MONASH University

Clinical Practice Guidelines for the Appropriate Use of Psychotropic Medications in People Living with Dementia and in Residential Aged Care

Technical Report Part 1

Guideline Methodology

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- NHMRC Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People: Clinical Practice Guidelines and Principles of Care for People with Dementia (2016)
- American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia (2016)
- Canadian Family Physician Clinical Practice Guidelines: Deprescribing Antipsychotics for Behavioural and Psychological Symptoms of Dementia and Insomnia (2018)

Permission to update and adapt guidelines was sought from respective authors. On clinical topics where the *update and adapt* approach was taken, evidence was always evaluated by the Guideline Development Group and considered within the Australian context.

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1 Guideline Methodology

Upon confirmation of funding for the development of the guideline, the Guideline Development Group (GDG) met in September 2020 to discuss the scope of the project. The GDG were unaware of any guidelines that were specifically focused on the appropriate use of psychotropic medications in people living with dementia and in residential aged care. The GDG agreed that there were a number of existing high quality guidelines and resources that could be adapted and updated. The GDG shortlisted guidelines that were deemed acceptable and relevant to the Australian context, including:

- Cognitive Decline Partnership Centre (CDPC) - Clinical Practice Guidelines and Principles of Care for People with Dementia (2016) (1)
- International Psychogeriatric Association (IPA) - Complete Guides to Behavioural and Psychological Symptoms of Dementia (BPSD) (2015) (2)
- Dementia Centre for Research Collaboration (DCRC) - Behaviour Management: A Guide to Good Practice (2012) (3)
- Assessment and Management of People with Behavioural and Psychological Symptoms of Dementia (BPSD): A Handbook for NSW Health Clinicians (2013) (4)
- SA Health Challenging Behaviour Toolkit (2015) (5)
- Therapeutic Guidelines: Psychotropic (2013, amended 2019) (6)
- Royal Australian College of General Practitioners (RACGP) - Aged Care Clinical Guide, Silver Book (2019) (7)
- Central Australian Rural Practitioners Association (CARPA) - Standard Treatment Manual (2017) (8)
- Australian Medicines Handbook: Aged Care Companion (2020) (9)

The project team also conducted an extensive search for other existing and relevant guidelines, both Australian and International. Guidelines were shortlisted if they were in English, recent and made recommendations regarding:

- people living with dementia and in residential aged care
- treatment of BPSD
- use of psychotropic medications

Search terms used for identifying relevant guidelines included “dementia”, “behavioural and psychological symptoms of dementia” and “psychotropic”, Table 1 outlines the search strategy used.

Table 1. Medline search terms for guidelines

Medline Search Terms for Guidelines.
(dementia OR BPSD OR 'behavioural and psychological symptoms of dementia' OR 'behavioral and psychological symptoms of dementia' OR 'Alzheimer* or 'non-cognitive symptom*') and (psychotropic* or antipsychotic* or management* or therapy* or prescrib*) AND (guide*) [limited to title]
(dementia OR BPSD OR 'behavioural and psychological symptoms of dementia' OR 'behavioral and psychological symptoms of dementia' OR 'Alzheimer* or 'non-cognitive symptom*') and (psychotropic* or antipsychotic* or management* or therapy* or prescrib*) AND (guide*) [limited to title]

Databases and websites searched included:

- Medline (via Ovid)
- Guidelines International Network (GIN)

- Google/Google scholar
- National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines Portal
- National Institute for Health and Care excellence (NICE) website
- Scottish Intercollegiate Guidelines Network (SIGN)

The shortlisted guidelines were screened and excluded according to whether the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used (10-18) to ensure alignment and consistency with the NHMRC requirements for approval (19). Five existing clinical practice guidelines employed the GRADE method and contained relevant contents for adaptation. Each guideline was appraised for their quality using the AGREE II tool (20). All five of the guidelines were found to be of high quality and were assessed for adaptation, see Table 2.

