GDG, and first comment text added to guideline as it is a good introduction to the topic.</p> <p>The GDG noted that the negative studies for antidepressants were in people with psychiatrist diagnosed mild-moderate depression, not just depressive symptoms in BPSD.</p> <p>Noted by GDG – the guideline does include the current evidence for this and a GPP, but not a recommendation given insufficient evidence for now.</p> <p>Discussed by GDG - recommendation needs to be brief, but the summary will include supporting text.</p> <p>Discussed by GDG- not possible to recommend any one agent.</p>

<p>There were three separate comments on the severity of depression indicating a trial of antidepressant:</p> <ul style="list-style-type: none"> • “Concern that only recommending meds in severe depression– good evidence for treating moderate also” • “Moderate depression in AD/dementia may benefit – can recommendation say ‘moderate-severe depression in AD/dementia’?” • “I use anti-depressants for treatment of moderate depressive disorders in dementia.” <p>One of the expert reviewers also felt that the decision on moderate depression was nuanced – suggested we altered the sentence to “Antidepressants may be considered to treat severe comorbid depressive episodes in people with dementia, <i>or those who whose depressions have not responded to non-pharmacological treatment.</i>”</p> <p>“In my clinical experience trazadone can be useful (cardiac side effects and sedation an issue though) and may have utility via sedative effects)”</p>	<p>Discussed by GDG – the studies for antidepressants in moderate depression in people with dementia were negative, but there is good evidence for antidepressants in treating moderate depression outside of dementia, which does introduce some caution in recommending against them. Decision that recommendation be reworded to include the ‘consideration’ of use of antidepressants in moderate depressive episodes <i>that have not responded to psychological treatment.</i></p> <p>Discussed by GDG - no evidence found relating to trazadone, so not included in recommendation.</p>
<p>Recommendation 18: Suggestion to change order for clarity.</p>	<p>Word order changed.</p>
<p>Recommendation 19:</p> <p>“For short term severe anxiety treatment, the guideline recommends to go to the SmPC for maximum duration. The supporting text then highlights the MMP recommendations. Rather than expecting people to read the guideline then go to multiple other documents as well, could the maximum be set as in the MMP guidance?”</p> <p>“Benzos can increase agitation – can we mention this?”</p> <p>“For z-drugs, can it be more specific rather than referring to another source- crucially important to reinforce just how short-term it should be.”</p> <p>“There is nothing about reviewing/ possible tapering long-term benzodiazepine (for anxiety or sleep) or z-drug – very specific instructions for tapering over a long period in the MMP document. Can we refer to these?”</p> <p>“Sleep disorders should probably refer to REM Sleep Behaviour Disorder and the evidence for melatonin and clonazepam etc”</p> <p>“Clinical experience and expertise would support use of the ‘Z’s and melatonin for sleep in many instances”.</p> <p>Will this open floodgates to off license use of mirtazepine as a hypnotic/agitation at night?</p>	<p>Discussed by the GDG – agreement to refer readers to the MMP but not SmPC. Exact recommendations from MMP now included.</p> <p>GDG agreed that important point- added to text.</p> <p>Discussed by the GDG – will state exactly what the MMP says.</p> <p>Discussed by the GDG- agreement to refer readers to the MMP guidance on discontinuation.</p> <p>REM sleep behaviour disorder (or RBD) is not within the scope of this guideline, as it is a very specific sleep disorder.</p> <p>Discussed by GDG- current evidence does not support the use of melatonin, hence recommendation. As no RCTs of Z-type hypnotics in dementia, current GPP wording is appropriate.</p> <p>A sentence referring to the hypnotic section has been added to the antidepressant section.</p>
<p>Appendix 12: “Ensure only medicines & brands licenced and available in Ireland are listed”.</p>	<p>Amended.</p>

Re: Consultation document - National Clinical Guideline for the Appropriate Prescribing of Psychotropic Medication in People with Dementia

14.2.2019

Dear Colleague,

I am writing to you to seek your views on the draft **National Clinical Guideline for the Appropriate Prescribing of Psychotropic Medication in People with Dementia**, that is currently open for consultation.

The aim of the guideline is to make recommendations on the appropriate use of psychotropic medications (including antipsychotics, antidepressants, anticonvulsants, benzodiazepines, z type drugs, acetylcholinesterase inhibitors and memantine), for managing non-cognitive symptoms of dementia (also termed behavioural and psychological symptoms of dementia; BPSD). Although some psychotropic medications have shown modest efficacy in the treatment of some BPSD, in many instances their use is not evidence based, and they are linked to significant adverse events, including a risk of death. The National Clinical Effectiveness Committee (NCEC) prioritised this guideline in October 2018.

The guideline is relevant to all people with dementia and in any setting (living in the community or in residential settings, including during episodes of admission to hospital).

The consultation period is from 14/02/2019 to 12/03/2019. We welcome any comments or suggestions you may have, not only in relation to content of the recommendations, but also the layout and ease of use of the document, and any comments you have on the implementation of the recommendations.

All comments received from organisations and individuals will be reviewed by the Guideline Development Group and used to inform the final guideline.

****Organisations should submit one collated response please****

Please submit your comments by completing the feedback form electronically and returning it by email to suzanne.timmons@hse.ie. The final date for submission of comments is 12/03/2019.

Thank you for your assistance in this work.

Yours Sincerely,



Dr Suzanne Timmons and Prof. Stephen Byrne
Co-chairs, Guideline Development Group



The National Guideline Development Group has been developing this guideline and now invites your feedback on the draft document:

National Clinical Guideline for the Appropriate Prescribing of Psychotropic Medication in People with Dementia

Consultation Feedback Form

Consultation opening date: This consultation opens on 14/02/2019

Consultation closing date: The deadline for comments is 12/03/2019

During the consultation period the draft guideline and the feedback form will be available from: <http://www.understandtogether.ie/>

Comments via email should be sent to: suzanne.timmons@hse.ie

Notes:

1. Feedback received may be edited and/or summarised.
2. This consultation is conducted in line with requirements of the Freedom of Information (FOI) Act.
3. Anonymous submissions will not be considered.

Consultation on: Draft National Clinical Guideline for the Appropriate Prescribing of Psychotropic Medication in People with Dementia.

February-March 2019.

Introduction

We would like to hear your views on the draft guideline National Clinical Guideline for the Appropriate Prescribing of Psychotropic Medication in People with Dementia.

All comments received on this form by the deadline will be considered and used to inform the final guideline. Irish National Clinical Guidelines are defined as “systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and service users’ decisions about appropriate healthcare for specific clinical circumstances across the entire clinical system”.

The implementation of guidelines can improve health outcomes for patients, reduce variation in practice and improve the quality of clinical decisions that patients and healthcare staff have to make. National Clinical Guidelines will inform patients about the care they should be receiving and assist them to make healthcare choices based on best available information.

The draft guideline contains a number of recommendations, each with a statement of the evidence used by the Guideline Development Group when they formed the recommendation.

Further information on the National Clinical Effectiveness Committee (NCEC) and National Clinical Guidelines is at: <https://www.gov.ie/en/publication/90221b-clinical-effectiveness/>

Scope of draft guideline

The aim of the guideline is to make recommendations on the appropriate use of psychotropic medications (including antipsychotics, antidepressants, anticonvulsants, benzodiazepines, z-drugs, acetylcholinesterase inhibitors and memantine), for managing non-cognitive symptoms of dementia (also termed behavioural and psychological symptoms of dementia; BPSD).

Although some psychotropic medications have shown modest efficacy in the treatment of some BPSD, in many instances their use is not evidence based, and they are linked to significant adverse events, including a risk of death. The NCEC prioritised this guideline in October 2018.

The guideline is relevant to all people with dementia and in any setting (living in the community or in residential settings, including during episodes of admission to hospital).

How to submit your feedback

- All feedback must be submitted on this form if it is to be considered
- Identify clearly the section feedback relates to by using the page, section and / or paragraph number
- Each comment should be in a separate box; add in extra boxes as needed
- You must explain the rationale for your comment, which should be written clearly and concisely
- Submit the form as a word document via email
- Use full terms for abbreviations on first use
- If you refer to sources of evidence, please detail the reference (with weblink if available)

Please ensure you complete your details on the next page
****Organisations should submit one collated response****

Your details

Name and title of person completing form	
Are you commenting? (tick box)	<input type="checkbox"/> As an individual <input type="checkbox"/> On behalf of an organisation
Organisation Name (if relevant)	
Contact Name (if different to above)	
Contact Telephone Number	
Contact Email Address	
Date of feedback	

Please comment on the following:

1. User friendliness

- a) Is the draft guideline easy to read?
- b) Do you think the guideline will be easy to use in practice?

2. Content

- a) Do the recommendations cover the stated scope of the draft guideline?
- b) Do the recommendations clearly link to the evidence presented?
- c) Does the draft guideline consider the views and needs of specific population groups?
- d) Does the draft guideline consider gaps in the current evidence?

3. Implementation

- a) Do any recommendations change current practice substantially?
If so, do you consider that the reasons given in the draft guideline explain why the change is necessary?
- b) Which areas do you think may be difficult to put into practice? Please explain why.
- c) What would help users to implement the guideline? (For example, useful checklists, patient information leaflets etc.)

Any Other Feedback

General comments e.g. overall layout, usefulness, ease of use of guidelines

Specific comments:

Appendix 5: Economic assessment

This Economic Evidence Summary and Budget Impact Analysis was performed by Dr. Aileen Murphy and Ms. Ruth Kelly, from the Department of Economics, Cork University Business School, University College Cork. Ms. Niamh O'Connor from the Centre for Gerontology and Rehabilitation assisted in literature searching.

Part A: Economic evidence summary

Introduction

Dementia is a debilitating syndrome characterised by a deterioration in cognitive function, often occurring alongside a decline in emotional control, social behaviour or motivation (WHO, 2017). The number of people living with dementia in Ireland is forecasted to rise from 55,266 in 2018 to 157,883 in 2046 (O'Shea et al., 2015). This increase in the number of people with dementia is expected to have a significant impact on Irish public health resources and expenditure.

A systematic literature review of economic evaluations examining the effectiveness of pharmacological and non-pharmacological interventions for the treatment of symptoms of dementia was undertaken. The objective of this is to collate, summarise and critically appraise the existing literature on the economic evidence surrounding psychotropic medications in dementia i.e. their cost-effectiveness. NICE (2018a) also conducted a systematic literature review to identify cost-utility analyses on the effectiveness of pharmacological and non-pharmacological interventions. The NICE (2018a) review examined papers published up to September 2017, while this review includes papers published in 2018. The results of this literature review will inform the subsequent budget impact assessment of the guideline.

Methods

Study selection criteria

A systematic search was performed to identify relevant articles published in both biomedical and health economic databases in the last 15 years, from 2003 to 2018. This search was conducted in accordance with the Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland (HIQA, 2014). The databases searched were CINAL, Medline, Embase, the Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. The review was undertaken using a PICOS framework as advocated and developed by Davies (2011) (See Table 5.a.1). In line with HIQA (2014) guidelines, the quality of the papers was evaluated using the British Medical Journal Checklist (Drummond, 1996) and the Consensus on Health Economic Criteria (CHEC) List (Husereau et al., 2013).

Appendix 5.a.1: PICOS for economic search

Population	Individuals with dementia
Intervention	Psychotropic medication
Comparator	Non-pharmacological intervention or placebo
Outcome	Resources, costs, expense, financial burden
Setting	All settings

Literature search strategy

The literature search covered people with dementia living in any setting. The search focused on the cost effectiveness of psychotropic medications. Psychotropic medications were defined by the search team as drugs which are used as a treatment of dementia. The eligibility criteria for inclusion in the systematic review is presented in Table 5.a.2. Search terms focused on people with dementia, psychotropic intervention type and cost/savings outcomes. After each search in the various databases, the initial hits were exported to EndNote and duplicates were removed. All articles were screened based on the inclusion and exclusion criteria, initially based on title and abstracts (NOC) and then based on the full text (AM&RK).

Data extraction

The evidence for this review was organised in a tabular format as advocated by national guidelines (HIQA, 2014). This data extraction format is employed to reduce bias and facilitate consistency and validity in the literature review (CRD, 2009). Data extracted from the papers included; setting, perspective and time horizon; costs and resource items; data sources of costs and resource items; data sources of outcomes and benefits; methods of measuring and valuing outfits and benefits, discounting, currency and sensitivity and uncertainty analyses; costs and resource use; avoided outcomes and costs.

Appendix 5.a.2: Inclusion and exclusion criteria

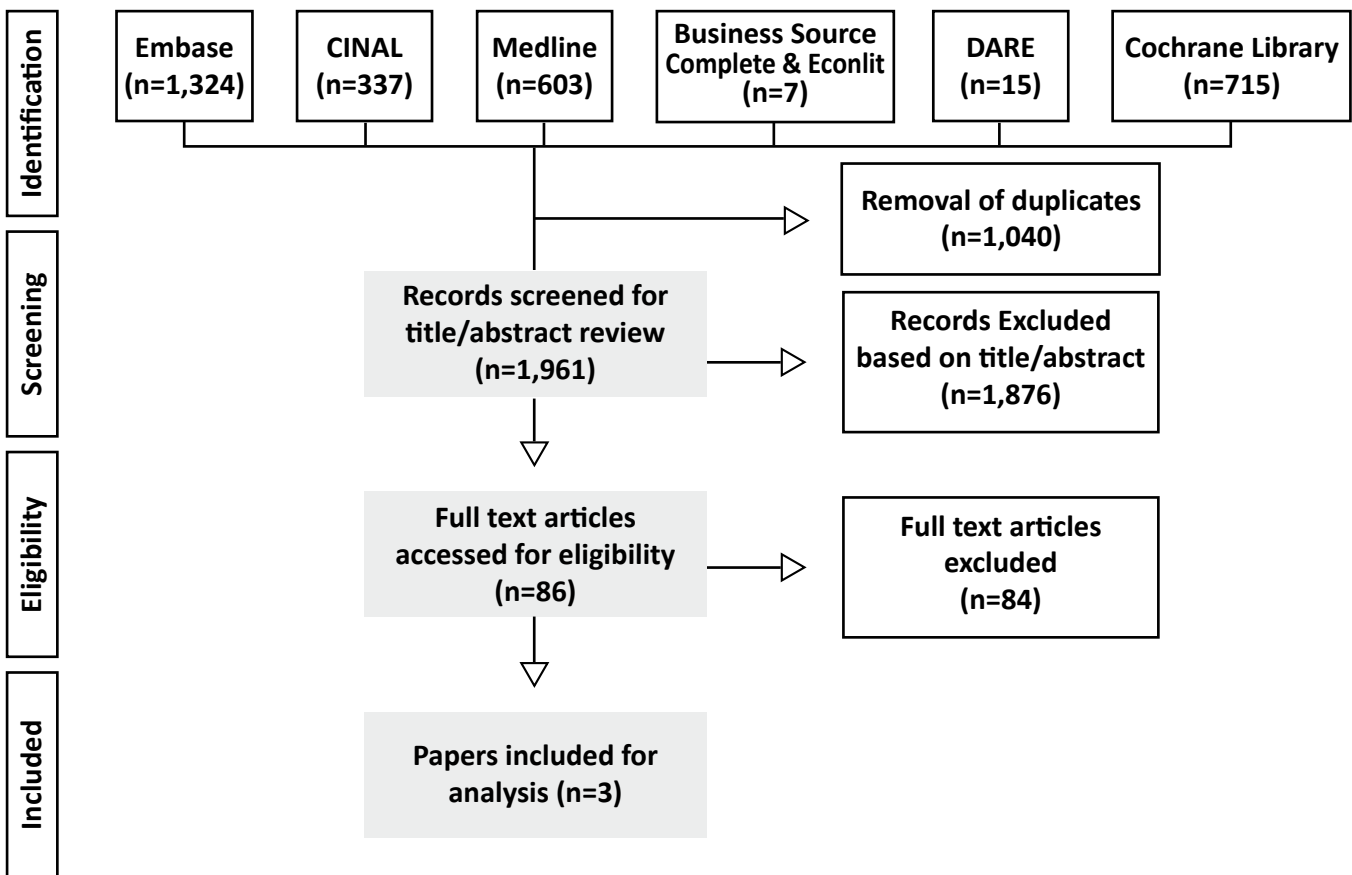
<p>Inclusion criteria</p>	<ul style="list-style-type: none"> • Studies whose study population consists of dementia patients in any setting (community, nursing home etc.). • Studies reporting a measure of the effectiveness of the intervention e.g. QALY. • Studies including any type of psychotropic medication used to treat dementia symptoms. • Studies with a focus on economic costs/benefits of intervention.
<p>Exclusion criteria</p>	<ul style="list-style-type: none"> • Any study deploying a non-pharmacological intervention only. • Studies reporting a non-dementia population (e.g. care givers, family). • Papers which do not provide information of costs, savings etc. • Non-English language studies. • Low level evidence such as reports, commentaries, study protocol/ design of interventions.

Results

A total of 1,961 records were identified for screening of title and/or abstract. 1,876 records were excluded due to irrelevant titles and abstracts. 86 records were included for full text screening (NOC). These papers were assessed (AM&RK) to ensure they met the economic and clinical criteria for this study. 83 of the 86 studies did not meet the inclusion criteria and were omitted from analysis. Many of these studies excluded from analysis focused on the economic evaluation of anti-dementia drugs such as memantine and acetylcholinesterase inhibitors as used for cognitive symptoms. This review focuses solely on psychotropic medications prescribed for treatment of non-cognitive symptoms in people with dementia.

Following screening, a total of three studies met the economic and clinical criteria for the review and were included for analysis. The selection process is illustrated in Figure 5.1 (PRISMA flow diagram).

Appendix 5.1: PRISMA flow chart of study selection process



Characteristics of economics papers

Three papers were identified as meeting all the inclusion criteria through the systematic literature search on the cost effectiveness of pharmacological and non-pharmacological interventions for the treatment of dementia. Two studies examined the cost effectiveness of antipsychotic medications. Both these studies were conducted in the USA and focused on a cohort of patients with Alzheimer’s disease (AD). In the first paper by Kirbach et al. (2008), a cost utility analysis was performed to examine the cost effectiveness of the atypical antipsychotic, olanzapine. The second paper by Rosenheck et al. (2007) also investigated the cost effectiveness of atypical antipsychotic medications including olanzapine, quetiapine and risperidone. Both of these papers employed data from the CATIE-AD trial (Schneider et al., 2006). The third paper identified by the systematic search was by Banerjee et al. (2013) and compared the cost effectiveness of antidepressant medications mirtazapine and sertraline with a placebo in England, employing data from the HTA-SADD trial.

