TITLE: Antidepressants in Elderly Patients with Behavioural and Psychological Symptoms of Dementia: A Review of Clinical Effectiveness and Guidelines

DATE: 31 August 2015

CONTEXT AND POLICY ISSUES

Almost 750,000 Canadians are have Alzheimer’s disease and other forms of dementia, with an estimated 14.9% of the population over the age of 65 being affected.\(^1\) In addition to the effects that dementia has on cognition and ability to function, it is also associated with noncognitive disturbances, referred to as the behavioural and psychological symptoms of dementia (BPSD).\(^2\)

Over 90% of patients with dementia will have BPSD.\(^3\) Examples of BPSD include anxiety, depression, irritability, aggression, agitation, eating disorders and inappropriate social or sexual behaviours.\(^4\) Such behaviours have a negative impact on quality of life, can increase the risk of placement in long-term care facilities and can pose a risk to the safety of the patient, caregivers and other patients or residents.\(^2,3\) A number of interventions, both pharmacological and nonpharmacological, can be used to help manage BPSD, including antidepressants.\(^3\)

Antidepressants are categorized into classes based upon their structure or the neurotransmitters that they affect, with therapeutic options including:

- Tricyclic antidepressants (TCAs, e.g. nortriptyline, amitriptyline)
- Selective serotonin reuptake inhibitors (SSRIs, e.g., paroxetine, citalopram)
- Selective serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine, desvenlafaxine, and duloxetine)
- Norepinephrine-dopamine reuptake inhibitors (i.e., bupropion)
- Noradrenergic/specific serotoninergic agents (i.e., mirtazapine)
- Serotonin 2 antagonists /serotonin reuptake inhibitor (i.e., trazodone)

Antidepressants have been used for the management of BPSD, but it is unclear if there is sufficient evidence of safety and efficacy to support their use for this indication in patients aged 65 and older. As well, it is uncertain if current evidence-based guidelines support their use.

The purpose of this Rapid Response report is to summarize the evidence of clinical efficacy and harms associated with antidepressant in adults aged 65 and older for the management of BPSD and current guideline recommendations.
RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

2. What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

KEY FINDINGS

There were no health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials or non-RCTs identified that compared the efficacy or safety of an antidepressant to another antidepressant, placebo, St. John’s Wort or a behavioural intervention in elderly patients (aged 65 and over) with behavioural and psychological symptoms of dementia.

One evidence-based guideline included recommendations for the use of antidepressants as an alternative to help manage inappropriate sexual behaviours, agitation, apathy, and sleep disturbances. These recommendations were based upon low quality evidence.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2000 and July 28, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Elderly patients ≥65 years of age in any setting (home, long-term care, hospital) with behavioural and psychological symptoms of dementia</th>
</tr>
</thead>
</table>
| Intervention | • Selective serotonin reuptake inhibitors (SSRIs)  
• Serotonin and norepinephrine reuptake inhibitors (SNRIs)  
• Tricyclic antidepressants  
• Norepinephrine-dopamine reuptake inhibitor (NDRIs)  
• Serotonin 2 antagonists /serotonin reuptake inhibitors (SARIs)  
• Noradrenergic and specific serotonergic antidepressant (NaSSAs) |
| Comparator | • All antidepressant classes (SSRIs, SNRIs, TCAs, NDRIs, SARIs, and NaSSAs)  
• Placebo  
• Non-pharmacologic interventions (e.g., environmental)  
• St. John’s Wort |
| Outcomes | • Clinical effectiveness (includes clinical benefit [e.g., minimal clinically important differences with different tools] and harms, safety)  
• Guidelines |
| Study Designs | Q1: Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs (safety only)  
Q2: Evidence-based guidelines |

HTA = Health technology assessment; MA = Meta-analysis; NaSSA = Noradrenergic and specific serotonergic antidepressant; NDRI = Norepinephrine-dopamine reuptake inhibitor; RCT = Randomized controlled trial; SARIs = Serotonin 2 antagonists /serotonin reuptake inhibitors; SNRI = Serotonin and norepinephrine reuptake inhibitors; SR = Systematic review; SSRI = Selective serotonin reuptake inhibitors

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2010. Articles that failed to report the age of the study population were excluded. As well, review articles that were not based upon a systematic literature search and guidance documents or consensus statements that did not include a description of the methodology used in their development, were not clearly evidence-based, or did not make explicit recommendations were not summarized in the report, but are listed in Appendix 2.

Critical Appraisal of Individual Studies

The included guidelines were assessed with the AGREE II instrument. Summary scores were not calculated for the included guidelines; rather, a review of the strengths and limitations of each included guideline were described.
SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 309 citations were identified in the literature search. Following screening of titles and abstracts, 296 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 14 publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

What is the clinical effectiveness and safety of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

No relevant literature was identified.