Table 2. AGREE II Appraisal of existing clinical practice guidelines relevant to psychotropic use in people living with dementia

Guideline	Agree II Score
The American Psychiatric Association (APA) - The APA Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia (US, 2016) (21)	5.5
National Institute for Health and Care Excellence (NICE) - Dementia: assessment, management and support for people living with dementia and their carers (UK, 2018) (22)	6.5
NHMRC Cognitive Decline Partnership Centre - Clinical Practice Guidelines and Principles of Care for People with Dementia. (Australia, 2016) (1)	6
Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia (Ireland, 2019) (23)	6.5
A European Academy of Neurology guideline on medical management issues in dementia (EU, 2020) (24)	4.4
The Canadian Family Physician Guidelines - Deprescribing Antipsychotics for Behavioural and Psychological Symptoms of Dementia and Insomnia (Canada, 2018) (25)	5.4

1.1 Selection of Key Clinical Questions

The key clinical questions used in the shortlisted guidelines were collated and sorted into medication-focused topics. The GDG were then surveyed to prioritise topics and clinical questions from most important to least important. Following a review of existing literature and rounds of feedback from the GDG and Stakeholder Advisory Group, the prioritised questions underwent some editing to align with the scope of the guideline. The final list of clinical questions were then presented back to the GDG for feedback and consensus.

Table 3 outlines how each clinical question maps on to the source guideline and Table 4 outlines the final clinical questions.

Table 3. Clinical question relevance to existing guidelines

Existing Source Guideline Clinical Question	This Guideline

NHMRC Cognitive Decline Partnership Centre - Clinical Practice Guidelines and Principles of Care for People with Dementia (2016) (1) • For people with behavioural and psychological symptoms of dementia (BPSD), does appropriate drug treatment when compared to placebo produce benefits/harm?	In people living with dementia and changed behaviours, what are the risks and benefits of antipsychotic medication use compared to not using antipsychotics?
	In people living with dementia and changed behaviours, what are the risks and benefits of benzodiazepine use compared to not using benzodiazepines?
	In people living with dementia and changed behaviours, what are the risks and benefits of antidepressant medication use compared to not using antidepressants?
The American Psychiatric Association (APA) - The APA Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia (2016) (21) • How do second-generation antipsychotic medications compare with other drugs, including first-generation antipsychotics, for the treatment of overall behavioural symptoms? • How do second-generation antipsychotic medications compare with other drugs, including first-generation antipsychotics, for the treatment of agitation in patients with Alzheimer's disease and other dementias • How do second-generation antipsychotic medications compare with other drugs, including first-generation antipsychotics, for the treatment of psychosis in patients with Alzheimer's disease and other dementias?	Should people living with dementia and changed behaviours be treated with second-generation compared to first-generation antipsychotics?
The Canadian Family Physician Guidelines - Deprescribing Antipsychotics for Behavioural and Psychological Symptoms of Dementia and Insomnia (2018) (25) • What are the effects (harms and benefits) associated with deprescribing compared with continuation of antipsychotic medication for the treatment of BPSD in adults?	For people living with dementia who have commenced on antipsychotic medication, should medication be discontinued?

Following the confirmation of clinical questions, a protocol was developed for each clinical question, please refer to Technical Report Part 2 for details. Each protocol included:

- Clinical question

- PICO for clinical question
- Literature review search strategy
- Criteria for selecting studies for review

Table 4. Finalised clinical questions

Clinical Questions
1. In people living with dementia and changed behaviours, what are the risks and benefits of antipsychotic medication use compared to not using antipsychotic medication?
2. Should people living with dementia and changed behaviours be treated with second-generation compared to first-generation antipsychotic medication?
3. For people living with dementia who have commenced on antipsychotic medication, should medication be discontinued?
4. In people living with dementia and changed behaviours, what are the risks and benefits of pro re nata (PRN) antipsychotic medication use compared to regular antipsychotic medication use?
5. In people living with dementia and changed behaviours, what are the risks and benefits of benzodiazepine use compared to not using benzodiazepine medication?
6. In people living with dementia and changed behaviours, what are the risks and benefits of pro re nata (PRN) benzodiazepine medication use compared to regular benzodiazepine medication use?
7. For people living with dementia who have commenced a benzodiazepine medication, should the medication be discontinued?
8. In people living with dementia and changed behaviours, what are the risks and benefits of antidepressants medication use compared to not using antidepressants?
9. For people living with dementia who have commenced an antidepressant, should the medication be discontinued?
10. What is the effectiveness of interventions to improve use and appropriateness of antipsychotic, benzodiazepine and antidepressant medication among people with dementia and in residential aged care?

1.2 Systematic Searching

The details for each clinical question can be found in the Technical Report Part 2, however each question followed a general protocol as explained below.

Each key clinical question was framed using the PICO process (Population, intervention, Comparator, Outcome) and informed specific search strategies. Search strategies were developed and then reviewed by Monash Institute Pharmaceutical Science University Librarian. Search strategies for each question were adapted for each database.