Quality of included studies

In line with HIQA (2014) Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies, the quality of the three papers was evaluated with the aid of the British Medical Journal Checklist and the Consensus on Health Economic Criteria (CHEC) List. While not all the criteria on the checklists were applicable to the papers, the studies were deemed to be of good quality for the review (See Table 5.a.3 and Table 5.a.4).

Appendix 5.a.3: British Medical Journal (BMJ) checklist

Item	Kirbach et al. (2008)	Rosenheck et al. (2017)	Banerjee et al. (2013)
Extract Study design			
1. The research question is stated.	+	+	+
2. The economic importance of the research question is stated.	+	+	+
3. The viewpoint(s) of the analysis are clearly stated and justified.	+	+	+
4. The rationale for choosing alternative programmes or interventions compared is stated.	+	+	+
5. The alternatives being compared are clearly described.	+	+	+
6. The form of economic evaluation used is stated.	+	+	+
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	+	+	+
8. The source(s) of effectiveness estimates used are stated.	+	+	+
9. Details of the design and results of effectiveness study are given (if based on a single study).	+	+	+
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).			
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	+	+	+
12. Methods to value benefits are stated.	+	+	+
13. Details of the subjects from whom valuations were obtained were given.	+	+	+
14. Productivity changes (if included) are reported separately.			
15. The relevance of productivity changes to the study question is discussed.			
16. Quantities of resource use are reported separately from their unit costs.	+	+	+
17. Methods for the estimation of quantities and unit costs are described.	+	+	+
18. Currency and price data are recorded.	+	+	+
19. Details of currency of price adjustments for inflation or currency conversion are given.	+		
20. Details of any model used are given.	+	+	
21. The choice of model used and the key parameters on which it is based are justified.	+	+	
22. Time horizon of costs and benefits is stated.	+	+	+
23. The discount rate(s) is stated.	+		
24. The choice of discount rate(s) is justified.	+	+	+
25. An explanation is given if costs and benefits are not discounted.		-	-
26. Details of statistical tests and confidence intervals are given for stochastic data.	-	+	+
27. The approach to sensitivity analysis is given.	+	+	+
28. The choice of variables for sensitivity analysis is justified.	+	+	+
29. The ranges over which the variables are varied are justified.	+	+	+
30. Relevant alternatives are compared.	+	+	+
31. Incremental analysis is reported.	+	+	+
32. Major outcomes are presented in a disaggregated as well as aggregated form.	+	+	+
33. The answer to the study question is given.	+	+	+
34. Conclusions follow from the data reported.	+	+	+
35. Conclusions are accompanied by the appropriate caveats	+	+	+

+ = category considered; - = category not considered; blank = not applicable
Adapted from Drummond (1996)

Appendix 5.a.4: Consensus on Health Economic Criteria (CHEC) list

Item	Kirbach et al. (2008)	Rosenheck et al. (2017)	Banerjee et al. (2013)
1. Is the study population clearly described?	+	+	+
2. Are competing alternatives clearly described?	+	+	+
3. Is a well-defined research question posed in answerable form?	+	+	+
4. Is the economic study design appropriate to the stated objective?	+	+	+
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	+	+	-
6. Is the actual perspective chosen appropriate?	+	+	+
7. Are all important and relevant costs for each alternative identified?		+	+
8. Are all costs measured appropriately in physical units?		+	+
9. Are costs valued appropriately?	+	+	+
10. Are all important and relevant outcomes for each alternative identified?	+	+	+
11. Are all outcomes measured appropriately?	+	+	+
12. Are outcomes valued appropriately?	+	+	+
13. Is an incremental analysis of costs and outcomes of alternatives performed?	+	+	+
14. Are all future costs and outcomes discounted appropriately?	+		
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	+	+	+
16. Do the conclusions follow from the data reported?	+	+	+
17. Does the study discuss the generalizability of the results to other settings and patient/ client groups?	+		
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	+		+
19. Are ethical and distributional issues discussed appropriately?	+	+	+

Adapted from Husereau et al. (1996)

Economic results

In this section, the three papers identified in the systematic search for inclusion in the analysis are discussed in detail. The two studies by Kirbach et al. (2008) and Rosenheck et al. (2007) evaluating the cost effectiveness of antipsychotics are first discussed. Details of the Banerjee et al. (2013) paper examining the cost effectiveness of antidepressants are then provided. The key features of these studies are summarised in Table 5.a.5 and Table 5.a.6.

(i) Antipsychotics

Kirbach et al. (2008) investigated the cost effectiveness of an atypical antipsychotic, olanzapine, for treatment of agitation and psychosis in patients with Alzheimer's disease (AD) in the USA. The cost effectiveness of olanzapine was determined by comparing it with no treatment. The study investigated the differences in outcomes and costs between the two treatments in a cohort of AD patients over 65 who were living in the community and nursing homes. Outcomes were measured in quality adjusted life years (QALYs), with estimates of QALYs utility weights obtained from a study by Murman and Colenda (2005). Costs were estimated using the incremental cost-effectiveness ratio (ICER). Effectiveness estimates of olanzapine obtained from the CATIE-AD study by Schneider et al. (2006) were employed.

A Markov model was employed to compare the expected costs and outcomes of olanzapine against no treatment in the cohort of people with AD. The Markov model had a six-month cycle, continuing for 13 years until all patients had died from AD or comorbidities. Indirect and direct costs were included in the study; however, the breakdown of these costs was not provided. The total 13-year cost for an individual with AD who was prescribed olanzapine to treat high levels of psychosis and/or agitation was \$39,781. The total cost for a person with AD and high behavioural disturbance taking a placebo was \$35,899, with the difference in these costs attributed to the cost of olanzapine medication. Prescription costs, inpatient and outpatient care costs and memantine costs were included in the cost analysis of patients receiving no treatment and those taking olanzapine. While treatment with olanzapine incurred higher costs, it afforded QALY gains, with an ICER of \$37,104 per QALY. To test the robustness of estimates, key parameters (including cost of care, olanzapine effectiveness and AD progression rates) were subjected to one-way, two-way and three-way sensitivity analyses. 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 a placebo in the treatment of psychosis and aggression in patients with AD in the USA. Like Kirbach et al. (2008), the analysis obtained effectiveness estimates of antipsychotic drugs (olanzapine, risperidone and quetiapine) from the CATIE-AD study by Schneider et al. (2006). Results of quality of life measures and healthcare costs including medication and monthly health service costs from the CATIE-AD study were also presented in this paper. Patient outcomes were assessed using QALYs from the Health Utilities Index initially and these were converted to monetary estimates to facilitate estimation of net benefit. Here, QALYs were estimated at \$50,000 and \$100,000 per QALY per year.

A net health benefits approach was employed in the cost benefit analysis when comparing the costs and effectiveness of the atypical antipsychotic drugs and the placebo. To estimate the net health benefits of each drug, monthly healthcare costs were subtracted from the monthly health benefits, measured in QALYs gained.

Results of the net benefit analysis 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 between trial participants who were assigned olanzapine, risperidone, quetiapine or placebo. The results also indicated that olanzapine was dominated by placebo, with placebo considered to be a less costly alternative that achieved better health benefits. When QALYs are valued at \$50,000 or \$100,000, none of the treatment strategies could be deemed cost-effective. The study noted a 49.33% difference in drug costs between those assigned placebo and an antipsychotic. An average difference of 34.51% in health and social care costs was also noted between the groups. While no difference was noted in effectiveness across the groups, the study concluded that a watchful waiting strategy, represented by the group prescribed a placebo, was less costly than undergoing active treatment, i.e. prescribing antipsychotic medications.

(ii) Antidepressants

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. The analysis was conducted from a health and social care agency perspective and a health, social care agency and informal carer's perspective. A cost utility analysis is performed alongside data from the HTA-SADD randomised control trial conducted in nine old age psychiatry services in England. The primary analysis in this study was a cost effectiveness analysis, examining the differences in the treatment costs of mirtazapine, sertraline and placebo. The primary outcome from this analysis was the Cornell Scale for Depression in Dementia (CSDD) score at 0 to 13 weeks and 0 to 39 weeks. The secondary analysis was a cost utility analysis using QALY measurements obtained from the EQ-5D and societal weights and conducted over a 39 week horizon.

Costs in the study were divided into three main categories. Medication costs were obtained from British National Formulary. Aggregated health and social care costs including primary care, outpatient hospital visits and community-based health and social care were obtained from Curtis (2010) and NHS Schedule Reference Costs (2009-2010). Cost of carer's time was also depicted. Non-parametric bootstrapping methods were employed to estimate 95% confidence intervals of mean costs. Cost-effectiveness acceptability curves were drawn to address uncertainty regarding costs and effectiveness estimates.

Results of the primary analysis from 0 to 13 weeks show no statistical difference in health service use among the treatment groups (mirtazapine, sertraline or placebo). At 39 weeks, the secondary analysis indicated that the mean QALY gain between placebo and sertraline was 0.03, between placebo and mirtazapine was 0.05 and between mirtazapine and sertraline was 0.02. No significant differences in costs and QALY gains was reported across treatment groups. Neither mirtazapine nor sertraline were considered cost effective when compared with placebo when CSDD scores were the primary outcome. When costs and QALYs were considered alongside each other, mirtazapine was the most likely to be cost effective. The study found a 19.7% difference in health and social care costs between those assigned a placebo and those prescribed an antidepressant. Like Rosenheck et al. (2007), Banerjee et al. (2013) advocate a watchful waiting strategy. The study does not support prescribing antidepressants as first line treatment for people with dementia and coexisting depression in old age psychiatry services.

Appendix 5.a.5: Extraction summary

Study	Intervention	Design	Conditions/Population Targeted	Study Type
Kirbach et al. (2008)	Olanzapine vs. No treatment	Decision Analytic Model - Markov Model	Individuals with AD and psychosis and/or agitation living in the community or nursing homes	Cost Utility Analysis
Rosenheck et al. (2007)	Atypical Antipsychotics (Olanzapine, Risperidone, Quetiapine Fumerate) vs. Placebo	Randomized placebo-controlled trial of atypical antipsychotics and CBA	Outpatients in the USA living in the community or nursing homes with AD and psychosis, aggression or agitation	Cost Utility Analysis
Banerjee et al. (2013)	Antidepressants (Mirtazapine, Sertraline) vs. Placebo	Randomized double blind placebo-controlled trial	Individuals with AD and depression in 9 old age community psychiatry services in England	Health Technology Assessment

Study	Outcome Measurement	1. Setting/Country	2. Perspective	3. Time Horizon
Kirbach et al. (2008)	QALYs, ICER	USA	US Public Health System	13 years
Rosenheck et al. (2007)	Health service use and costs, Drug costs, QALYs, Net health benefits	USA	US Health Services	9 months
Banerjee et al. (2013)	CSDD Score, QALYs, Healthcare Costs	England	(i) Health and social care agency (ii) Health, social care agency and informal carer's perspective	0-13 weeks 0-19 weeks

Appendix 5.a.6: Analysis and result details

Study	1. Included costs (cost type, cost categories) and resource items	2. Data source costs and resource items	3. Data source outcomes and benefits	4. Methods of measuring/ valuing outcomes and benefits	5. Discounting
Kirbach et al. (2008)	Direct and indirect costs, drug costs, in-pt. care, out-pt. care, community care, nursing home care	Literature (Schneider et al., 2006; Murman et al., 2002; 2006 Red Book; Care Scout survey on nursing home costs)	Literature (Murman and Colenda, 2005; Neumann et al., 2000)	QALY, ICER	Costs and QALYs discounted at 3% (rate recommended by the Panel on Cost-Effectiveness in Health and Medicine)
Rosenheck et al. (2007)	Direct costs of experimental and concomitant medications, monthly health service costs, out-pt services	Literature (Schneider et al., 2006; 2002 Market Scan dataset)	Literature (Schneider et al., 2006; Health Utilities Index, 2002)	QALY	N/A
Banerjee et al. (2013)	Direct costs, in-pt. care, out-pt. care, community costs, health service costs, informal care costs	HTA-SADD, Curtis (2010), NHS Reference Costs 2009-2010	EQ-5D and societal weights	QALY, ICER	N/A

Study	6. Currency	7. Sensitivity Analysis	Cost and Resource Use	QALY Outcomes	Results
Kirbach et al. (2008)	US Dollar (\$)	One-way, two-way and three-way sensitivity analyses	Total 13-year cost of olanzapine for AD (high levels of psychosis and/or agitation) \$39,781 Total cost for pt. with no treatment \$35,899 Costs reported in US Dollar (\$) as at Feb 2008).	0.15 QALYs gained per patient on olanzapine	In terms of QALY gained, olanzapine is cost-effective for agitation and psychosis in people with AD, versus no treatment.
Rosenheck et al. (2007)	US Dollar (\$)	Sensitivity analysis, QALYs estimated at \$50,000 and \$100,000 per annum	Average monthly drug costs: Olanzapine \$327 , Risperidone \$308 , Quetiapine \$342 , Placebo \$165 <i>Costs reported in US Dollar (\$) as at Nov 2007</i>	Olanzapine 0.15 Risperidone 0.22 Quetiapine 0.21 Placebo 0.20	Lower health costs for placebo. 49.33% difference in drug costs (placebo v. AP). 34.51% difference in health and social care costs (placebo v. AP). None of treatments considered cost-effective. Watchful waiting strategy advocated.
Banerjee et al. (2013)	Sterling (£)	One-way sensitivity analysis	Medication costs and health and social care costs: Placebo £2,146 , Mirtazapine £1,550 , Sertraline £2,839 (Feb 2013) <i>Costs reported in Sterling (£) as at Feb 2013</i>	Placebo 0.55 Mirtazapine 0.60 Sertraline 0.57	Neither mirtazapine nor sertraline cost effective. 19.7% difference in health and social care costs between placebo and antidepressants. Watchful waiting strategy recommended.

AP = antipsychotic; pt. = patient

Discussion

This systematic review of existing literature on the economic evaluation of psychotropic medications for people with dementia was undertaken in accordance with national guidelines (HIQA, 2014). All papers included for analysis in this paper were also evaluated in the review conducted for the NICE guideline “Dementia assessment, management and support for people living with dementia and their carers” (NG97, 2018). The systematic search undertaken here highlights the shortage of economic evaluations on psychotropic medications, with only three papers meeting the inclusion criteria. Although antipsychotic medications incur relatively inexpensive manufacturing costs, the increased prescribing of these drugs has resulted in an increase in costs to the Irish public health service (Connolly, 2014). This escalation in healthcare costs is due to the associated increased risk of adverse side effects such as falls, fractures, stroke and death (Tampi et al., 2016).

Both Kirbach et al. (2008) and Rosenheck et al. (2007) employed data from the CATIE-AD study (details provided in Schneider et al., 2006). However, the findings of these studies conflict with one another, as was similarly noted by NICE (2018a). Results from Kirbach et al. (2008) suggest that when compared with no treatment, olanzapine is cost effective in terms of QALYs gained in the treatment of psychosis and or agitation in people with AD. In contrast, results from Rosenheck et al. (2007) find that olanzapine is less effective and more costly than placebo in the treatment of psychosis, aggression or agitation in people with AD. There are limitations to both studies. In Kirbach et al. (2008), the breakdown of indirect and direct costs included for analysis was not given. Therefore, costs past the reference case may have been included (NICE, 2018c). Authors of the Rosenheck et al. (2007) paper disclosed that they had previously worked for and received financial support from pharmaceutical companies that manufacture antipsychotic drugs. While a conflict of interest may apply to this study, it is noted that the paper was peer reviewed and published.

Meanwhile, Banerjee et al. (2013) report that the antidepressants mirtazapine and sertraline are not cost effective for the treatment of depression in people with dementia in psychiatry services in England. However, the economic evaluation does not extrapolate beyond the short time horizon analysis of the clinical study (39 weeks) nor are the findings extrapolated to people with severe dementia or depression, as noted by NICE (2018c). Despite this, this systematic review supports findings from Banerjee et al. (2013) that a watchful waiting strategy should be initiated before prescribing an antidepressant.

Results from the Rosenheck et al. (2007) paper suggest that there are no health economic or effectiveness benefits associated with the prescribing of antipsychotic medications. Similarly, findings from Banerjee et al. (2013) suggest that the antidepressants mirtazapine and sertraline are no more effective than placebo. Both studies advocate a watchful waiting strategy where patients are monitored and receive support and medical management from healthcare staff before active treatment is initiated. If this strategy fails, psychotropic medications should then be prescribed for treatment of non-cognitive symptoms of dementia.

Conclusion

The number of individuals living with dementia in Ireland is forecasted to increase significantly, while rates of inappropriate prescribing of psychotropic medications also continue to rise. The systematic literature search performed here highlights that there is a dearth of economic evaluations performed on these controversial medications. While the findings of the two antipsychotic papers examined here are at odds with one another, this study supports findings from NICE (2018c) that Rosenheck et al. (2007) offer a more robust analysis. The NICE (2018a) review supports the view that treatment with antipsychotics and antidepressants should be limited to urgent cases. This study thus supports the recommendation by

Rosenheck et al. (2007) to initiate a watchful waiting strategy with AD patients before beginning on an antipsychotic. A watchful waiting strategy is similarly advocated by Banerjee et al. (2013). The findings discussed in this review support the recommendations in this guideline that psychotropic medications, in particular antipsychotics, should not be the first line of treatment in BPSD.

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Part B: Budget impact analysis

Key message: Despite limitations in existing evidence to support a robust Budget Impact Analysis, a reduction in healthcare costs is anticipated following a reduction in the rates of inappropriate prescribing of psychotropic medications, following guideline implementation.

Introduction

The resource impact of overall guideline implementation is considered in this Budget Impact Analysis (BIA), with reference to specific recommendations as relevant.

Four key categories of additional resources have been identified:

- 1. Direct implementation costs: The cost of additional staff required for a national implementation team to support guideline implementation (one coordinator, two national trainers and part-time administrative support), dissemination/awareness raising costs, and the cost of developing an online training programme**
- 2. Auditing and evaluation costs: The resource impact of auditing hospitals and residential units to monitor the implementation of the guideline, and for evaluation at the end of the implementation period**
3. Training attendance costs: The cost of attendance by local HSE staff at train-the-trainer sessions
4. New practice costs: Costs associated with changes to clinician practice, i.e. a more comprehensive assessment of people with dementia being considered for prescription of a psychotropic medication (Rec. 1), and subsequent multidisciplinary meeting with the person with dementia/ Decision Supporter for risk/benefit discussion and decision-making (Rec. 7).