What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

One evidence-based guideline from the Agency for Health Quality and Assessment of Catalonia, 2010 met the inclusion criteria for this Rapid Response report. The guideline was intended for use by healthcare and other professionals who provide care to and make clinical decisions for patients with dementia, for example, general practitioners, neurologists, geriatricians, psychiatrists, neuropsychologists, psychologists, nurses, pharmacists, internists, physiotherapists, occupational therapists, and social workers. As well, patients with dementia and their caregivers were identified as users of the guideline. The major areas of focus considered in this guideline were prevention, detection, diagnosis, genetic counselling, pharmacological and nonpharmacological treatment, prognosis, health and social resources and aid, monitoring and care at end-of-life stage for patients with dementia. The methodology of the included guideline is summarized in Appendix 3.

Summary of Critical Appraisal

What is the clinical effectiveness and safety of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

No relevant literature was identified.

What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?
The strengths and limitations of the guideline produced by the Agency for Health Quality and Assessment of Catalonia, 2010 are summarized in Appendix 4. The methodology used in guideline development appeared to be rigorous, based upon the standard process used by the Agency for Health Quality and Assessment of Catalonia and meeting most items of the AGREE II checklist. The objectives and research questions were clearly stated and relevant professional groups were included in the guideline development process. A systematic search was conducted to identify evidence, though it was unclear whether grey literature was searched. Little detail was provided, however, on the methodology for selection of the relevant evidence or for formulating recommendations. The standard methodology used in their systematic reviews was referred to in the guideline document and is available on the Agency’s website, however, it was only available in Spanish so could not be accessed for additional detail.

Summary of Findings

What is the clinical effectiveness and safety of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

No relevant literature was identified.

What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with behavioural and psychological symptoms of dementia in any setting (home, long-term care, or hospital)?

The included guideline made recommendations related to antidepressant use for a number of different behaviours, including inappropriate sexual behaviours, sleep disturbances, apathy and agitation and aggression. These recommendations are summarized in Table 2. All recommendations were graded as D, meaning that they were derived from level 3 or 4 evidence or that evidence from studies rated as 2+ was extrapolated to make the recommendation. Further detail on the levels of evidence and grading of recommendations is provided in Appendix 3. While some recommendations cited specific antidepressants (trazodone and bupropion), the other recommendations were more general or broad (SSRIs or no specific agent or class identified). Antidepressants were recommended, alongside other treatment options, to manage a variety of behaviours.

<table>
<thead>
<tr>
<th>Table 2: Summary of Recommendations from Included Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline, Publication Year</strong></td>
</tr>
<tr>
<td>Agency for Health Quality and Assessment of Catalonia, 2010.</td>
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</table>

SSRI=Selective serotonin reuptake inhibitor
Limitations

There was no literature identified that evaluated the efficacy of an antidepressant compared to another antidepressant, placebo, St. John’s Wort or a behavioural intervention in elderly patients (aged 65 and over) with BPSD. While there were systematic reviews and RCTs identified from the literature search and full-text article screening that assessed the efficacy of antidepressants for BPSD, these studies were excluded as they did not meet the age threshold of 65 years specified in the inclusion criteria for this review or compared the antidepressant with an atypical antipsychotic. Generally, the literature was selected for inclusion into SRs or HTA reports on the basis of a diagnosis of dementia, not according to age (Appendix 2). Similarly, the inclusion criteria for RCTs would specify dementia or Alzheimer’s disease, but not include or exclude potential participants on the basis of age. However, it is not clear if the results from younger populations would be reflective of the age-related changes that affect antidepressant safety and efficacy. One evidence-based guideline was identified that addressed antidepressant use for the management of BPSD. Recommendations regarding antidepressant use in that guideline were based off of a limited number of studies that were low in quality which resulted in “D” grades of recommendations. Of note, this guideline was published in 2010 and would be considered in need of updating in the near future according to the criteria set forth in the guideline for updates (i.e., a maximum of five years).

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There was no literature identified that evaluated the efficacy of an antidepressant compared to another antidepressant, placebo, St. John’s Wort or a behavioural intervention in elderly patients (aged 65 and over) with BPSD. One guideline, based upon low quality evidence, endorsed the use of antidepressants and other options for the management of a number of different behavioural symptoms; however, the grade of recommendation was low. This limits the ability to make policy decisions based on this single guideline.