The following databases were searched:

- Medline (via Ovid)

- Embase (via Ovid)
- PsychINFO (via Ovid)
- CINAHL (via EBSCO)
- Cochrane CENTRAL Library

If adapting from an existing guideline, the search was restricted according to the last search date reported in the source guideline.

1.3 Study Selection

A hierarchical approach to updating evidence was adopted and each systematic search was restricted to systematic reviews of randomised controlled trial (RCT) and RCTs. When high quality evidence was not available, other sources of evidence were considered, including systematic review of observational studies, large observational studies and other clinical guidelines.

A title and abstract screen, and a full text screen were performed by two reviewers independently and results were compared. If major disagreements were found, a further ten percent of samples were screened by two reviewers until consistency was achieved. Major disagreements were defined as discrepancies between the two reviewers in more than five percent of the studies screened. Studies labelled as unsure were included into the full text review. A third reviewer was used to adjudicate when consensus was not reached by the two reviewers.

1.3.1 Inclusion and Exclusion Criteria

Each clinical question had a specific inclusion and exclusion criteria, outlined in Technical Report Part 2. Broadly, studies were included if they met the following criteria:

- Available in the English language
- Target population was people living with dementia
- High quality level of evidence according to the NHRMC levels of evidence (e.g. systematic review or RCT)
- Use either antipsychotics, benzodiazepines, and antidepressants as an intervention

Studies were excluded if they:

- Had a primary focus on the acute hospital setting
- Focused on treatment of conditions other than changed behaviour (such as delirium or other mental health conditions)
- Focused on treating cognitive symptoms with no reference to changed behaviour treatment
- People living with dementia receiving palliative care or end of life care
- Reports, commentaries, conference proceedings

Outcomes of interest for each clinical question were defined and prioritised by the GDG in advance, however, broadly, the outcomes of interest included:

- Changed behaviours (encompassing BPSD)
- Mortality
- Serious adverse events
- Quality of life
- Adverse events
- Health resource use

- Patient/Resident satisfaction
- Caregiver burden (informal and formal carers, staff, family members, substitute or supportive decision makers,)

1.3.2 Selection of Index Systematic Review, Quality Assessment and Data Extraction

All systematic reviews that met the PICO criteria were assessed and compared for suitability to become the 'index' systematic review and the basis of information for the evidence profiles. Suitability was determined by the following criteria:

1. Most relevant based on eligible studies (addressed the PICO and study design)
2. Most comprehensively reported in terms of the study characteristics
3. Recency of search
4. Meeting the A MeaSurement Tool to Assess systematic Reviews (AMSTAR II tool) criteria (26)

On occasions where there was an absence of RCT evidence relating to harms associated with psychotropic medication, a pragmatic search was conducted via PubMed to identity systematic reviews of observational studies. It was considered appropriate as often the duration of RCTs are not sufficient to identify long term serious adverse event or adverse events that may arise from psychotropic medications. Only the most recent, comprehensive and high quality systematic reviews of RCTs and RCTs were incorporated into the evidence profile. Any additional RCTs that were identified in the search but were not included in the selected index systematic review were incorporated into an updated meta-analysis, where possible. Studies were independently assessed for methodological quality using the AMSTAR II tool (26) and the Cochrane Risk of Bias tool (27) was used for RCTs. A reviewer extracted relevant outcome data from index systematic review. In cases where studies have reported multiple results, the results were discussed. However, only baseline and relevant time points were presented. Meta-analysis and forest plot were used to summarise results, if a meta-analysis was not possible, results were presented narratively. Summary statistics were calculated when appropriate. Where possible:

- Results were pooled to provide an overall estimate
    - Mean differences were calculated if scales are the same
    - Standardised mean difference will be used for outcomes with different scales
- A meta-analysis were conducted to estimate an overall summary effect
- Subgroup analyses were undertaken, if possible

Subgroups of interest include but were not limited to Aboriginal and Torres Strait Island people, types of dementia, people from culturally and linguistic diverse background and people living with intellectual disabilities.

1.4 Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

All results for critical and important outcomes were assessed and presented using the GRADE approach (11-18). A succinct summary of findings from the body of evidence for each clinical question was presented in evidence profile tables.