The GDG considers a national implementation team and resources to support online training, evaluation and monitoring to be crucial to successful implementation (items in bold above) and this requires investment. The costs of local trainers being trained is also included, as there is an opportunity cost associated with them attending training. However, the GDG acknowledges this could be considered as part of their usual work, depending on the usual role of the local trainer. In addition, best practice in prescribing does require more clinician time than poor practice. However, it is not envisioned that extra resources will be provided specifically for this care, but rather that an appropriately skilled and properly resourced dementia service working in and across settings would incorporate this best practice into usual care. Nevertheless, for indicative purposes the opportunity cost associated with the change in clinical practice is included in the BIA. Similarly, in practice, costs of auditing associated with this guideline may be absorbed into usual practice, however, for indicative purposes the costs associated with the audit are included here.

Costs avoided from the implementation of the new guideline are also estimated, noting that there is little economic evidence to support the model, and so some caution must be exercised.

1 Direct implementation costs

1.1 National Implementation Team

It is proposed to employ a project implementation officer for three years initially to facilitate the national implementation of the guideline (Grade VIII Clerical Officer (FTE 1.0)). The total annual salary cost of the project implementation officer is €101,805 (HSE, 2019). Travel expenses are also included (10% of annual salary cost), totalling €10,181. The total cost of the project implementation officer is €335,960 (See Table 5.b.1.1).

Staff training is required for guideline implementation. It is proposed to use a train-the-trainer model to deliver this training, with national trainers delivering training to a selection of staff, from: acute hospitals that provide services to adults (HSE-provided, voluntary and private); residential units (HSE-provided, voluntary and private); acute mental health units; community mental health teams; and primary care teams.

It is proposed that two 1.0 FTE trainers (Clinical Nurse Manager Grade 1 (CNM1) or equivalent) would be required to deliver training to staff nationally over a two-year period. The trainers will organise the train-the-trainer sessions, working closely with local implementation teams to select appropriate local trainers, and will deliver the train-the-trainer sessions. They will also assist in the development of training materials for the train-the-trainer session, including details of the guideline and accompanying toolkit, and training in quality improvement, leadership and audit training. They will also develop training materials to be used by local trainers for face-to-face training, and input to the content of an online training programme for HSE staff and General Practitioners (GPs). The total cost of two national trainers is €304,560 (See Table 5.b.1.1).

To support the implementation of the guideline across multiple settings nationally, it is proposed that a 0.5 FTE administrative support is provided to the national implementation team for three years (grade IV clerical officer). The administrative duties of this person will include scheduling meetings, typing minutes and keeping training databases up to date. By performing this routine administrative work, the post supports efficient use of the time of the coordinator and trainers. The total cost of administrative support is €76,578 (See Table 5.b.1.1).

1.2 Online training modules

It is proposed that the national trainers and national implementation team will develop a HSELand online training programme. This programme will contain information for HSE staff on the new guideline and its recommendations, with an embedded quiz and downloadable certificate of completion. The estimated cost of developing this online tool is €30,000 for initial module development (using a portable platform), then €7,000 total for two content updates over a 5-year period.

In addition, the content will be modified for GPs and hosted on the Irish College of GPs website (estimated €13,000 for this additional module development/hosting). Thus the total estimated cost is €50,000.

1.3 Targeted dissemination to GPs and community pharmacists

It is proposed that an awareness campaign targeting GPs and community pharmacists will be run, as these have been identified as potentially difficult to reach groups (not being based within a residential

or hospital unit or HSE-provided service). This will require tailored information for each discipline (i.e. a discipline-specific infographic) plus a summary of the guideline to be emailed and posted to all GPs and community practices. In addition, it is anticipated that awareness raising will involve presentations at national conferences; articles in relevant journals, etc. The total cost is estimated at €10,000.

Appendix 5.b.1.1: Direct implementation costs

National Staffing	FTE	Cost per annum (€)	Total Cost over three years (€)
Project Implementation Officer– salary ¹	1.0	101,805.08	
Project Implementation Officer – travel ²		10,180.51	
Total		111,985.59	335,956.77

National Trainer-salary ³	2.0	138,436.36	
National Trainer-travel ⁴		13,843.64	
Total		152,280.00	304,559.99

Administrative support ⁵	0.5	25,526.13	76,578.39
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Online Training Programme ⁶		50,000.00	50,000.00
Dissemination/awareness raising ⁷		-----	10,000.00

Total Implementation Costs⁸			777,095.15
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¹ Salary cost of a Grade VIII Clerical Officer is calculated using HSE (2019) salary scales, in accordance with HIQA (2018) guidelines. The midpoint salary of a Grade VIII worker is €72,848. When PRSI (at a rate of 10.75%), pensions (at a rate of 4%) and overheads (at a rate of 25%) are included, the total annual cost is €101,805.08. This person will be employed for three years.

² Travel expenses are included in the total annual cost of the project implementation officer. It is expected that travel expenses will be provided at a rate of 10% of the total annual salary. The total travel expenses of the project implementation officer per annum are €10,180.51.

³ The salary cost of a CNM1 is estimated using HSE (2019a) pay scales, in accordance with national guidelines (HIQA, 2018). The midpoint salary of a CNM1 is €49,530. When PRSI (at a rate of 10.75%), pensions (at a rate of 4%) and overheads (at a rate of 25%) are included, the total annual cost of a CNM1 is €69,218.18. Two people will be employed for two years.

⁴ Travel expenses are included in the total annual cost of the national trainers. It is expected that travel expenses will be provided at a rate of 10% of the total annual salary. The total travel expense of each national trainer per annum are €6,921.82.

⁵ The annual salary cost of a Grade IV Clerical Officer is calculated using HSE (2019) salary scales, in accordance with HIQA (2018) guidelines. The midpoint salary of a Grade IV worker is €35,592. When PRSI (at a rate of 10.75%), pensions (at a rate of 4%) and overheads (at a rate of 25%) are included, the total annual cost is €51,052.27. The person will be employed in a 0.5FTE (€25,526.13 per annum) for three years.

⁶ A HSE LanD module will be developed at an estimated cost of €30,000 for initial module development (including the cost of developing some video content, and using a portable platform to facilitate transfer to the ICGP), then €7000 total for two content updates over a 5-year period. This cost includes tracking access and generating reports per sector. In addition, the content will be modified for GPs and hosted on the Irish College of GPs website (estimated €13,000 for this additional module development/hosting). Total estimated cost €50,000.

⁷ Discipline specific infographics will be developed (estimated €500 each) for GPs and community pharmacists, and posted, along with a summary of the guideline to all GPs and community pharmacists (€2 postage x 2,500 GPs and 1,800 community pharmacies: total postage cost €8,600). Including presentations at national conferences; articles in relevant journals, total estimated cost of awareness raising is €10,000.

⁸ Total staff, online module development and dissemination activity costs over a 3 year period are €777,095.15.

2 Monitoring and evaluation

2.1 Evaluation

The Guideline Development Group strongly recommends that there is a formal evaluation of the implementation of this guideline, to guide future implementation of related guidelines, and other national quality improvement initiatives. Most of the data will be available from the within-implementation monitoring process (online education usage, training records across implementation sites, pre-and post-implementation audit data, where available). However, there are three additional components required to transform this multi-modal crude data into usable data presented in a brief report:

- i. A pre-implementation chart review (using the baseline practice version of the residential care audit tool) in a sample of HSE-provided residential care units to establish baseline practice. This data is not currently available and would be invaluable to inform and support training in residential care, and also to demonstrate implementation success at the end of the implementation programme (when compared to post-implementation practice).
- ii. A user survey within residential care units (aiming that acute hospital experiences can be captured through the national patient experience survey), performed pre- and post-implementation, to capture the experience of the person with dementia and their family in assessment and decision making around psychotropic medications, as this is a key outcome of successful implementation of the guideline and will not be captured by a chart audit.
- iii. Collation and presentation of key implementation data in an implementation report.

It is proposed that these evaluation projects would be separately tendered to academic groups nationally, pending a budget for this being available (although this support could be provided directly by a researcher employed by the National Dementia Office, again requiring a budget). Successful groups would work closely with the National Implementation Coordinator and the National Dementia Office. Outsourcing the pre-implementation data collection and report would allow the National Implementation Coordinator to focus on implementation, not data collation and analysis.

i) Pre-implementation chart review

It is proposed that a 25% random sample of the 130 HSE-provided Older Persons residential care units (n=32), and 10 purposively selected congregated disability residential care units where a high proportion of residents have dementia, will have baseline practice established (using the baseline version of the residential care audit tool). In line with GDPR requirements, the data would be collected by the residential staff site (subject to the site having capability to provide this resource), and the anonymous paper-based data would be entered into a database and analysed by the academic group, with a written report generated. The cost of this project in terms of management, liaison and support of the residential sites, data entry, analysis and report is estimated at €16,000.

ii) User survey

As proposed by the lay members of the Guideline Development Group, it is important to capture the experience of the person with dementia and their family, as this key outcome is not captured by chart audit. It is proposed that within a small sample of 10 residential care units in two regions, pre- and post-implementation surveys would be performed with a person with dementia/family member dyads, in year 1. As this would require novel survey tool generation, and ethics applications, the cost for this project is estimated at €24,000. A similar cost for the post-implementation survey is expected, in year 3.

iii) Collation and presentation of key implementation data in an implementation report

This would use existing data from the implementation monitoring process, such as education and training data (online education activity, analysed by discipline and setting temporally; training records across implementation sites), and pre-and post-implementation chart review/chart audit data, and data on the reach of the public awareness campaign, and would occur in year 3.

Appendix 5.b.2.1: Evaluation costs (pre and post implementation data collection; final report)

Evaluation costs	Year of implementation	Project cost
1. Baseline review residential care ¹	1	15,854.08
2. Baseline user experience survey ²	1	23,781.13
3. Post-implementation user experience survey ³	3	24,970.18
4. Implementation report ⁴	3	28,540.61
Total Evaluation Cost⁵		93,146.00

¹ For the pre-implementation chart review, costs are estimated for a point 1 on scale postdoctoral researcher salary, with a basic salary of €37,874 as per IUA pay scale for Jan 2020, plus 10.75% PRSI and 20% employers PRSI contribution (annual total €49,558). This person would be employed for 4 months at 0.6FTE – total cost €9911.60. Total project travel and postage is estimated at €400. University overheads of 25% for desk-based research would apply to the total cost (€10,311.60*0.25). Adding VAT at 23% to this total of €12889.50, the final project cost is €15,854.08.

² Baseline user survey project cost is estimated for a point 1 on scale postdoctoral researcher salary, with a basic salary of €37,874 as per IUA pay scale for Jan 2020, plus 10.75% PRSI and 20% employers PRSI contribution (annual total €49,558). This person would be employed for 6 months at 0.6FTE – total cost €14867.40. Total project travel and postage is estimated at €600. University overheads of 25% for desk-based research would apply to the total cost (€15,467.40*0.25). Adding VAT at 23% to this total of €19,334.25, the final project cost is €23,781.13.

³ Post-implementation user survey project: the user survey would be repeated in year 3 of implementation, allowing 5% inflation in costs in that period, bringing the total cost to €24,970.18.

⁴ Implementation report project is estimated for a point 5 on scale postdoctoral researcher salary, with a basic salary of €42,559 as per IUA pay scale for Jan 2020, plus 10.75% PRSI and 20% employers PRSI contribution (annual total €55,689). This person would be employed for 4 months at 1.0FTE – total cost €18,563.00. University overheads of 25% for desk-based research would apply to this salary (€4,640.75). Adding VAT at 23% to this total of €23,203.75, the final project cost is €28,540.61.

⁵ This is the total cost of activities 1-4 over the 3 years of implementation. Items 1 and 2 occur in year 1 (total cost €39,635.21) and items 3 and 4 in year 3 (total cost €53,510.79).

2.2 Audit

It is expected that residential care units and acute hospitals throughout Ireland will self-audit to determine if guideline recommendations are being followed and put into practice within their unit, to inform their training plan and promote good practice/identify if more support is required to improve practice around psychotropic prescribing. It would not be feasible to audit practice for people living in the community due to case-finding difficulties and expected low frequency per GP practice. Specialist clinics may choose to self-audit – this would typically be performed by an NCHD as part of their professional training requirement to perform one audit per year.

The GDG recognise that while in practice auditing activities linked to the recommendation will most likely be absorbed into usual activity, it does represent an increased workload with associated opportunity costs. We estimate those costs as follows:

2.2.1 Hospitals

Auditing in the 40 HSE-provided and voluntary acute and orthopaedic public hospitals that admit people with dementia (with respect to compliance with the guideline) would be expected to take ten hours per site (30 minutes to review a chart, and 20 charts thus reviewed per site). This excludes the cost of data analysis/report and action plan generation, which is expected to be performed by the site local implementation team, envisioning that the audit may be supported by a Dementia Specialist Nurse, Advanced Nurse Practitioner, or non-consultant hospital doctor, whose role includes audit. A proxy cost is calculated for the audit data collection using HSE (2019a) salary scales. It is assumed that each audit

will be performed by a Grade V Clerical Officer, and hospitals will self-audit annually from year 3. A Grade V Clerical Officer is estimated at an annual cost across hospitals of €16,761 from year 3 (See Table 2.2). (Baseline practice will be available in all these hospitals from the 2019 INAD-2, the national dementia audit in acute hospitals, where the chart review of prescribing practice is being incorporated into the chart review for the audit).

2.2.2 Residential care units

Audits should also be carried out in each of the 130 HSE provided residential care units in Ireland (nursing homes Ireland, 2019). A proxy cost is again calculated using HSE (2019a) salary scales and assuming that each audit will be performed by a Grade V Clerical Officer. A Grade V Clerical Officer is estimated at total cost of €65,368. It is expected that residential units will self-audit in year 3 and 5. The total cost is €108,947 (See Appendix 5.b.2.2). (It is planned that baseline practice in a sample of residential care units will be performed as part of the evaluation- see section 2.1).

The total estimated cost of auditing in hospital and residential care units from year 3 to year 5 is €159,230 (See Appendix 5.b.2.2).

Appendix 5.b.2.2: Cost of auditing residential care units and hospitals for compliance with guideline recommendations

Audit of Residential Care Units and Hospitals	No. Units/ Hospitals ¹	No. of Hours Auditing per unit ²	Total no. of hours	Cost of Audit Staff per hour(€) ³	Total Cost / Cycle (€)	Audit Cycle Length (Years) ⁴	Total Cost over 3 years(€)
Acute and Orthopaedic Hospitals	40	10	400	41.90	16,761.01	1	50,283.21
Residential Care Units	130	10	1,300	41.90	54,473.47	1.5	108,946.95
Total Cost					71,234.48		159,230.16

¹ 40 Irish public hospitals would be expected to undertake self-audit (HSE, 2019b); 130 residential units will similarly be expected to self-audit (nursing homes Ireland, 2019).

² It is anticipated that hospital audits and residential care unit audits should take 10 hours each (excluding data collation and analysis that would be undertaken by the local implementation team in each site).

³ Grade V Clerical Officers would be the typical grade performing audits in hospitals (where audit staff are available). The HSE salary of a Grade V Clerical Officer is also used as a proxy cost to determine the costs of auditing residential units. The midpoint salary of a Grade V Clerical Officer is €46,054. PRSI (10.75%) pensions (4%) and overheads (25%) are included. The annual salary cost is €64,360. On average, a Grade V Clerical Officer works 221 days per annum (HSE, 2009). The daily salary cost of a Grade V Clerical Officer is €291.22 (€64,360.47/221). On average, a HSE worker works 6.95 hours a day (Department of the Taoiseach, 2009). The hourly cost of this professional is therefore €41.90.

⁴ All 40 hospitals should undertake a yearly audit to assess their compliance with guideline recommendations from year 3-5. The 130 residential units would be expected to self-audit in year 3 and year 5.

3 Training costs

The following analysis presents estimates for the opportunity costs for local services of local trainers attending a train-the-train session local to their place of work, and travel costs. (The cost of the national trainers has been presented in section 1, and these will deliver these training sessions within their workload).

To estimate these training costs, the cost of the local trainer training-up time is identified, measured and valued in line with HIQA guidelines (2019). As per the guidelines, these estimates will include overheads (25%) associated with training.

Doctors, nurses or pharmacists from acute hospitals, residential units, acute mental health units, community mental health teams and primary care teams will attend local train the trainer sessions in years one and two. Hospitals, residential units, acute mental health units, community mental health teams and primary care teams will be grouped based on their locations for these training sessions- so that all residential care units (HSE-provided, voluntary or private) in an area would be invited to attend one session, all acute hospitals in an area would attend another session, etc. It is thus proposed that a number of training sessions will be provided per hospital group, and per community health organisation (CHO) region.

Hospitals: It is proposed that on average, three CNM1s from each of the 40 relevant acute and orthopaedic hospitals will attend an eight-hour train-the-trainer session in their local area. Total estimated cost of this is €42,681.60.

Public residential units: It is proposed that one CNM1 from each of the 130 public residential units will attend an eight-hour training session. Total estimated cost of this is €46,238.40. *Note: training will also be offered to healthcare professionals from private residential units. Private residential units will be informed when training sessions are taking place in their vicinity. Local trainer costs for private and voluntary residential units have not been included.*

Acute mental health units: It is proposed that a CNM1 from each of the 31 public acute mental health units will attend an eight-hour training session. Total estimated cost of this is €11,075.68

Community mental health teams: It is proposed that one public health nurse from each of the 97 community mental health teams will attend an eight-hour training session. Total estimated cost of this is €35,913.28.

Primary care teams: It is proposed to organise training for primary care teams via clusters per CHOs. With 20 sessions per CHO, 180 public health nurses will participate in an eight-hour training session. Total estimated cost of this is €66,643.20.

Disability centres: There are 1,250 of these nationally, of varying size (i.e. some have 2-3 people supported to live in the community, some are congregated settings; a small minority of residents overall have dementia). Local implementation teams within each CHO will prioritise who needs training at local level. It is thus proposed that overall, 100 local trainers will attend an eight-hour training session. Total estimated cost of this is €32,011.20.

The estimated total cost of this is €258,019, which includes the opportunity cost of healthcare professionals attending train the trainer education sessions (estimated using salary costs: €234,563.36), plus 10% travel costs (See Appendix 5.b.3.1). This will be spread over two years as follows; 25% of the training costs will occur in year one (allowing for initial development of education and planning of the roll-out in year 1) and 75% will be in year two (where most of the training will take place). Of note, it is expected that HSE venues for training will be available free of charge.