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REFERENCES


APPENDIX 1: Selection of Included Studies

309 citations identified from electronic literature search and screened

296 citations excluded

13 potentially relevant articles retrieved for scrutiny (full text, if available)

2 potentially relevant reports retrieved from other sources (grey literature, hand search)

15 potentially relevant reports

14 reports excluded:
- irrelevant population (8)
- irrelevant comparator (3)
- irrelevant intervention (3)

1 report (guideline) included in review
APPENDIX 2: Additional Literature of Potential Interest

Health Technology Assessment Reports and Systematic Reviews (Not Age Specific)


Guidelines (Not clearly evidence-based)


APPENDIX 3: Summary of Study Characteristics

Table A1: Characteristics of Included Guidelines

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Evidence Quality and Strength</th>
<th>Recommendations development and Evaluation</th>
<th>Guideline Validation</th>
</tr>
</thead>
</table>
| **Evidence collection, Selection and Synthesis**                          | Quality assessment of the included literature and evidence synthesis for each question was according to recommendations from SIGN.  
                                | Classification of the evidence and grading of the recommendations was according to SIGN.  
                                | **Classification of Evidence:**  
                                | 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias  
                                | 1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias  
                                | 1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias  
                                | 2++ High quality systematic reviews of case control or cohort or studies  
                                | High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal  
                                | 2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal  
                                | 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal  
                                | 3 Non-analytic studies, e.g. case reports, case series  
                                | 4 Expert opinion  
                                | Process for formulating recommendations was not clearly described.  
                                | Where evidence insufficient, group consensus was used to arrive at recommendations.  
<pre><code>                            | Reviewed by external experts from a number of medical societies.                          |
</code></pre>
<table>
<thead>
<tr>
<th>Evidence collection, Selection and Synthesis</th>
<th>Evidence Quality and Strength</th>
<th>Recommendations development and Evaluation</th>
<th>Guideline Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade of Recommendations</strong></td>
<td></td>
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<tr>
<td><strong>A</strong></td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or</td>
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<tr>
<td></td>
<td>A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
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<tr>
<td><strong>B</strong></td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or</td>
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<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 1++ or 1+</td>
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<tr>
<td><strong>C</strong></td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or</td>
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<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 2++</td>
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<tr>
<td><strong>D</strong></td>
<td>Evidence level 3 or 4; or</td>
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<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 2+</td>
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SIGN = Scottish Intercollegiate Guidelines Network
APPENDIX 4: Summary of Critical Appraisal

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The overall objective was clearly described.</td>
<td>• Selection criteria for the evidence were not well described.</td>
</tr>
<tr>
<td>• All health questions covered by guideline specifically were clearly stated.</td>
<td>• Method for formulating recommendations not described in detail.</td>
</tr>
<tr>
<td>• Population to whom the guideline is meant to apply was specifically described.</td>
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<tr>
<td>• Relevant professional groups were included in the guideline development</td>
<td></td>
</tr>
<tr>
<td>o Collaboration with clinical specialists, pharmacists, nurses, patient groups/societies</td>
<td></td>
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<tr>
<td>• Target users of the guideline were clearly defined</td>
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<tr>
<td>o Health professionals who have direct contact and make decisions about the care of people with dementia</td>
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</tr>
<tr>
<td>o Professionals from other areas that have direct contact with people affected by dementia</td>
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</tr>
<tr>
<td>o People with dementia</td>
<td></td>
</tr>
<tr>
<td>o Caregivers</td>
<td></td>
</tr>
<tr>
<td>• Sought views and preferences of the target population.</td>
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<tr>
<td>• Systematic methods used for literature search, but it did not appear that grey literature was searched.</td>
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<tr>
<td>• Strengths and limitations of the body of evidence were clearly described.</td>
<td></td>
</tr>
<tr>
<td>o Quality of literature was assessed according to SIGN.</td>
<td></td>
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<tr>
<td>• Health benefits, side effects, risks considered in formulating recommendations.</td>
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<tr>
<td>• Specific and unambiguous recommendations were made.</td>
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<tr>
<td>• External review by a group of experts</td>
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<tr>
<td>o Reviewed by individuals from expert societies</td>
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<tr>
<td>• There was an explicit link between recommendations and supporting literature.</td>
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<tr>
<td>• Options for management (both pharmacological and nonpharmacological) were clearly described.</td>
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</tr>
<tr>
<td>• Recommendations were easily identifiable.</td>
<td></td>
</tr>
<tr>
<td>• Description of monitoring and auditing criteria, facilitators and barriers to application, advice for implementation, and resource implications were all provided.</td>
<td></td>
</tr>
<tr>
<td>• Competing interests of the development group members were stated.</td>
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</tr>
<tr>
<td>• A procedure was described for future updates to the guidelines.</td>
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<tr>
<td>o No later than five years or sooner if a significant advance is made.</td>
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</tbody>
</table>

SIGN = Scottish Intercollegiate Guidelines Network