The GRADE evidence profile include:

- a list of all outcomes considered to be critical and important for making a recommendation,
- the results for each outcome, reported as the absolute and relative magnitude of effect (if both are appropriate),

- the number of participants and studies contributing to the result for each outcome (the body of evidence)
- a GRADE assessment of the overall certainty of the body of evidence for each outcome (high, moderate, low or very low certainty)
- an informative statement that provides a lay description of the size of the effect and certainty of evidence for each result (plain text summary)
- an explanation of the reasons for any decision to rate down the certainty of evidence (based on consideration of five GRADE domains: risk of bias, imprecision, inconsistency, indirectness and bias due to missing results [publication bias])

1.4.1 Evidence to Decision Framework and Formulation of Recommendations

A series of guideline development meetings were held over the course of August to November 2021. At each guideline development meeting, the evidence for each clinical question was reviewed and discussed by the GDG. Each meeting was chaired by both the methodological chair and clinical chair. The GRADE Evidence to Decision (EtD) Framework was used to facilitate a thorough and transparent process towards decision making and formulating recommendations (10-12). All evidence was presented digitally on the MAGICapp platform (MAking Grade the Irresistible Choice).

When considering formulating the recommendation, evidence relating to the following factors were considered for each clinical question:

- Benefits and Harms – the magnitude and balance of the desirable and undesirable effects.
- Certainty of evidence – a comprehensive assessment of quality of the evidence contributing to the evidence profile. Refer to
- Table 5.
- Preference and values – consideration of how people living with dementia (or others affected, such as carers) value the main outcomes.
- Resources – considerations of the direct costs associated with the intervention.
- Equity – considerations of potential introduction of inequities related to the intervention, with particular consideration to the abovementioned sub-populations of interest.
- Acceptability – consideration of the acceptability of consumers, health professionals and other implementers.
- Feasibility – consideration of the feasibility to implement the recommendation in clinical practice.

1.4.1.1 Equity and Preferences and Values

During the scoping of the Guideline no specific issues, relating to subpopulation of interests and psychotropic medication use for changed behaviours, were identified to warrant a systematic search specific to the abovementioned subpopulations. However, any potential issues were considered in the equity section.

During the evidence review, a search strategy was developed to identify literature relating to equity, psychotropic medication use and people living with dementia. This was a broad search to inform the evidence to decision framework and was restricted to Australian literature only. This was not systematic.. The search was conducted on Medline via Ovid and Embase via Ovid on 18 June 2021. The equity search strategy included concepts relating to CALD communities, Aboriginal and Torres Strait Islander peoples and people from low socioeconomic backgrounds. The relevant findings from this search are outlined in each

equity sections within the Guideline. The search strategy used can be found in Technical Report Part 2.

To identify literature on relating to preferences and values of people living with dementia and the use of psychotropic medication, a broad scoping search was conducted. This search was not systematic. The search was conducted on Medline via Ovid and Embase via Ovid on 18 June 2021. Search terms included concepts relating to resident and consumer/resident preferences, decision-making and consumer/resident engagement. Findings from the search are outlined in the preferences and values sections within the Guideline. The search strategy used can be found in Technical Report part 2.

1.4.2 Guideline Development Meetings

Each meeting had a range of multidisciplinary expertise present; however, it was considered essential that each meeting had at a minimum of one representative with lived experience (included former carers), a person who directly worked in an aged care facility and a nurse. On occasions where additional expertise was needed, additional experts were invited to the meeting to address potential gaps. The list of additional experts invited to participate can be found in the administrative report.

During each guideline development meeting, the GDG voted on judgements for each of the above factors. Following review and discussion of the EtD framework, the GDG were requested to vote on the direction of the recommendation was determined (ie a recommendation *for* or *against* the intervention). See Table 6 for the different types of recommendations.

When drafting the recommendations and good practice statements, other existing Australian guidelines (e.g., electronic Therapeutic Guidelines, Australian Medicines Handbook and RACGP Silver Book) were considered and aligned with when appropriate.

Table 5. GRADE definitions for ratings for quality of evidence

Grade	Definition
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 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
Hultcrantz et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 (18)	

Table 6. GRADE definitions for rating strength of recommendation

Recommendation	Definition
Strong Recommendation for	A strong recommendation for an intervention is given when the certainty of evidence is high or moderate. The benefits outweigh harms for almost everyone and all or nearly all people would likely want the recommended intervention.

Strong Recommendation against	A strong recommendation against an intervention is given when the certainty of evidence is high or moderate. There are clear harms attributed to the intervention and they outweigh the benefits. Most people would decline the intervention.
Conditional Recommendation for	A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.
Conditional Recommendation against	A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.
Good Practice Statements	Good Practice Statements are ungraded statements that represent the GDG's view of optimal practice. Good practice statements are used in instances where high quality indirect evidence is available; however, conducting a formal evidence review would not be a good use of resources.
Guyatt et al. Going from evidence to recommendations. BMJ 2008 (10)	

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