Following training, the local trainers will in turn will deliver training to their colleagues in their unit/organisation. It is assumed that this local training will be performed as part of the usual work of the local trainers, using naturally occurring training opportunities (e.g., hospital grand rounds, community hospital MDT meetings, Primary Care Team meetings, etc.). It is not possible to quantify the time involved for the local trainer or the attendees, as this will vary significantly. In addition, many doctors, nurses

and pharmacists may undertake the online training rather than face-to-face training. The Guideline Development Group acknowledges that there is an opportunity cost in all training, but equally many disciplines have fixed annual Continuous Professional Development education requirements, and thus may select this guideline as a preferred topic.

Appendix 5.b.3.1: Local trainer costs

National training delivery attendee costs	No. of units	No. of staff per unit	Total staff for local training	Length of training session (hours) ¹	Total hours	Hourly cost per person (€) ²	Total cost (€)
Hospital ³	40	3	120	8	960	44.46	42,681.60
Residential ⁴	130	1	130	8	1,040	44.46	46,238.40
Acute Mental Health Units ⁵	31	1	31	8	248	44.66	11,075.68
Community Mental Health Teams ⁶	97	1	97	8	776	46.28	35,913.28
Primary Care Teams ⁷	484	-	180	8	1,440	46.28	66,643.20
Disability Centres ⁸	1,250	-	90	8	720	44.46	32,011.20
Total Training Cost for Years 1+2 ⁹							234,563.36
Travel costs at 10% ¹⁰							23,456.34
Total Cost							258,019.70

¹ It is anticipated that each train-the-trainer session will last eight hours for all healthcare professionals; this includes limited travel time (as training will be local).

² In accordance with HIQA (2018) guidelines, HSE (2019a) pay scales were employed to calculate the hourly cost of healthcare professionals. A CNM1 will attend the training for hospitals and public residential units. When PRSI, pensions and overheads are accounted for, the hourly cost of a CNM1 is €44.46. A mental health CNM1 will attend training for acute mental health units. The hourly cost of these professionals is €44.66. A public health nurse will attend training for community mental health and primary care teams. The hourly cost of these workers is €46.49.

³ The guideline is relevant for 40 acute hospitals (HSE, 2019b).

⁴ One CNM1 will attend training from the 130 public residential units (nursing homes Ireland, 2019).

⁵ There are 31 acute mental health teams in Ireland (Mental Health Commission, 2019).

⁶ There is one community mental health team for every 50,000 inhabitants in Ireland (HSE National Vision for Change Working Group, 2012). When the population of Ireland, 4,838,259 is divided by 50,000, there are 97 community mental health teams in Ireland (Eurostat, 2019).

⁷ The population of Ireland is 4,838,259 (Eurostat, 2019). There should be one primary care team for every 10,000 inhabitants of Ireland (HSE, 2019c). Thus, there are notionally 484 primary care teams in Ireland (although some are not yet formed/functional). Thus, it has been estimated that 20 local trainers will be trained per CHO region, approximating one local trainer per three PCTs.

⁸ There are 1,250 disability centres in Ireland. Most do not house a person with dementia. It is pragmatically estimated that 10 local trainers will be trained per CHO region, i.e. 90 in total, focusing most training efforts on larger congregated units.

⁹ The total cost of training over years one and two of guideline implementation is €234,563.36.

¹⁰ Travel expenses are estimated at 10% of salary cost.

4 Costs of new practice following implementation

The National Clinical Guideline requires that a comprehensive assessment of a person with dementia should be performed by an appropriate healthcare professional before considering any psychotropic medication for a person with dementia and non-cognitive symptoms (Recommendation 1). Following assessment, a decision is made about whether to start a medication. For antipsychotic medication, this includes a discussion with the person with dementia, and/or their Decision Supporter, about the risks/benefits (Recommendation 7). The latter has been modelled as a multidisciplinary meeting including the person with dementia, and/or their Decision Supporter, noting that MDT meetings should be occurring as a matter of course on a regular basis for a person with dementia with non-cognitive symptoms, as part of integrated care. In some services, the good practice recommended in the guideline is already

occurring, but this is not by any means universal, as supported by the consultation feedback. The costs of a comprehensive assessment and the subsequent decision-making meeting are estimated here to capture the opportunity cost associated with the change in practice.

4.1 Number of people requiring assessment

The costs of these assessments and decision-making meetings will vary by setting. The number of people requiring assessment in hospitals, residential units and the community per annum, from year 2 (once appropriate staff are trained) is estimated as follows (see Appendix 5.b.4.1):

Hospitals: It is estimated there will be 65,531¹¹ people with dementia in Ireland in 2020 (year 2 in the analysis) (Pierce, Cahill and O’Shea, 2014). 3% are hospitalised each year, totalling 1,966 people (Connolly et al., 2014). 24% of those hospitalised (i.e. 472 people) are prescribed a new or increased dose of antipsychotic (Gallagher et al., 2016). Data is scarce on the prescribing of other psychotropic medications to people with dementia in acute hospitals Ireland. Therefore, it is assumed that 472 people with dementia are newly prescribed a psychotropic when hospitalised per annum, thus requiring comprehensive assessment.

Residential units: 34% of people with dementia in Ireland live in residential care (22,281 people) (O’Shea et al., 2015, Connolly et al., 2014). Of these, 41% are prescribed antipsychotic medication (Bermingham et al., 2017; de Siún et al., 2014). Thus, an estimated 9,135 people in residential care are prescribed a psychotropic medication and will require comprehensive assessment each year (22,281*0.41). [Not all of these are new prescriptions within a year, but some people will receive more than one course of psychotropic medications within a year, and many existing prescriptions also need review, so this is a useful approximate figure]

Community: 19% of people with dementia are prescribed a psychotropic medication, totalling 12,451 people (65,531*0.19) (Connolly et al., 2014; O’Shea et al., 2015). To estimate the number of people with dementia prescribed a psychotropic medication in the community, the number of people in residential care (9,135) and hospitals (472) is subtracted from the total number (12,451). Thus, an estimated 2,844 people in the community with dementia will require comprehensive assessment. [Not all of these are new prescriptions within a year, but some people will receive more than one course of psychotropic medications within a year, and existing prescriptions also need review, so this is a useful approximate figure]

Appendix 5.b.4.1: Estimated number of people with dementia requiring a comprehensive assessment for non-cognitive symptoms per annum, in each setting of care per annum

Setting	Number requiring assessment per annum
Acute Hospitals	472
Residential Care	9,135
Community	2,844
Total	12,451

¹¹ Pierce, Cahill and O’Shea (2014) estimate 54,793 with dementia in Ireland in 2016 and 68,216 by 2021. 2020 estimates are calculated assuming an even distribution per annum.

4.2 New practice costs (assessment and decision-making meeting)

4.2.1 Assessment costs: hospital

To model the cost of the new practice of comprehensive assessment and risk-benefit discussion, in acute hospitals, it is assumed that the comprehensive assessments will be undertaken by NCHDs (focusing on delirium assessment; 30 minutes required) and staff nurses (focusing on behaviour triggers; 30 minutes required). Following the assessment, it is modelled that the NCHD and staff nurse will attend a MDT meeting, lasting 45 minutes, along with another Allied Health Professional, and the person with dementia/Decision Supporter.

Thus, the total cost of assessment and the subsequent discussion per person with dementia in a hospital is €131.11 (See Appendix 5.b.4.2).

Appendix 5.b.4.2: Cost of assessment of people with dementia and MDT meetings in hospitals

Hospital assessments	Hours ¹	Cost per hour (€)	Unit cost per professional (€)
NCHD Assessment ²	0.50	46.48	23.24
Nurse Assessment ³	0.50	33.86	16.93
NCHD MDT Meeting ⁴	0.75	46.48	34.86
Nurse MDT Meeting ⁵	0.75	33.86	25.39
Therapist MDT Meeting ⁶	0.75	40.93	30.69
Total⁷			131.11

¹ It is proposed that assessments of individuals with dementia in hospitals will be undertaken by a NCHD and a staff nurse, lasting 30 minutes per patient. The decision-making meeting between the person with dementia and their Decision Supporter, a NCHD, staff nurse and an AHP should last 45 minutes.

² HSE consolidated salary scales as of the 1st of January 2019 are employed to estimate the hourly cost of a NCHD. The midpoint pay of a NCHD is €51,543. When PRSI (10.75%), pensions (4%) and overheads (25%) are included, the annual salary cost of a NCHD is €101,805. On average, a NCHD is entitled to 26 days annual leave (HSE, 2009). As Irish healthcare professionals work 249 days per annum, a NCHD works 223 days per annum (Department of the Taoiseach, 2009). On average, HSE professionals work 6.95 hours a day (Department of the Taoiseach, 2009). The hourly cost of a NCHD is €46.48. The assessments of people with dementia last 30 minutes, thus the unit cost of a NCHD performing one assessment is €23.24.

³ As per HIQA (2018) guidelines, HSE pay scales are employed to estimate the costs of staff nurses performing assessments. With PRSI (10.75%), pensions (4%) and overheads (25%) included, the annual salary cost of a staff nurse is €52,941. A staff nurse is entitled to 24 days annual leave, working 225 days in the average working year (INMO, 2015; Department of the Taoiseach, 2009). The daily cost of a staff nurse (€235.30) is divided by the average number of hours worked, 6.95 (Department of the Taoiseach, 2009). The hourly cost is €33.86. As an assessment takes 30 minutes, the unit cost of a nurse assessing a patient is €16.93.

⁴ A 45-minute meeting is held after the assessment. The unit cost of a NCHD attending one of these meetings is €34.86 (€46.48*0.75).

⁵ A staff nurse also attends the 45-minute meeting post assessment. The unit cost of a nurse attending a meeting is €25.39 (€33.86*0.75).

⁶ An AHP attends the 45 minute MDT meeting. HSE (2019) pay scales are used to determine the hourly cost of an OT, as a typical AHP that would be involved. With PRSI (10.75%), pensions (4%) and overheads (25%) included, the annual cost is €63,145. The hourly cost is €40.93, thus the cost per meeting is €30.69 (Department of the Taoiseach, 2009).

⁷ The total cost of the assessments and meetings in hospitals per person with dementia is €131.11.

4.2.2 Assessment costs: residential units

In residential units, it is proposed that the costing is based on the assessments being performed by a GP (30 minutes) and a staff nurse (30 minutes). A meeting will then be held with the GP, staff nurse, a health and social care professional (assumed to be an occupational therapist for cost purposes) and the person with dementia and/or their Decision Supporter. In practice, the assessment and MDT meeting may sometimes be performed by a visiting psychiatry of old age or geriatric medicine service, at much greater cost, in a residential care facility (be that public or private). Equally, the cost of assessments in private nursing homes may be borne by the facility or the person with dementia directly (e.g. accessing a therapist privately). Thus, pragmatically, the cost has been modelled on a GP/local nurse and occupational therapist time. The total cost of assessment and the subsequent MDT meeting per person with dementia is €163.79 (See Appendix 5.b.4.3).

Appendix 5.b.4.3: Cost of assessments and decision-making meetings in residential units

Residential assessments	Hours ¹	Cost per hour (€)	Unit cost per professional (€)
Doctor Assessment ²	0.50	72.62	36.31
Nurse Assessment ³	0.50	33.86	16.93
Doctor MDT Meeting ⁴	0.75	72.62	54.47
Nurse MDT Meeting ⁵	0.75	33.86	25.39
Therapist MDT Meeting ⁶	0.75	40.93	30.69
Total⁷			163.79

¹ As per Table 4.2: Assessments will last 30 minutes and multidisciplinary meetings will last 45 minutes.

² The hourly cost of a salaried GP is €72.62 (McElroy et al., 2017). The unit cost of a GP assessing a person with dementia is €36.31.

³ The unit cost of a nurse performing a 30-minute assessment is €16.93 (Table 4.1).

⁴ The unit cost of a salaried GP attending a 45-minute meeting is €54.47 (McElroy et al., 2017).

⁵ The unit cost of a staff nurse attending one meeting is €25.39 (Table 4.1).

⁶ The unit cost of an OT attending one meeting is €30.69 (Table 4.1).

⁷ The cost per person of assessing people with dementia who are prescribed a psychotropic and attending MDT meetings in residential units is €163.79.

4.2.3 Assessment costs: community

In the community, it is modelled that half of the assessments of people with dementia who are prescribed a psychotropic medication will take place in a GP setting. The remaining assessments and meetings will take place in a specialist clinic setting.

4.2.3.1 Assessment costs: General Practice (GP) setting

In a GP setting, it is modelled that the assessment of a person with dementia who is taking psychotropic medication is carried out solely by a GP (15 minutes), and at a second visit, if non-pharmacological interventions haven't worked, the GP has a discussion with the person with dementia and/or their Decision Supporter, without other MDT input, again lasting 15 minutes. The cost per person is thus €36.31 (See Appendix 5.b.4.4).

Appendix 5.b.4.4: Cost of assessment of people with dementia in a GP setting

Community assessments GP setting	Hours	Cost per hour (€)	Unit cost per professional (€)
GP Assessment ¹	0.5	72.62	36.31 ¹

¹ This includes two 15-minute discussions.

4.2.3.2 Assessment costs: clinic setting

In a clinic setting, it is modelled that a person with dementia is assessed separately by a consultant geriatrician/psychiatrist of old age and a specialist nurse (30 minutes each). Following this, a meeting is held with the geriatrician and staff nurse alongside an AHP and the person with dementia and/or their Decision Supporter (45 minutes). The cost of assessment and attendance at MDT meetings per person with dementia who live in a clinic setting in the community is €286.49 (See Appendix 5.b.4.5).

Appendix 5.b.4.5: Cost of assessments and meetings for people with dementia living in the community in a clinic setting

Community assessments clinic setting	Hours	Cost per hour (€)	Unit cost per professional (€)
Consultant Assessment ¹	0.5	170.78	85.39
Nurse Assessment ²	0.5	33.86	16.93
Consultant MDT Meeting ³	0.75	170.78	128.08
Nurse MDT Meeting ⁴	0.75	33.86	25.39
Therapist MDT Meeting ⁵	0.75	40.93	30.69
Total⁶			286.49

¹ It is anticipated that the assessments in a clinic setting will be performed by a geriatrician. The midpoint salary of a Category I Geriatrician with a Type A contract is €185,150. When PRSI (10.75%), pensions (4%) and overheads (25%) are included, the annual salary cost of a geriatrician is €258,747. These professionals are entitled to 31 days annual leave (HSE, 2012). On average, a geriatrician works 218 days per annum (249-31) (Department of the Taoiseach, 2009). An average HSE professional works 6.95 hours per day. Thus, the hourly cost of a geriatrician is €170.78. The unit cost of a geriatrician performing one assessment is €85.39.

² The unit cost of a staff nurse performing one assessment is €16.93 (Table 4.2).

³ It is expected that each MDT meeting will take 45 minutes. The unit cost of a geriatrician attending one of these meetings is €85.39 (€170.78*0.75).

⁴ The unit cost of a staff nurse attending one meeting is €25.39 (Table 4.2).

⁵ The unit cost of an OT attending one meeting is €40.93 (Table 4.2).

⁶ The total cost of assessments in a clinic setting per person with dementia prescribed a psychotropic and living in the community is €286.49.

4.3 Total cost of assessments

The total cost of new practice (assessing people with dementia prior to prescribing psychotropic medication and a subsequent decision-making meeting) is thus estimated at €2.03 million for the first year when staff are trained in the new practice (which corresponds to year 2) (See Appendix 5.b.4.6). In subsequent years, post guideline implementation, we assume 50% of those who would have been prescribed psychotropic medication in the absence of the guideline now require annual assessment (see Section 6 and Appendix 5.b.6.2 for population estimates).

Appendix 5.b.4.6: Total annual cost of assessments and discussions for people with dementia prescribed a psychotropic medication -Year 2

Care setting/unit	Cost per person (€)	Number of people	Total costs (€)
Hospital	€131.11	472	62,359.16
Residential	€163.79	9,135	1,505,323.49
Community (GP)	€36.31	1,422	53,065.82
Community (Clinic)	€286.49	1,422	408,829.63
Total Cost of Assessments and Meetings		12,451	2,029,578.10

5 Costs avoided

Dementia places a significant burden on Irish public healthcare funds, costing an estimated €1.69 billion per annum (Pierce et al., 2014). The recommendations provided in the guideline aim to support more appropriate prescribing of psychotropic medications for people with dementia. Once the guideline is implemented, all appropriate HSE staff are trained and assessments are conducted, it is anticipated that inappropriate prescribing of psychotropic medications and associated adverse events will be avoided. Thereby avoiding costs of psychotropic medication and health and social care costs. For the purpose of the BIA, these costs avoided are informed by two papers identified in the systematic literature search on the cost effectiveness of psychotropic medications (Banerjee et al. (2013) and Rosenheck et al. (2007)). Irish cost estimates from Connolly et al. (2014), a cost of illness study of the economic and social costs of dementia in Ireland, are employed to estimate costs avoided.

5.1 Psychotropic medication costs

Rosenheck et al. (2007) report a 49.33% difference in drug costs between patients receiving an atypical antipsychotic versus placebo. Results from Connolly et al. (2014) indicate that the annual cost of psychotropic medications for people with dementia is €2.439 million, or €58.44 per person (adjusted for inflation) (CSO, 2019). With guideline implementation, it is expected that on average €28.83 of drug costs should be avoided per person with dementia (See Appendix 5.b.5.1).

5.2 Health and social care costs

A 27.11% reduction in health and social care costs is expected following guideline implementation (Rosenheck et al., 2007; Banerjee et al. 2013). When adjusted for inflation, the total annual health and social care costs of dementia are €132.97 million or €3,186 on average per person (Connolly et al., 2014; CSO, 2019). Implementing the guideline and reducing health and social care costs results in annual cost avoidance of €863.56 on average per person with dementia. Of note, many of the people for whom it is expected outcomes will improve from better practice, and hence less adverse events, are already in residential care, and thus the full cost avoidance may be over-estimated in this cohort, as their requirement for residential care cannot change. However, resource utilisation costs will still be significantly reduced within this cohort from the expected reduction in strokes, acute hospitalisations due to adverse events (falls, fracture, head injury, pneumonia, etc.), rehabilitation requirements, and in HSE-provided services.

It is thus estimated that a total of €892.39 could be avoided per person with dementia (reduced medication cost and health and social care costs) if the guideline is implemented and inappropriate prescribing of psychotropic medications is reduced (See Appendix 5.b.5.1).

Appendix 5.b.5.1: Estimating annual cost avoidance per person due to guideline implementation

Cost type	Cost per annum (€) ¹	Number of people with dementia ²	Cost per person per annum (€)	% Cost reduction from no Psychotropic	Total avoided per person per annum (€)
Medications (Psychotropic only) ³	2,439,362.63	41,740	58.44	0.4933	28.83
Health and Social Care Costs ⁴	132,971,142.76	41,740	3,185.70	0.2711	863.56
Total	135,410,505.39		3,244.14		892.39

¹ Costs obtained from Connolly et al. (2014) and adjusted for inflation using the CSO (2019) CPI Calculator.

² Analysis by Connolly et al. (2014) reports 41,740 people living with dementia in Ireland.

³ When adjusted for inflation, the annual cost of psychotropic drugs for people with dementia is over €2.439 million (Connolly et al., 2014). This figure is divided by 41,740 (the number of people with dementia) to determine the cost per person. The cost per person is €58.44. Rosenheck et al. (2007) report a 49.33% difference in drug costs between people prescribed a placebo and those assigned the atypical antipsychotic, olanzapine. When €58.44 is multiplied by 0.4933, the total drug cost avoided per person is €28.83.

⁴ When adjusted for inflation, the total annual health and social care costs of dementia in Ireland are €132.97 million (Connolly et al., 2014; CSO, 2019). The cost per person with dementia is €3,185.70 (€132,971,143/41,740). Rosenheck et al. (2007) identified a 34.51% difference in monthly health service costs between those assigned a placebo and those taking an atypical antipsychotic. Banerjee et al. (2013) identified a 19.7% difference in health service costs between those assigned a placebo and those taking an antidepressant (mirtazapine or sertraline). The average of these figures is 27.11% ((34.51+ 19.7)/2). When a cost reduction of 27.11% is applied to €3,185.70, the total health and social care costs avoided per person with dementia are €863.56.

5.3 Total costs avoided due to guideline implementation

There is good evidence that psychotropic use can be reduced, both from clinical trials and from Irish quality improvement projects in residential care (Section 2.3.1). In the UK, following the implementation of national policies, prescribing of antipsychotic medications was reduced by 48.42% (Donegan et al., 2017). (This UK data is the best available evidence). It is expected that this reduction will be achieved in Ireland from the second year of guideline implementation (when all training is completed). Of note, Section 6.3 reports a sensitivity analysis based on less marked reductions in prescribing, at 30% and at 20% reductions. The total medication and health and social care costs avoided for people with dementia prescribed a psychotropic medication in residential care is estimated at €4.537 million (See Appendix 5.b.5.2).

Appendix 5.b.5.2: Total costs avoided due to guideline implementation-Year 2

Cost avoided	Number of people	Reduced prescribing from guideline ¹	Number of people no longer prescribed	Cost avoided per person (€) ²	Total costs avoided (€)
Total people with dementia on a psychotropic³	12,451	0.484	6,026	892.39	5,377,781

¹ Donegan et al. (2017) report a 48.42% reduction in the prescribing of antipsychotic medication to people with dementia following the implementation of national strategies and policies in the UK. In this model, it is anticipated that a reduction in prescribing of 48.42% will occur in Ireland in year two of guideline implementation.

² From Table 5.1. An estimated €892.39 should be avoided per person with dementia.

³ It is estimated that in total 12,451 people with dementia in Ireland are prescribed a psychotropic drug (Connolly et al., 2014). It is anticipated that 6,026 of these people will no longer be prescribed psychotropic medications following guideline implementation (12,451*0.4842).

6 Budget impact assessment

The resource impact of the guideline over a five-year horizon, as advocated by HIQA (2018), is estimated. Details of estimates of the reduction in the number of people with dementia prescribed a psychotropic following guideline implementation are provided. Total costs and total costs avoided over five years are also discussed.

6.1 Population estimates: people requiring assessment and people avoided

To forecast the number of people with dementia in the years post guideline implementation, estimates for the number of people with dementia in Ireland from Pierce et al. (2014) were utilised. Pierce et al. (2014) forecast by 2021 there will be 68,216 people in Ireland with dementia increasing to 77,460 by 2026. Annual estimates are extrapolated from Pierce et al. (2014) assuming an even annual distribution. An estimated 19% of people with dementia are prescribed a psychotropic (Connolly et al., 2014). This figure is applied to determine the total number of people with dementia prescribed a psychotropic should the guideline not be implemented. (See Appendix 5.b.6.1).

It is anticipated that a 48.42% reduction in psychotropic prescribing to people with dementia will be achieved in year two of guideline implementation (Donegan et al., 2017; see section 2.3.1 also). This figure is applied to the population estimates (from Appendix 5.b.6.1) to determine the reduction in psychotropic prescribing due to the guideline. It is estimated that 6,026 people with dementia will be prescribed a psychotropic following guideline implementation in year two, rising to 6,698 people in year five, owing to the expected increase in the prevalence of dementia (See Appendix 5.b.6.2).

Appendix 5.b.6.1: Population estimates of levels of psychotropic prescribing without guideline implementation

Year ¹	Total number of people with dementia ²	% People prescribed psychotropic ³	No. of people w/dementia prescribed a psychotropic ⁴
2	65,531	0.19	12,451
3	68,216	0.19	11,256
4	70,527	0.19	12,012
5	72,838	0.19	12,766

¹ Year one corresponds with 2019, year 2 with year 2020 etc.

² Pierce et al. (2014) forecast by 2021 there will be 68,216 people in Ireland with dementia increasing to 77,460 by 2026. Annual estimates are extrapolated from Pierce et al. (2014) assuming an even annual distribution.

³ Connolly et al. (2014) report that 19% of people with dementia in Ireland are prescribed a psychotropic.

⁴ The number of people with dementia prescribed a psychotropic drug each year is estimated by multiplying the total number of people with dementia by the percentage of people prescribed a psychotropic (19%).

Appendix 5.b.6.2: Population estimates of levels of psychotropic prescribing following guideline implementation

Year	Total number of people with dementia ¹	% People prescribed psychotropic ²	% Reduction in prescribing from guideline ³	No. of people w/dementia prescribed a psychotropic
2 ⁴	65,531	0.19	0.4842	6,026
3 ⁵	68,216	0.19	0.4842	6,273
4 ⁶	70,527	0.19	0.4842	6,486
5 ⁷	72,838	0.19	0.4842	6,698

¹ From Appendix 5.b.6.1.

² Connolly et al. (2014) report that 19% of people with dementia in Ireland are prescribed a psychotropic.

³ Donegan et al. (2017) report a 48.42% reduction in levels of antipsychotic prescription in dementia from 2005 to 2015 following the implementation of national policy and strategies. It is anticipated that prescribing will fall by 48.42% in Ireland following year two of guideline implementation.

⁴ In year two, an estimated 6,026 people with dementia will be prescribed a psychotropic medication following guideline implementation ($65,531 \times 0.19 \times 0.482$).

⁵ In year three, an estimated 6,273 people will be prescribed psychotropic medication ($68,216 \times 0.19 \times 0.4842$).

⁶ In year four, an estimated 6,486 people will be prescribed psychotropic medication ($70,527 \times 0.19 \times 0.4842$).

⁷ In year five, an estimated 6,698 people will be prescribed psychotropic medication ($72,838 \times 0.19 \times 0.4842$).

6.2 Economic impact of guideline implementation

The number of people with dementia is rising rapidly, resulting in an increase in people with BPSD who may be prescribed psychotropic medications. Therefore, it is anticipated that the guideline will lead to cost avoidance rather than cost reduction as prescribing rates should fall by 48.42%, while prevalence of dementia is set to double (Donegan et al., 2017). To estimate the economic impact over a five-year horizon, total costs and total costs avoided are taken into account.

Implementation costs include national implementation officer, half-time admin support person, national trainers, on-line training, awareness activities and local trainers' time and expenses. From year two onwards assessment costs are incurred and from year three onwards audit and evaluation costs arise. Total costs therefore are estimated to be €379,427 in year one. These are expected to increase in subsequent years, to €2.4 million in year two, €1.5 million in year three, €1.1 million in year 4 and €1.2 million in year 5. Total discounted costs over five years are €6.6 million.

Reductions in the prescribing of psychotropic medications are expected from year two (over €5 million annually). It is expected that €22.7 million in costs will be avoided due to guideline implementation. The total potential net cost avoidance expected over the five-year horizon is €16.2 million (See Appendix 5.b.6.3).

Appendix 5.b.6.3: Total costs and costs avoided from guideline implementation over a five-year horizon (48.42% reduction in prescribing)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
National Implementation¹	339,791.72	299,791.72	137,511.72			777,095.15
Evaluation²	39,635.21		53,510.80			93,146.01
Audit³			71,234.54	16,761.07	71,234.54	159,230.16
Local Training⁴		64,504.93	193,514.78			258,019.70
Assessment⁵		2,029,578.10	1,049,844.24	1,085,410.53	1,120,976.82	5,285,809.69
Total Costs⁶	379,426.93	2,393,874.75	1,505,616.08	1,102,171.60	1,192,211.36	6,573,300.71
Cost Avoided⁷		5,377,780.89	5,598,090.40	5,787,740.73	5,977,391.06	22,741,003.09
Net Cost Avoided⁸	-379,426.93	2,983,906.14	4,092,474.32	4,685,569.13	4,785,179.70	16,167,702.38

¹ The national implementation officer and the 0.5FTE admin support will be in post for three years; the two national trainers for two years; the online learning development; the GP/community pharmacist dissemination and awareness activities (see Appendix 5.b.1.1).

² Evaluation will include two baseline projects, and two end of implementation projects (see Appendix 5.b.2.1).

³ Auditing of hospitals and public residential units, beginning in year three, once all appropriate staff is trained (see Appendix 5.b.3.1).

⁴ The cost of training in year one includes 25% of local trainer costs (for train-the-trainer sessions). Training in year two includes 75% of local trainer costs (see Appendix 5.b.3.1).

⁵ In year one, there are no assessment costs as appropriate HSE staff have not all received training. Assessment costs in year two are estimated at €2.2 million (see Appendix 5.b.2.5). To estimate assessment costs post guideline implementation in year three onwards we assume 50% of those who would have been prescribed psychotropic medication in the absence of the guideline require annual assessment (see Appendix 5.b.6.2).

⁶ The cost of training, national staffing, auditing and assessment are added together to estimate total costs.

⁷ There is no cost avoidance in year one as the reduction in levels of psychotropic prescribing has not commenced. In year two, an estimated €5.4 million of dementia-related costs will be avoided (see Appendix 5.b.5.2). In years three, to five it is estimated that less people will be prescribed psychotropic medication (see Appendix 5.b.6.2). The annual cost avoidance (€892.39, from Table 5.1) is applied to those who it is expected will not be prescribed psychotropic medication in light of the guideline (see Appendix 5.b.6.2).

⁸ The potential cost avoided is calculated by subtracting the total costs from the costs avoided.

6.3 Sensitivity analysis

A sensitivity analysis is conducted to determine if guideline implementation still results in cost avoidance for the HSE when assumptions in the model are varied. Previously, a 48.42% reduction in prescribing rates was anticipated (Donegan et al., 2017). Here, more conservative reductions of 20% and 30% are estimated.

When a 30% reduction in prescribing of psychotropic medication is assumed, total costs are estimated at €6.6 million and costs avoided are estimated at €14.1 million; this results in a total net cost avoidance of €7.5 million over five years (See Appendix 5.b.6.4).

When a 20% reduction in prescribing of psychotropic medication is assumed, total costs are estimated at €6.6 million and costs avoided are estimated at €9.4 million; this results in a total net cost avoidance of €2.8 million over five years (See Appendix 5.b.6.5).

Appendix 5.b.6.4: Sensitivity analysis of total cost savings from guideline implementation (30% reduction in prescribing)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
National Implementation¹	339,791.72	299,791.72	137,511.72			777,095.15
Evaluation²	39,635.21		53,510.80			93,146.01
Audit³			71,234.54	16,761.07	71,234.54	159,230.16
Local Training⁴		64,504.93	193,514.78			258,019.70
Assessment⁵		2,029,578.10	1,049,844.24	1,085,410.53	1,120,976.82	5,285,809.69
Total Costs	379,426.93	2,393,874.75	1,505,616.08	1,102,171.60	1,192,211.36	6,573,300.71
Cost Avoided⁶		3,333,335.26	3,469,890.75	3,587,442.60	3,704,994.46	14,095,663.07
Net Cost Avoided⁷	-379,426.93	939,460.51	1,964,274.67	2,485,271.00	2,512,783.10	7,522,362.36

^{1,2,3,4} As per base-case Appendix 5.b.6.3.

⁵ The total cost is calculated by adding together the cost of training, national staffing, audit and assessment.

⁶ With less people with dementia will be prescribed psychotropic medications prescribed cost avoided per person is €892.39 is applied.

⁷ The potential cost saving is calculated by subtracting total costs from costs avoided.

Appendix 5.b.6.5: Sensitivity analysis of total cost savings from guideline implementation (20% reduction in prescribing)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
National Implementation¹	339,791.72	299,791.72	137,511.72			777,095.15
Evaluation²	39,635.21		53,510.80			93,146.01
Audit³			71,234.54	16,761.07	71,234.54	159,230.16
Local Training⁴		64,504.93	193,514.78			258,019.70
Assessment⁵		2,029,578.10	1,049,844.24	1,085,410.53	1,120,976.82	5,285,809.69
Total Costs	379,426.93	2,393,874.75	1,505,616.08	1,102,171.60	1,192,211.36	6,573,300.71
Cost Avoided⁶		2,222,223.51	2,313,260.50	2,391,628.40	2,469,996.31	9,397,108.72
Net Cost Avoided⁷	-379,426.93	-171,651.24	807,644.42	1,289,456.80	1,277,784.95	2,823,808.01

^{1,2,3,4} As per base-case Appendix 5.b.6.3.

⁵ The total cost is calculated by adding together the cost of training, national staffing, audit and assessment.

⁶ With less people with dementia will be prescribed psychotropic medications prescribed cost avoided per person is €892.39 is applied.

⁷ The potential cost saving is calculated by subtracting total costs from costs avoided.

Conclusion

The direct implementation cost over a 5-year cycle (additional staff for a national implementation team; dissemination/awareness raising; online training programme; audit and evaluation) is €0.87million. This is an actual cost, necessary for successful implementation. The ‘provided within usual service’ cost for the extra time required for new practice (including local trainer training-up time, audit and assessment and discussion) over a 5-year cycle is €5.7 million – it is anticipated this cost will be borne by individual services. This does not include the local training time – it was not possible to quantify the time involved for the local trainer or the attendees, as this would vary significantly within and between settings. In addition, many doctors, nurses and pharmacists may undertake the online training rather than face-to-face training. The Guideline Development Group acknowledges that there is an opportunity cost in all training, but equally many disciplines have fixed annual Continuous Professional Development education requirements, and thus may select this guideline as a preferred topic.

As detailed in Section 3.1, there is good evidence that prescribing rates for psychotropic medications can be reduced. If we match the UK reduction in the prescribing of antipsychotic medications of 48.42% following implementation of policy there (benefit expected from year 2 of our implementation), we estimate a cost avoidance of €22.7 over 5 years from reduced medication costs and from reduced health and social care costs related to psychotropic medication adverse events. More conservative 30% and 20% reductions in prescribing yield a cost avoidance of €14.1m and €9.4m, respectively, over 5 years. The net cost avoidance is thus between €2.8m and €16.1m. In reality, this cost avoidance may be lower, due to the exclusion of the unquantifiable costs of local education to support compliance with the recommendations, but this is offset by our assumption that no services were currently following “best practice”, whereas it is likely to be part of usual care in some services.

With the caveat that there was scant evidence to guide the modelling of cost avoidance, a reduction in healthcare costs is anticipated following more appropriate prescribing of psychotropic medications, linked to the expected associated reduced prescribing of these medications. The cost of providing non-pharmacological interventions was not within the scope of this BIA, but is likely to be significant, and this should be costed in the future.

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Appendix 6: Implementation plan

Introduction

The following implementation plan and logic model is designed to provide a framework to guide the actions required to promote and support effective implementation locally and nationally of the National Clinical Guideline for Appropriate Prescribing of Psychotropic Medication for People with Dementia in Ireland. There is good evidence that the rates of prescribing of psychotropic medications can be reduced by multifactorial interventions (Section 2.3.1). The national implementation of this National Clinical Guideline will ultimately improve health outcomes for people with dementia, reduce variation in practice and improve the quality of clinical decisions that healthcare staff have to make. This guideline will promote the involvement of people with dementia in this decision making, using an appropriate decision support process.

The Irish National Audit of Dementia, which audited dementia-related care in acute hospitals in 2013, found that 25% of people with dementia in acute hospitals received new or increased antipsychotic medication during their hospitalisation. The reason for this medication was not always documented, and where it was, the indication was not always in line with the known evidence for the medication. Although similar prescribing data from the community or residential care is not available for Ireland, international evidence shows that psychotropic medications are also used inappropriately in these settings, and anecdotally this is also the case in Ireland.

This National Clinical Guideline aims to guide HCPs in decision making around prescribing psychotropic medications to people with dementia, avoiding prescribing for an inappropriate indication, but also supporting appropriate prescribing, where there is a valid indication and a good process around prescribing. **To support this National Clinical Guideline, the NDO has also developed a guidance document for healthcare professionals “Non-cognitive Symptoms in Dementia (NCS): Guidance on Non-pharmacological interventions for Healthcare and Social Care Practitioners”, which will be available with the National Clinical Guideline and will be referenced in all education and training related to the National Clinical Guideline (<https://dementiapathways.ie/publications>).** The implementation of this guidance document is outside the scope of this National Clinical Guideline, and heavily relies on adequate supports for people with dementia who have non-cognitive symptoms.

The core objectives of this implementation plan are to:

- raise awareness of the risks of psychotropic medications in people with dementia and raise awareness of the National Clinical Guideline as a resource to guide clinical decision making, among doctors, nurses, pharmacists, health and social care professionals, people with dementia and their families, and other key stakeholders
- provide training to relevant doctors, nurses and pharmacists across all relevant settings on the content of the National Clinical Guideline, using a “train the trainer” process
- support regional and local implementation teams in implementing the guideline in their setting
- provide training to relevant staff (within and outside the HSE) on the content and performance of the audit to assess compliance with the doctors, nurses, pharmacists and health and social care professionals.

Corporate responsibilities

The National Clinical Guideline should be reviewed by senior management (or equivalent legal entities) in acute hospitals, residential care units (including those in mental health and disability services), acute mental health units, and in community healthcare organisations, to plan the implementation of the recommendations, as follows.

Acute hospitals:

Within **public and voluntary** acute and orthopaedic hospitals who admit people with dementia (n=38), the hospital *Chief Executive Officer (CEO)*, supported by the *Clinical Director*, has corporate responsibility for supporting implementation of the guideline within the hospital and for ensuring that all relevant staff are appropriately trained to implement the guideline. This includes out-patient clinics attached to the acute hospital. Each hospital should set up a local implementation team (LIT) with clear reporting structures, actions and standing agenda items to ensure successful implementation. Records of staff training in the guideline content will be required to be maintained, and annual self-audit is expected to inform quality improvement initiatives.

The LIT should identify the staff that require general National Clinical Guideline awareness training and full National Clinical Guideline content training, should assess local enablers and barriers, identify within-hospital trainers (to receive train-the-trainer education), and within-hospital champions, and should pay particular attention to reaching surgical and orthopaedic services and ED staff, as well as medical services. Education and training on the National Clinical Guideline in acute hospitals should include hospital pharmacists, who will play an important role in promoting the National Clinical Guideline and supporting appropriate psychotropic prescribing by doctors. It is envisioned that compliance with the National Clinical Guideline will be monitored by self-audit in all acute hospitals at years 3, 4 and 5 of the implementation programme. The relevant hospital group management team, including the group lead for quality, shares corporate responsibility with the individual hospital for the guideline implementation, and should support individual hospitals through shared learning and promotion events, common documentation policies, and annual group-level review of individual hospital audit results to inform quality improvement.

Private acute hospitals fall outside the governance of the HSE, and compliance with this guideline is therefore voluntary in private hospitals. These will be offered implementation support (access to the suite of implementation resources, including online education and train-the-trainer education) by the National Implementation Team, as per HSE-funded hospitals. Geriatricians and psychiatrists of old age who provide consultation services or have part-time working commitments in private hospitals will be asked to act as champions for the National Clinical Guideline in the private hospital.

Community services:

Within the current structure of nine Community Healthcare Organisations (CHOs), the CHO *Chief Officer* has overall corporate responsibility for supporting the implementation of the National Clinical Guideline within the region and is expected to work with the local management team, particularly the heads of service for primary care, mental health, and social care/disabilities, to facilitate local implementation.

Within **disability residential services**, there are currently 1250 designated units, with a varying number of residents per unit (some are 2-3 people sharing a house in the community, others are much larger congregated settings). These residents are of varying ages, and only a small proportion overall have dementia, which makes efficient implementation challenging. Many of these residential services are provided by voluntary agencies with HSE funding.

Disability residential services are required to comply with HIQA's National Standards for Residential Services for Children and Adults with Disabilities (2013). This standard requires the development of local policies for "restrictive practices" and "provision of behavioural support", with work in progress at national level towards providing guiding principles for this local policy development in 2019. The National Clinical Guideline can usefully inform the development of these guiding principles and local policies and it is envisioned that self-auditing of compliance with the HIQA standard could potentially incorporate key audit metrics for the National Clinical Guideline. The Guideline Development Group have made contact with the Quality Improvement Team for Disability Services in this regard, and the National Implementation Team can continue this linkage in due course.

Mental health services relevant to this National Clinical Guideline include acute mental health units, residential mental health units, and community old age mental health teams. Within general acute mental health units, a very small number of in-patients would be expected to have dementia, unless the unit incorporates an older age unit. Some residential units have a dedicated dementia unit, but overall people with dementia would be a small minority of residents.

The HSE Mental Health Management Team has corporate responsibility for supporting the implementation of the National Clinical Guideline within mental health services nationally, and for ensuring that all relevant staff are appropriately trained to implement the guideline. Each CHO's head of service for mental health should set up a local implementation team (LIT) with clear reporting structures, actions and standing agenda items to ensure successful implementation. Records of relevant staff training in the National Clinical Guideline content will be required to be maintained, and annual self-audit in selected services (e.g. old age mental health services, specific old age acute units, services providing consultation to intellectual disability services) is expected to inform quality improvement initiatives. The LIT should identify the staff that require general guideline awareness training versus full National Clinical Guideline content training, should assess local enablers and barriers, and should identify within-service trainers and champions. It is envisioned that compliance with the National Clinical Guideline will be monitored by self-audit in old-age specific acute units and dementia-specific residential units at year 3 and year 5 of the implementation programme.

Within HSE-provided **residential settings for older people** (community hospitals and community nursing units; n=130), the units' General Manager or Director of Nursing, as relevant (depending on the local governance structure of the unit), has corporate responsibility for supporting the implementation of the National Clinical Guideline within the residential unit and for ensuring that all relevant staff are appropriately trained to implement the guideline.

Each CHO residential services manager should set up a local implementation team (LIT) with clear reporting structures, actions and standing agenda items to ensure successful implementation. Records of relevant staff training in the National Clinical Guideline content will be required to be maintained, with annual self-audit expected to inform quality improvement initiatives. The LIT should identify the residential staff that require general guideline awareness training versus full National Clinical Guideline content training, should assess local enablers and barriers, and should identify within-service trainers and champions. This education and training needs to include pharmacists associated with the unit. It is envisioned that compliance with the National Clinical Guideline will be monitored by self-audit at year 3 and year 5 of the implementation programme (ideally with baseline practice data from a proposed baseline evaluation project for comparison).

80% of residential services are operated by **private providers** and these have no obligation to train staff in this guideline, although some may do so in the interest of good resident care. Private nursing homes are required to comply with statutory regulations (Health Act 2007 (Care and Welfare of Residents in Designated Centres for Older People) Regulations, 2013; Assisted Decision-Making (Capacity) Act, 2015), and non-statutory regulations (National Standards for Residential Services for Children and Adults with Disabilities, 2013; National Standards for Residential Care Settings for Older People in Ireland, 2015). Evidence of education and training in the National Clinical Guideline content, and evidence of aiming to achieve compliance same (e.g. the performance of self-audit and documentation of resulting quality improvement initiatives) would be supportive of compliance with these relevant regulations, as assessed during HIQA inspections.

Primary Care Teams (PCTs), where they exist and are functional, should be aware of the National Clinical Guideline, and certain staff, like Public Health Nurses, and Dementia Care Coordinators, should receive education and training in the content of the National Clinical Guideline. GPs working within PCTs should also receive education and training on the National Clinical Guideline content. The head of service for primary care in each CHO should set up a local implementation team to consider the training needs locally and nominate discipline-appropriate local trainers to receive train-the-trainer education (or a single team may pragmatically cover both primary and residential care).

General practice:

GPs see people with dementia in two main settings - people with dementia living in residential units (sometimes working in the capacity of a medical officer in that unit) and people with dementia living in the community who attend the GP's practice.

GP training and education falls outside the governance of the HSE, and the HSE has no ready means to measure GP compliance with the National Clinical Guideline. In the external consultation with national stakeholders, it was raised by several groups that the GP contract should be linked to compliance with standards relating to residential care, including this National Clinical Guideline.

The National Implementation Team will work with the ICGP to develop an online education resource that is specific to GPs (pending funding for this resource). An infographic summarising the context and content of the National Clinical Guideline will be emailed to all GPs, along with a guideline summary, and a link to the full guideline. This will be supplemented by a posted copy of the brief summary (pending funding). The benefit of the National Clinical Guideline should be promoted at national GP conferences, and in GP journals (e.g. The Forum). GPs who work within a Primary Care Team should receive education and training on the National Clinical Guideline content alongside other members of the PCT. The selection of psychotropic prescribing as the GP's annual audit (for professional competence purposes) should be encouraged at all opportunities.

Community pharmacists:

Community pharmacists can play an important role in supporting appropriate prescribing and review of psychotropic medication for people with dementia and non-cognitive symptoms, whether the person with dementia is living in the community, or in residential care. The CHO local implementation teams should consider how best to reach their local community pharmacists, depending on local contexts. The National Implementation Team will work with relevant national groups to target community pharmacists (e.g. the Pharmaceutical Society of Ireland, the Irish Institute of Pharmacy).

Individual doctor, nurse, and health and social care professional responsibilities

Apart from the corporate responsibilities, above, to ensure education and training is provided in the National Clinical Guideline content, and to monitor compliance with the National Clinical Guideline in practice, individual healthcare professionals also have responsibilities. Standard 2.4 from the National Standards for Safer Better Healthcare requires that “An identified healthcare professional has overall responsibility and accountability for a service user’s care during an episode of care.” This emphasises the personal responsibilities of doctors and nurses for a person’s care, in any setting.

All **doctor and nurses** with responsibility for the care of people with dementia are required to:

- Exercise due regard for these recommendations, while still exercising clinical and professional autonomy in line with their own professional standards.
- Maintain their competency for the assessment and treatment of people with dementia, including non-cognitive symptoms.

All **pharmacists** who are linked to services that provide care to people with dementia are required to:

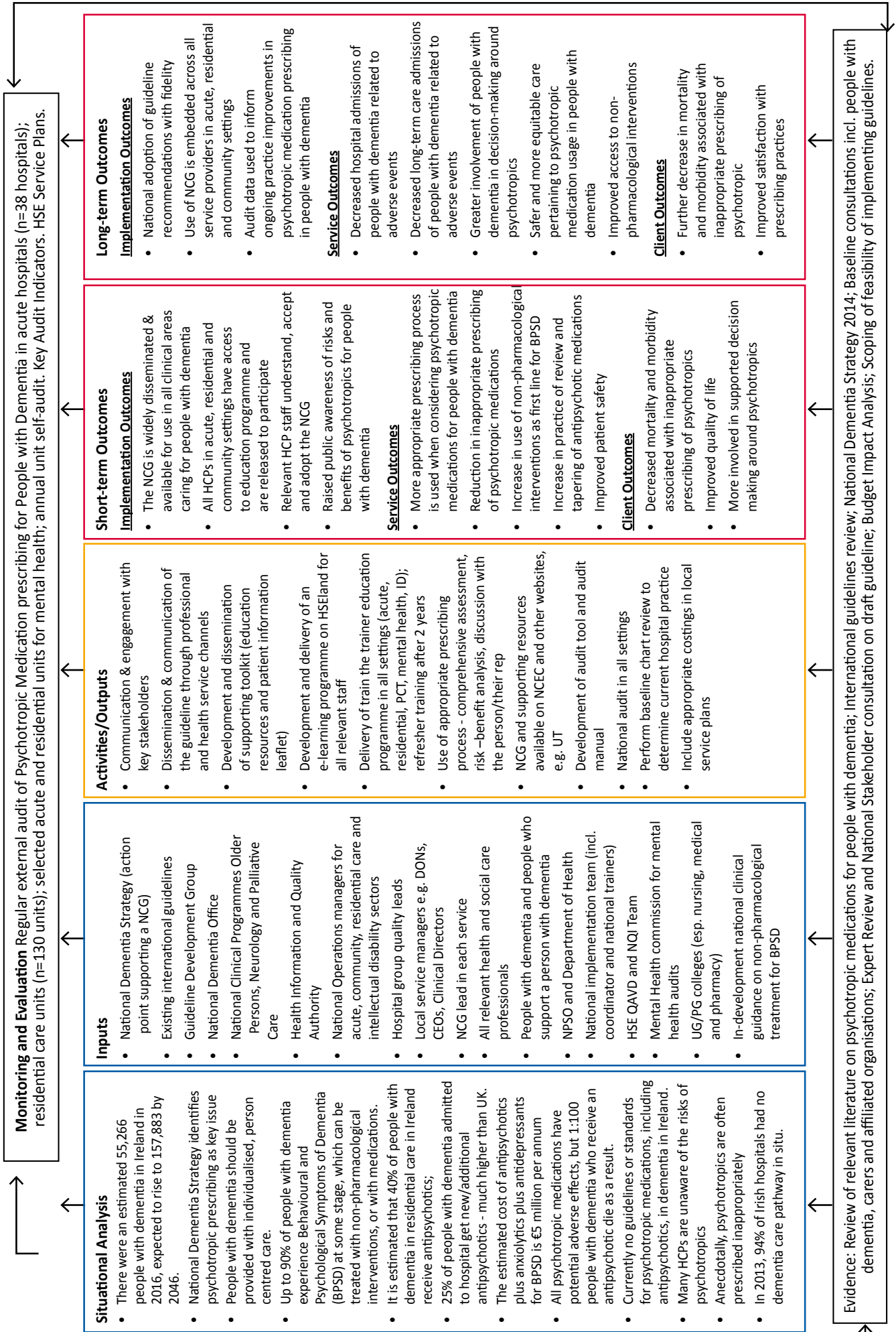
- Exercise due regard for these recommendations, while still exercising clinical and professional autonomy in line with their own professional standards.

All other **health and social care professionals** who care for people with dementia are required to be aware of the existence of this guideline and to act in a manner that supports practice in line with the guideline.

Implementation of overall guideline

While the implementation plan is specific to the individual recommendations in the guideline, some actions will assist with guideline implementation as a whole. These include establishing an implementation team; developing a dissemination and communication plan and developing specific implementation tools and resources. The following logic model and plan details the actions required to facilitate implementation of the guideline.

Logic Model for National Clinical Guideline-Appropriate Prescribing of Psychotropic Medication in People with Dementia



Implementation plan (key recommendations (1, 2, 3, 10, 11, 19) are presented in bold text)

Guideline recommendation or number(s)	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
All Recommendations	<p>Barriers:</p> <ul style="list-style-type: none"> Poor HCP knowledge of appropriate indications for psychotropics in dementia HCP not aware of risks of psychotropics in dementia HCP not aware of alternatives to psychotropics in dementia Insufficient knowledge of Person Centred Dementia care HCP resistance to change Insufficient dementia specialist staff in all settings Insufficient non-pharmacological activities in community and residential care PwD/ families not aware of risk of psychotropics in dementia <p>Enablers:</p> <ul style="list-style-type: none"> National Dementia Strategy Implementation Action Point 3.6 National Dementia Education programmes Implementation Team Current focus on patient advocacy, e.g. national advocacy service, SAGE Alzheimer Society of Ireland advocacy and promotion Media coverage Existing Dementia Quality Improvement Teams 	<p>Each unit to put in place NCG leads (each acute hospital, residential care unit, etc)</p> <p>Develop national network of NCG champions</p> <p>Roll-out of dissemination and communication plan</p> <p>Develop resources to support delivery of general awareness sessions at local level (slides, handouts etc)</p> <p>Develop and disseminate recipient-specific infographics summarising key NCG points and signposting sources of additional information- e.g. to GPs (by post and mailshot), community pharmacists, residential care units, etc</p> <p>Delivery of general training on non-cognitive symptoms/responsive behaviours (plus limited role of psychotropics, presence of NCG and audit tool), to clinical staff² (e.g. 15 min awareness session with handout)</p>	<p>Local service managers¹</p> <p>National Implementation Team / Local Implementation teams</p> <p>National Implementation Team/ HSE Comms</p> <p>National Implementation Team</p> <p>Local Implementation Teams</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>	<p>Outcome: Local NCG implementation teams promoting and implementing the NCG</p> <p>Verification: local management to confirm with Implementation Team</p> <p>Outcome: More promotion and support for NCG implementation</p> <p>Verification: Champion network database</p> <p>Outcome: Improved awareness and knowledge of NCG</p> <p>Verification: Records of dissemination activities</p> <p>Outcome: Availability of a suite of dissemination/ awareness raising resources, to support implementation</p> <p>Verification: Resources developed, records of dissemination of resources</p> <p>Outcome: All clinical staff who treat/care for people with dementia are aware of alternatives to psychotropic medications, the NCG and audit tool</p> <p>Verification: staff training records; hits/downloads recorded.</p>		

Guideline recommendation or number(s)	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
	<ul style="list-style-type: none"> Dementia Nurse Specialists / Candidate ANPs CHO Dementia Strategy Groups National Nursing Quality Care Metrics programme HIQA Dementia Thematic Inspections Patient Liaison Officers 	Liaison with ICGP for targeted GP education (e.g. national conferences, inclusion in GP CME curriculum, GP-read journals); linking with residential care special interest group, etc	National Implementation Team	X			Outcome: More GPs are familiar with NCG content and audit tool/ toolkit Verification: Records of dissemination and training activities
		Dissemination through existing education programmes from the NDO	National Implementation Team/ NDO	X			Outcome: All relevant NDO education and training programmes refer to and promote the NCG Verification: Modified NDO programme content; Records of dissemination and training activities
		Development of e-learning module on the NCG content	National Implementation Team / HSEland / ICGP	X			Outcome: Improved access to education on content of guideline Verification: HSEland report; ICGP module available
		Develop train-the-trainer programme	National Implementation Team	X			Outcome: Improved access to face-to-face training on guideline Verification: programme developed
		Delivery of education/training on appropriate prescribing in dementia for relevant staff ³ in each setting	National Trainers / Local Implementation Teams		X		Outcome: Relevant HCP are familiar with guideline content and audit tool Verification: staff training records.
		Submit Business Case for dementia specialist staff in acute hospitals	National Dementia Office	X	X	X	Outcome: Increased dementia specialist staff in acute hospitals Verification: Business case submitted; Staff in place
		Submit Business Case for increased non-pharmacological activities in community settings ⁴	National Dementia Office / National Clinical Lead for NCP Older Persons/ Head of Operations Older Persons			X	Outcome: All residential settings have access to non-pharmacological interventions Verification: Staff in place; activities log
		Include psychotropic medication prescribing for people with dementia in service risk register	Service managers		X		Outcome: greater focus by management on risk of psychotropic medications for people with dementia Verification: risk registers

Guideline recommendation or number(s)	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
		Liaise with relevant IT system managers to explore how guideline monitoring can be incorporated into existing systems, e.g. EHR, Mental Health IT system	National Implementation Team		X		Outcome: better data and monitoring processes Verification: inclusion in ICT systems
		Liaise with NCP Older Persons, Neurology, Acute Care, Mental Health and Palliative Care to identify synergies that will support implementation	National Implementation Team	X			Outcome: linkage to other relevant national initiatives Verification: reference to guideline in NCP framework/model of care related documents
		Liaise with relevant audit bodies to agree national audit processes in each setting	National Implementation Team	X			Outcome: Improved access to current data Verification: Audit plan
		Develop, pilot and disseminate audit tools	National Implementation Team	X			Outcome: Services are supported to complete self-audits Verification: Audit tool downloads and feedback from service managers
1. Prior to considering psychotropic medication in a person with dementia, a comprehensive assessment should be performed, by an appropriately trained healthcare professional and should be done, where appropriate, in conjunction with their family/advocate.	Barriers: <ul style="list-style-type: none"> HCP time required for comprehensive assessment (CA) and documentation versus usual care Lack of access to appropriately qualified HCPs in Community care Enablers: <ul style="list-style-type: none"> Comprehensive assessment skill already a core HCP competency 	Recommendation 1 is audited in all relevant settings	Relevant audit groups ⁵			X	Outcome: Compliance with key audit item - <i>Prior to the prescribing of any psychotropic medication to a person with dementia, a comprehensive assessment has been performed by a suitably trained healthcare professional</i> Verification: Annual self-audit; other audits as per Appendix 8
		Review impact of CA on staff time and capacity and use results to inform local service planning	Local service managers		X		Outcome: Staff time and capacity is monitored and used to inform service planning Verification: Feedback from service managers
		Advocate for more specialist posts in dementia care in all settings	National Dementia Office / Alzheimer Society of Ireland / Local service managers		X		Outcome: Enhanced resources to support dementia assessments and care Verification: Staff in place

Guideline recommendation or number(s)	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
<p>2 Non-pharmacological interventions should be used initially to treat behavioural and psychological symptoms of dementia (BPSD), unless there is severe distress, or an identifiable risk of harm to the person and/or others.</p>	<p>Barriers:</p> <ul style="list-style-type: none"> Poor access to non-pharmacological interventions (NPI) in most settings; Pressure from other HCP or family to prescribe <p>Enablers:</p> <ul style="list-style-type: none"> HCP familiar with NPI; Increased focus on NPI within National Dementia Strategy implementation 	<p>Contract team to complete guidance document on non-pharmacological interventions developed and available in all settings; HCP training includes reference to this document</p>	National Dementia Office (NDO)	X			<p>Outcome: Guidance document available online (UT website) and relevant HCP aware</p> <p>Verification: staff training records; hits/downloads recorded</p>
<p>3-6, 8, 9. Prescribe antipsychotics with caution and only in severe BPSD, where aggression, agitation or psychosis and identifiable risk of harm or severe distress.</p> <p>Atypicals should be preferentially used. Treatment should be at lowest possible dose and titrated slowly, to the minimum effective dose.</p>	<p>Barriers:</p> <ul style="list-style-type: none"> Poor HCP knowledge of appropriate indications for AP in dementia Pressure from other HCP or family to prescribe <p>Enablers:</p> <p>“Start low, go slow” is a common theme in prescribing for older people</p>	<p>Recommendation 2 is audited in all settings</p> <p>See also “all recommendations”</p>	Relevant audit groups			X	<p>Outcome: Compliance with key audit item - Prior to the prescribing of any psychotropic medication to a person with dementia, non-pharmacological interventions have been tried initially (unless there is an identifiable risk of harm to the person with dementia and/or others or severe distress in the person with dementia).</p> <p>Verification: Annual self-audit; other audits as per Appendix 8</p>
<p>3-6, 8, 9. Prescribe antipsychotics with caution and only in severe BPSD, where aggression, agitation or psychosis and identifiable risk of harm or severe distress.</p> <p>Atypicals should be preferentially used. Treatment should be at lowest possible dose and titrated slowly, to the minimum effective dose.</p>	<p>Barriers:</p> <ul style="list-style-type: none"> Poor HCP knowledge of appropriate indications for AP in dementia Pressure from other HCP or family to prescribe <p>Enablers:</p> <p>“Start low, go slow” is a common theme in prescribing for older people</p>	<p>Recommendation 3 is audited in all settings</p> <p>See also “all recommendations”</p>	Relevant audit groups			X	<p>Outcome: Compliance with key audit item - Antipsychotic medication is only prescribed 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 with dementia</p> <p>Verification: Annual self-audit; other audits as per Appendix 8; PCRS prescribing data pre-and post-implementation</p>

Guideline recommendation or number(s)	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
7. A full discussion with the person and/or their family/advocate about the benefits and risks, including the increased risk of stroke, transient ischemic attack and mortality, should occur before antipsychotic medication is commenced.	<p>Barriers:</p> <ul style="list-style-type: none"> HCP time required for discussion and documentation Logistical difficulties of arranging meeting with family members Changing legal status re. decision making in Ireland <p>Enablers:</p> <ul style="list-style-type: none"> Assisted Decision making Act enactment Current focus on advocacy 	<p>Education/training on the need for discussion and documentation provided to relevant staff in each setting as part of national education programme (as above)</p> <p>Develop information leaflet on risk of psychotropic medications for PWD and families</p> <p>Disseminate information leaflet, e.g. UT and Alzheimer Society of Ireland websites, send to local services</p> <p>ADMA enactment</p>	National Training Officers / Local Implementation Teams	X		<p>Outcome: Relevant HCP have received training</p> <p>Verification: staff training records</p> <p>Outcome: PwD and families aware of risks of psychotropic meds</p> <p>Verification: hits/downloads recorded</p>	
10,11,12. If positive response to antipsychotic, decision making about possible tapering within 3 months, with discussion. If no clear clinical benefit, antipsychotic tapered and stopped; with discussion. Asses for re-emergence regularly during tapering, and after discontinuation.	<p>Barriers:</p> <ul style="list-style-type: none"> HCP time required for review and documentation Transitions of care from specialist to GP care Transitions across settings <p>Enablers:</p> <ul style="list-style-type: none"> Existing requirement for "Three monthly medication reviews" by HIQA Clear documentation of follow-up plans 	<p>Education/training on tapering/ need for review provided to relevant HCP in each setting as part of national education programme (as above)</p> <p>Recommendation 10 is audited in all settings</p>	Decision Support Unit National Training Officers / Local Implementation Teams	X	X	<p>Outcome: Supported decision making is enacted</p> <p>Verification: via audit.</p> <p>Outcome: Relevant HCPs have enhanced knowledge</p> <p>Verification: staff training records</p> <p>Outcome: Compliance with key audit item - There is documented evidence of review of newly prescribed antipsychotic medication for effectiveness and side effects, within three months</p> <p>Verification: Annual self-audit; other audits as per section 8</p> <p>Outcome: Meeting with NCAGL and ONMSD and NIT reps.</p> <p>Verification: meeting minutes</p>	
13,14,15,16. AChEi and memantine indications.	Nil Specific	Liaise with National Clinical Lead for Older Persons and ONMSD to explore if current/future Transfer Tools (or other documents) could support communication of planned reviews between settings	National Implementation Team				

Guideline recommendation or number(s)	Implementation barriers/enablers/ gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
17. Consider psychological treatments in mild to moderate dementia and mild to moderate depression and/or anxiety. Antidepressants may be considered for severe comorbid depressive episodes, but NOT mild to moderate depressive symptoms in BPSD.	<p>Barriers:</p> <ul style="list-style-type: none"> Limited access to psychological treatments for PwD in most settings. <p>Enablers:</p> <ul style="list-style-type: none"> Enhanced funding for mental health services in 2019 health budget 	Liaise with National Mental Health Services to explore improving access to psychological treatments, including for depression/anxiety for PwD	National Implementation Team			X	<p>Outcome: Staff in place who are trained to treat a PwD.</p> <p>Verification: Staff in place; staff training records.</p>
18. Anticonvulsant medication indication.	Nil specific						
19. Benzodiazepines should be avoided for the treatment of BPSD, and usage strictly limited to the management of short term severe anxiety episodes.	<p>Enablers:</p> <ul style="list-style-type: none"> MMP guidance on the appropriate prescribing of benzodiazepines and z-drugs (BZRA) in the treatment of anxiety and insomnia. 	Recommendation 19 is audited in all settings	Relevant audit groups			X	<p>Outcome: Compliance with key audit item - Benzodiazepines are not prescribed for treatment of BPSD.</p> <p>Verification: Annual self-audit; other audits as per section 8</p>
20,21. A personalised sleep management regimen can be considered for sleep disorders in a person with dementia. Melatonin should NOT be used.	<p>Enablers:</p> <ul style="list-style-type: none"> MMP guidance on the appropriate prescribing of benzodiazepines and z-drugs (BZRA) in the treatment of anxiety and insomnia. Use of non-pharmacological interventions 	Nil specific					

¹ Local service managers:

Acute hospitals/out-patients: hospital group CEO, working with individual hospital CEOs

Mental health services: acute, residential and linked community services: CHO Head of Service for mental health

Non-mental health residential care units (including ID): CHO residential care manager, working with residential facility's CEO (occasionally no CEO, in which case DON is responsible)

Community based memory services: CHO Chief Officer

Primary care services: CHO Chief Officer, working with CHO Head of Service for Primary Care

² Clinical staff: All clinical staff working in services who treat or care for adults with dementia. Includes nurses, doctors, health and social care professionals, porters, healthcare assistants and any other staff who provide a "specialising" service.

³ Relevant staff: All nurses, doctors and pharmacists working in services who treat adults with dementia.

⁴ Business case for non-pharmacological interventions (not included in Budget Impact Analysis for this National Clinical Guideline, as non-pharmacological interventions were not in scope).

⁵ Relevant auditing groups: (responsible person listed, noting that audit data will be collected by local champions, local audit staff, NCHDs, etc.)

Acute hospitals/out-patients: Hospital group and individual hospital CEO; working with quality and safety officers

Acute and residential mental health services: CHO Head of Service for mental health

Non-mental health residential care units: CHO Head of Service for social care and disability; working with residential services manager

Community based memory services: CHO Chief Officer

Primary care services: CHO Head of Service for primary care

The following three tables summarise how the above actions will be incorporated into the implementation of the guideline:

Appendix 6.1: Implementation governance

National level:

National governance will be provided by the National Dementia Office, working in partnership with the Office of the National Director Community Operations for most settings, and the Office of the National Director Acute Operations for acute hospital settings (in-patients and out-patients).

National implementation team:

It is proposed that this team includes an Implementation Co-ordinator; representatives from Office of National Director Acute Operations, National Director Community Operations (to cover Mental Health, Primary Care, and Disability Services), QAVD, National Quality Improvement Team; Service Users; National Dementia Office; College of Psychiatry of Ireland; Irish College of GPs; Office of Chief Nursing Officer (Department of Health); ONMSD; National Metrics Lead; National HSE Comms.

New national posts will be required to support implementation:

- Implementation Coordinator – Full-time for 3 years initially
- National Trainer - Two full-time posts for 2 years
- Administrative Support – Part-time post for three years

Local level:

Local governance will be provided by the relevant local management structures (including Hospital Groups and Hospital CEOs; CHO Chief Officers, residential care managers, CHO heads of service for primary care, mental health and social care/disability), as delineated in more detail per setting in Table 1, footnote 1.

The following implementation teams will be established for a period of 3 years initially:

Local implementation teams:

Acute hospitals/out-patients: Individual hospital implementation teams – these will be the Dementia/Delirium Quality Improvement Group, where they exist; in other hospitals suggest representation from hospital management board, nursing management, Clinical Director, Quality and Safety, Liaison Psychiatry, Gerontology /Older Person Services, HSCP (including Psychology), Pharmacy, Patient Advocacy Group, Carers Group, Education/Training Body.

Other settings: Advise development of implementation team to include Director of Nursing, Practice Development, Quality and Safety, physician and pharmacy rep, and relevant others as decided locally.

Suggested meeting schedule for local implementation teams: every two months in year 1; then quarterly in years 2 and 3.

Training: All team members will be trained in the content of the NCG; otherwise, they are expected to have the required skills for their role in the team (i.e. a background in training, operations, etc).

Appendix 6.2: Dissemination and communication plan:

Dissemination will be through multiple media and channels:

- Many relevant stakeholders are aware of the pending NCG from the GDG, whose role included knowledge transfer and exchange with their group/organisation.
- The NCG, Summary NCG, and patient information leaflet will be published on the NCEC website, the Dementia Pathways website (hosted by the NDO), and these documents as relevant will be linked to other relevant websites (e.g the Alzheimer Society of Ireland website, Carers Alliance, RCPI, etc).
- Local and national media will be used to publicise the NCG.
- The NDO have promoted the NCG, since its prioritisation in Oct 2018, at all relevant national and local meetings and will continue to do so at every opportunity.
- The NCG will be linked to the development of acute hospital dementia/delirium integrated care pathways and dementia quality improvement teams.
- The National Implementation Team will liaise with key stakeholders in the relevant settings to use appropriate dissemination methods including HSE email cascades, ICGP email lists, relevant Irish medical publications (The Forum, Irish Medical Times, etc).
- GP and community pharmacist dissemination will be targeted through specific key information disseminated via email and post.
- The NCG will be shared with Medicine and Health Colleges in the national universities, to inform undergraduate and postgraduate education of current and future HCPs.

In addition, the in-development national guidance document for non-pharmacological interventions for people with dementia will be launched by the NDO in 2019, and both documents will reference and link to each other.

The planned baseline audit in acute hospitals in 2019 (being performed as part of INAD-2, to establish current practice across all acute hospitals to inform the implementation of the NCG) will also serve to raise awareness of the NCG.

Future local self-audit, and potentially external audits, of compliance with the NCG once implemented, with feedback of the results, will serve to sustain awareness of the NCG.

Appendix 6.3: Implementation tools

Implementation tools:

- NCG and brief summary: NCEC and NDO (Dementia Pathways) and other relevant websites
- Patient information leaflet (see Appendix 7): NCEC, Alzheimer Society of Ireland, Understand Together websites
- Education and training resources: slides and handouts, tailored for each setting and for university use- to be developed by Implementation Team (subject to funding); e-learning tool to be developed and hosted on HSEland/ Irish College of GPs. Case studies may be developed to illustrate the requirement for the NCG
- Supporting algorithm for nurses, doctors and pharmacists (see Appendix 7)
- Supporting infographics: to be developed by Implementation Team (subject to funding) and available on NCEC and NDO and other relevant websites (see Appendix 7)
- Audit tools and audit user manuals for each setting- in development by the GDG.

Appendix 7: Supporting tools

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

- Clinical audit tool for acute hospital (<https://dementiopathways.ie/resources-for-practice/non-cognitive-symptoms-of-dementia>).
- Algorithm to support decision making for clinicians (<https://dementiopathways.ie/resources-for-practice/non-cognitive-symptoms-of-dementia>).
- Information guide for people with dementia and their families/carers (<https://dementiopathways.ie/resources-for-practice/non-cognitive-symptoms-of-dementia>).

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>

Appendix 8: Monitoring and audit

1 Monitoring

1.1 Monitoring the implementation process

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.

One focus of monitoring and evaluation will be the reach of the training and education programme, namely that the guideline is widely disseminated and available for use in all clinical areas caring for people with dementia, and that all doctors, nurses and pharmacists in acute, residential and community settings have access to the education programme and are released to participate (or complete the online education module). This will be achieved through the monitoring of training records and online learning by the Implementation Coordinator.

The monitoring of the face-to-face local training relies on local training records so the implementation coordinator will emphasise this to the local implementation teams. The monitoring of online learning is facilitated by the HSElanD module tracking capabilities wherein users have to log in to access the module. This allows monitoring of the total numbers who have engaged with the module, but also the disciplines, settings, and geographical regions that have most/least uptake. Together, this will allow for adaptation of the implementation process, with enhanced dissemination/engagement/promotion by champions as required.

Similarly, the reach of the public awareness campaign as to the risks and benefits of psychotropics for people with dementia will be relatively easily monitored through website “hits”, “likes” and downloads. It may be possible to gauge public knowledge and understanding through the Alzheimer Society of Ireland and the Understand Together website.

The other key implementation process outcome is that doctors, nurses and pharmacists understand, accept and adopt the NCG. This will be monitored through chart audit, from year 3-5 of the implementation programme, as described below.

1.2 Monitoring the outcome on service

The key service outcome for this guideline overall is that a more appropriate prescribing process is used 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. A key purpose of the guideline is to decrease variation (both within and between services and regions) and to guide care to an appropriate standard across the healthcare system. This outcome will be monitored through chart audit, from year 3-5 of the implementation programme, in most settings (see audit section below).

The possibility of comparing prescription rates of antipsychotic medication pre and post implementation will be explored with the Primary Care Reimbursement Scheme and hospital pharmacies (for example using rates of prescribing of antipsychotics in people aged 80+ (where schizophrenia and psychotic depression is rare, and rates of these mental health illnesses can be assumed to remain stable over time) as a proxy for overall prescribing practice. Thus, any reduction in rates of prescribing of antipsychotics in the 80+ population can be taken to strongly reflect reduced prescribing for non-cognitive symptoms of dementia.

1.3 Monitoring the outcome on patient-related outcomes

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 could be readily evaluated by reviewing the frequency of adverse events related to psychotropic medications causing admission, in a sample of hospital admissions from the pre- and post- implementation period. Of note, such adverse event-related admissions reflect psychotropic prescribing practice in all settings, not just the acute hospital. The National Implementation Team will liaise with researchers with special interest in adverse drug events to explore data collection through existing research programmes. In addition, user satisfaction with the decision-making process around psychotropic medication prescribing will be proposed for inclusion in the national patient experience survey, supplemented by targeted surveys in residential care. The funding of this evaluation is subject to service planning and estimates processes (see formal evaluation below).

Another linked outcome that is outside the scope of this implementation plan, but closely linked is improved access to non-pharmacological interventions for people with dementia and non-cognitive symptoms. The implementation team will explore ways to evaluate this.

2 Evaluation

2.1 Formal evaluation of the implementation programme

The Guideline Development Group strongly recommends that there is a formal evaluation of the implementation of this guideline, to guide future implementation of related guidelines, and other national quality improvement initiatives. Most of the data will be available from the within-implementation monitoring process (online education usage, training records across implementation sites, pre-and post-implementation data, where available). However, there are three additional components required to transform this multi-modal crude data into usable data in a brief report:

- i) A pre-implementation audit of a sample of HSE-provided residential care units to establish baseline practice. This data is not currently available, and would be invaluable to inform and support training, and also to demonstrate implementation success at the end of the implementation programme.
- ii) A user survey within residential care units (and/or acute hospitals if not possible through the national patient experience survey) pre- and post-implementation to capture the experience of the person with dementia and their family, as this is a key outcome of successful implementation of the guideline and will not be captured by chart audit
- iii) Collation and presentation of key implementation data in an implementation report.

These evaluation projects will be separately tendered to academic groups nationally, pending a budget for this being available (see Appendix 5: Budget Impact Analysis). Successful groups would work closely with the National Implementation Coordinator and the National Dementia Office. Out-sourcing the pre-implementation data collection and report would allow the National Implementation Coordinator to focus on implementation, not data collection.

3 Audit plan

There is a need for two levels of clinical audit to maximise the success of implementation of the guideline- local self-audit, and national monitoring audit.

3.1 Local self-audit

It is important that the implementation of the guideline is audited to ensure that this guideline positively impacts on the care of a person with dementia. It is envisioned that local services will self-audit to support local implementation – feedback of local results to local clinicians and management can support culture change by demonstrating a need for improved practice, or demonstrating good practice, and/or can support local business cases for enhanced resources to support quality improvement.

Thus, it is recommended that local services ideally perform a “baseline” practice review early on in the implementation programme, and a follow-up audit once local staff have received training and practice change is expected to have embedded (e.g. year 3). Depending on the results, it is recommended that the audit is repeated annually to year 5 of implementation.

The audit tool developed by the Guideline Development Group is suitable for use as a self-audit tool, and comes with a detailed user manual which includes practical tips on selecting a random sample of charts, and explicit instructions on how to score each item. This is being piloted currently in residential care and acute hospital settings.

The following settings should consider self-audit, as follows:

- All acute hospitals at years 3, 4, 5 of guideline implementation (consecutive sample of 30 charts from all discharges coded with dementia within a period). This audit is ideally performed by the hospital Dementia Quality Improvement Team, supported by the Dementia Nurse Specialist/ Advanced Nurse Practitioner/Occupational Therapist. In the absence of a dementia team or specialist dementia staff, the local implementation team (LIT) should be responsible for the audit performance, likely working closely with the geriatric/psychiatry of old age service. The results of the audit should be fed back to the Dementia Quality Improvement Team or LIT for action, and also available to the National Implementation Team. A baseline practice review (prior to the Guideline Implementation) is being performed as part of the Second Irish National Audit of Dementia in acute hospitals in 2019, with local data available for each hospital on request, and composite data being released to each hospital group on the relative performance within and across all hospitals in their group. This baseline data will facilitate comparison with post-implementation local hospital data.
- All acute psychiatric units at years 3, 4, 5 of guideline implementation (consecutive sample of 30 charts from all discharges coded with dementia within a period). The local implementation team (LIT) within mental health should work closely with the acute unit to identify audit champions and potentially non-consultant hospital doctors willing to perform the audit as part of their annual audit requirement for professional competence assurance. Some acute psychiatric units have specific old-age units, and these should be particularly targeted for audit. The results of the audit should be fed back to the Mental Health LIT for action, and also available to the National Implementation Team.
- All HSE-provided (older persons) residential care units at years 3, 4, 5 of guideline implementation (random selection across all residents with known or highly likely dementia- aiming for at least 20 per unit - see audit tool for details). Ideally a Dementia Nurse Specialist or Advanced Nurse Practitioner or the guideline champion/trainer in each unit would lead this audit, reporting

results to the Director of Nursing. The results of the audit should also be fed back to the LIT for broader consideration (which includes the local residential services manager), including the need for enhanced resources to facilitate best practice. Results should also be available to the National Implementation Team.

- All memory clinics, memory assessment services, and community psychiatry of old age services should perform self-audit of their service at years 3, 4, 5 of guideline implementation (random selection of case notes across service attendees with a diagnosis of dementia). The National Dementia Office are developing a framework for integrated dementia diagnostic and post-diagnostic services in Ireland, and compliance with the guideline (and hence regular self-audit) should be part of any minimum standards that are developed for memory assessment and support services. It is envisioned that the audit would be performed by non-consultant hospital doctors as part of their annual audit requirement for professional competence assurance, or by the dementia nurse specialist or Advanced Nurse Practitioner, with the lead service consultant responsible for action on the audit result. Results should also be available to the National Implementation Team.
- Congregated disability units should also perform this audit where it is identified that a proportion of the residents have dementia. The LIT in each Community Healthcare Organisation will need to decide which units should be audited, given that there are 1250 units in total nationally, and a relatively small proportion overall would have dementia, and many are voluntary rather than HSE-provided. Pragmatically, the larger congregated units should be targeted for economy of scale, but case finding may also be aided by selecting people with intellectual disability over the age of fifty, or a similar process. It is envisioned that the key audit items may be incorporated within units' self-auditing for compliance with local policies for "restrictive practices" and "provision of behavioural support", aligned with the HIQA standards for disability services.
- Mental health dementia-specific residential units, at years 3, 4, 5 of guideline implementation (random selection across all residents with known or highly likely dementia- see audit tool for details). The selection of units for audit should be decided by the local implementation team (LIT) within mental health, working closely with the unit to identify audit champions and potentially non-consultant hospital doctors willing to perform the audit as part of their annual audit requirement for professional competence assurance. The results of the audit should be fed back to the Mental Health LIT for consideration, and also available to the National Implementation Team.
- General Practitioners (GPs)/Primary Care Teams: Ideally, GPs and GP practices would self-audit as per other services. However, although GPs have to perform one audit annually, there is no onus on them to choose an audit on psychotropic prescribing for a person with dementia. The National Implementation Team will work closely with the Irish College of GPs and GP dementia champions to promote the value of this audit, as part of the engagement around GP training in the guideline content. The possibility of Primary Care Teams performing an audit within their service will be explored with the Community Healthcare Organisation LIT.

3.2 National monitoring/evaluation audits

As well as local self-audits that will support local implementation, it is important to ultimately demonstrate that the national implementation programme was successful, and also, during implementation, to highlight settings or regions where it has not reached full potential and who may need further support or resources to improve practice. The Guideline Development Group consider this monitoring mid-implementation and final evaluation to be a key part of the overall implementation programme, but recognise that this level of audit requires resourcing.

The following national audits are recommended:

- An external audit in a sample of all acute hospitals at years 3 and 5 of guideline implementation, purposively sampled within and across hospital groups. It is proposed that this would be performed by the HSE Quality Assurance and Verification team, using the hospital self-audit data, where possible, with the required quality assurance and collation of data into a national report. The results can be compared with the baseline data from INAD-2 in 2019, thus providing robust pre-post implementation data.
- An external audit in a sample of HSE-provided residential care facilities at years 3 and 5, purposively sampled within and across community healthcare organisations. It is proposed by the Guideline Development Group that this would be performed by the National Office of Clinical Audit, if funding was available.

The National Implementation Team will explore with Mental Health and Disability Services the possibility of auditing their services for key audit items as part of other audits or initiatives.

3.3 Key audit quality metrics

Although all items in the audit tool directly link to recommendations in the National Clinical Guideline, within these recommendations, some are linked to key changes in practice. Thus, the following five audit criteria will be considered as key audit quality metrics:

For Recommendation 1:

- Prior to the prescribing of any psychotropic medication to a person with dementia, a comprehensive assessment has been performed by a suitably trained doctor or nurse.

For Recommendation 2:

- Prior to the prescribing of any psychotropic medication to a person with dementia, non-pharmacological interventions have been tried initially (unless there is an identifiable risk of harm to the person with dementia and/or others or severe distress in the person with dementia).

For Recommendation 3:

- Antipsychotic medication is only prescribed 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 with dementia.

For Recommendation 10/11:

- There is documented evidence of review/planned review of newly prescribed antipsychotic medication for effectiveness and side effects, within three months.

For Recommendation 19:

- Benzodiazepines are not prescribed for treatment of non-cognitive symptoms for a person with dementia.

Appendix 9: Levels of evidence in existing guidelines

The grading system of the three main guidelines that informed the recommendations of this National Clinical Guideline are described below, namely the American Psychiatric Association guideline (2016), the National Institute for Health and Clinical Excellence (2018), and the National Health and Medical Research Council (2016).

American Psychiatric Association (APA) system:

Although this guideline stated that it followed the GRADE system (Guyatt et al., 2011), it did so generally for the strength of evidence, but adapted this significantly for the level of evidence – using only three levels of quality of evidence, whereas GRADE also includes “very low” (Table 9.1).

Appendix 9.1: Grades of recommendations used by the APA guideline (2016)

Grade	Interpretations
Strength of recommendation	
“APA recommends”	Indicates confidence that the benefits of the intervention clearly outweigh the harms. Statement begins with “APA recommends” and the number 1 follows the statement. <i>Corresponds to “strong” in GRADE system</i>
“APA suggests”	Indicates uncertainty (i.e., the balance of benefits and harms is difficult to judge, or either the benefits or the harms are unclear). Statement begins with “APA suggests” and the number 2 follows the statement. <i>Corresponds to “conditional” in GRADE system</i>
Quality of Evidence	
A (High)	High confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect.
B (Moderate)	Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate.
C (Low)	Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is likely to change the estimate.

Thus, an APA statement may be rated 1A or 1B or 1C, or 2A, 2B or 2C. In reality, all the statements in the guideline are either 1B or 1C.

National Institute for Health and Clinical Excellence (NICE) system:

Interventions that must (or must not) be used

Usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a ‘strong’ recommendation

Use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer...’) when confident that an intervention will not be of benefit for most patients.

Interventions that could be used

Use ‘consider’ when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation, and so the HCP should spend more time considering and discussing the options with the patient.

National Institute for Health and Clinical Excellence (NHMRC) system:

This guideline was formed using the ADAPTE process in which recommendations from an existing high quality guideline (the NICE Guideline “Dementia: supporting people with dementia and their carers in health and social care; 2006) were adapted to suit the Australian context. The adaptation process included conducting systematic reviews to ensure that the Clinical Guideline reflected the most recent research evidence at the time. The guideline group followed the GRADE system (Guyatt et al., 2011) in terms of rating the quality of the evidence and the strength of the resulting recommendation (Table 9.2).

Appendix 9.2: GRADE system*, as used by the NHMRC guideline

Grade of Quality of Evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

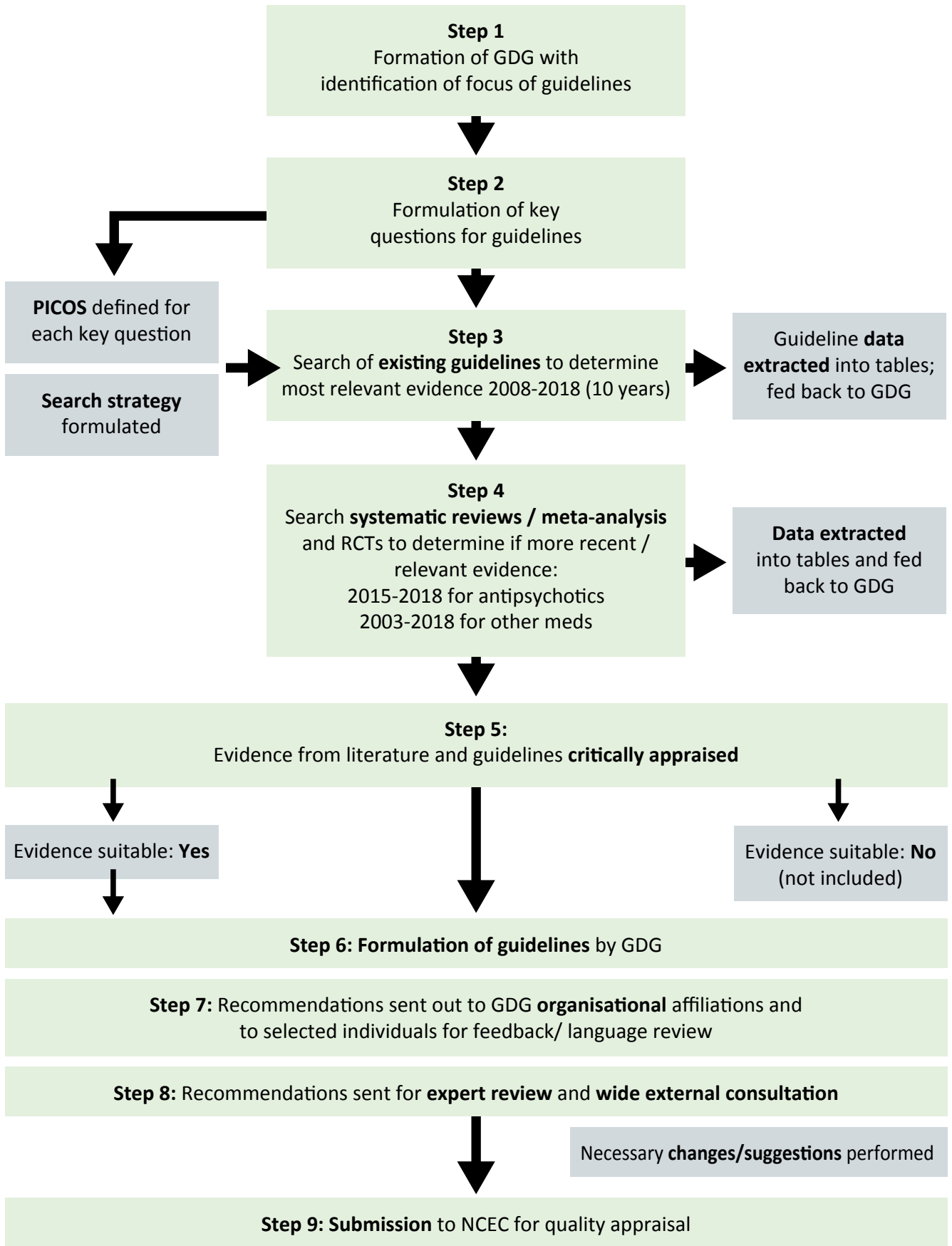
*As per the GRADE convention, a strong recommendation implies that most or all individuals will be best served by the recommended course of action. Strong recommendations use the term ‘should’ or ‘should not’. A weak recommendation implies that not all individuals will be best served by the recommended course of action and there is a need to consider individual patients’ circumstances, preferences and values. Weak recommendations use the term ‘should/could be considered’ or ‘suggested’ or ‘may be offered’.

In addition, the Guideline Development Group assigned the following designations to each recommendation (Table 9.3).

Appendix 9.3: Additional designations for each recommendation

Type of Recommendation	Description
Evidence-based Recommendations (EBR):	Recommendation formulated after a systematic review of the evidence, with supporting references provided
Consensus-based Recommendations (CBR):	Recommendation formulated in the absence of quality evidence, when a systematic review of the evidence has failed to identify any quality studies meeting the inclusion criteria for that clinical question
Practice Points (PP):	Recommendations based outside the scope of the search strategy based for the systematic evidence and is based on expert opinion

Appendix 10: Flowchart of guideline development process



Appendix 11: Side effects associated with psychotropic medication**

Classification	Generic Name (Common trade names)	Indications	Contraindications/ precautions for use	Side Effects	
				General	CNS
Antipsychotics	Haloperidol (Haldol) Risperidone (Risperdal, Perdamel, Rispera, Risperone) Olanzapine (Zyprexa, Rolyprexa, Zalasta) Quetiapine (Seroquel, Quetex, Seropia) Aripiprazole (Abilify) Clozapine (Clozaril, Denzapine)	Psychosis (paranoia, delusions, hallucinations) Combativeness Violence Agitation	CNS depression Hypotension Parkinsonism Hepatic dysfunction Glaucoma Bone marrow depression	Decreased quality of life Increased risk of Death Infections Urinary tract infections Worsening of dementia symptoms	Confusion, Delirium Exacerbation of existing cognitive impairment Sedation (drowsiness) Dizziness/light headedness, Gait disturbances, Parkinsonism Akathisia, Anticholinergic effects, Extra-pyramidal symptoms
Antidepressants (excludes Tricyclic Antidepressants and rarer medications)	Citalopram (Cipramil, Ciprotan, Citrol) Escitalopram (Lexapro, Etalopro, Esciprex) Sertraline (Zoloft, Lustral, Seretral, Serimel, Serlan, Deprega) Paroxetine (Parox, Paroser, Seroxat) Fluvoxamine (Faverin) Fluoxetine (Prozac, Prozamel, Prozit, Fluzac, Gerozac) Duloxetine (Cymbalta) Venlafaxine (Effexor, Irevex, Vedikal, Venex, Venlofax)	Depression	Existing use of anti-depressants Bleeding disorders Bipolar Diabetes Mellitus Epilepsy Kidney disease Heart disease	Agitation/Anxiety Indigestion/ stomach aches Diarrhea/ constipation Loss of appetite Reduced libido / Erectile dysfunction Diabetes	Dizziness Insomnia Headaches Hyponatremia-psychosis Serotonin syndrome-confusion, muscle twitch, sweating, agitation
Benzodiazepines	Alprazolam (Xanax, Gerax) Bromazepam (Lexotan) Clobazam (Frisium) Diazepam (Valium, Anxicalm) Lorazepam (Ativan) Prizepam (Centrax) Flurazepam (Dalmane) Lormetazepam (Noctamid) Nitrazepam (Mogadon) Temazepam (Normem) Triazolam (Halcion)	Anxiety / Severe anxiety Insomnia	Older age With MAOIs With Opiates	Rebound effects Dependency Increased morbidity/mortality Overdose Tolerance	Over sedation Drowsiness Increased agitation Cognitive deterioration Worsening of dementia
Z-drugs	Zolpidem (Nytal, Stilnoct) Zopiclone (Zilese, Zimovane, Zoldem, Zoptan)	Insomnia	Severe sleep apnoea Severe respiratory insufficiency Severe hepatic insufficiency	Irritability Stomach aches Dependency	Headaches Dizziness Daytime sleepiness
Anticonvulsants	Carbamazepine (Tegretol) Sodium valproate (Epilem) Gabapentin (Neurontin, Neurostil, Gabin) Lamotrigine (Lamictal, Lamoro, Larig) Topiramate (Topamax)	Behavioural dyscontrol Aggression Agitation	Pulmonary disease Hypersensitivity	Rash Bleeding Liver function	Sedation Dizziness Confusion
Acetylcholinesterase inhibitors and memantine (Anti-dementia)	Donepezil (Aricept, Donecept, Donesyn, Dozept) Galantamine (Razadyne, Reminyl, Galsya) Rivastigmine (Exelon) Memantine (Ebixa, Nemdatine)	Memory loss Decreased alertness Reduced motivation Judgement afflications in: mild to moderate AD Severe AD	Liver disease History of seizures	Nausea, Vomiting Diarrhea, Constipation Cough Muscle cramps Infection (influenza) Urinary retention	Insomnia Dizziness Headache Seizures (less common)

AD: Alzheimer's disease; CNS: central nervous system; MAOI: monoamine oxidase inhibitor; Resp: respiratory system; WBC: white blood cells.
**Please note that this is not an exhaustive medication or trade name list. This is not a definitive guide to the indications or adverse effects of each medication. Prescribers are referred to the SmPC of each medicine for full prescribing information.

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