Systematic Review and Meta-Analysis: Antidepressants for Depression in Frail Older Adults, Dementia and the Neuropsychiatric Symptoms of Dementia
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Acronyms and Abbreviations

ADAS-cog  Alzheimer’s Disease Assessment Scale cognitive subscale
ADCS-ADL  Alzheimer's Disease Cooperative Study - Activities of Daily Living
ADCS-CGIC  Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change
ADRDA  Alzheimer’s Disease and Related Disorders Association
AE  Adverse event
AIREN  Association Internationale pour la Recherche et l'Enseignement en Neurosciences
BEHAVE-AD  Behavioural Pathology in Alzheimer’s Disease
BRSD  Behavioural Rating Scale for Dementia
CDR  Clinical Dementia Rating sum of the boxes
CERAD  Consortium to Establish a Registry for Alzheimer’s Disease
CFS  Clinical frailty scale
CGIC  Clinical Global Impression of Change
CI  Confidence interval
CitAD  Citalopram for Agitation in Alzheimer Disease Study
CMAI  Cohen Mansfield Agitation Inventory
CPG  Clinical practice guideline
CSDD  Cornell Scale for Depression in Dementia
DBRCT  Double blind randomized controlled trial
DLB  Dementia with Lewy bodies
DSM  Diagnostic and Statistical Manual of Mental Disorders
FAST  Functional Assessment Staging
GDS  Geriatric Depression Scale
HAMD  Hamilton Depression Scale
HDRS  Hamilton Depression Rating Scale
ICD  International Classification of Diseases
LTC  Long term care
mADCS-CGIC  modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change index
MADRS  Montgomery Åsberg Depression Rating Scale
MAOI  Monoamine oxidase inhibitor
MD  Mean difference
MDD  Major depressive disorder
MMSE  Mini Mental State Examination
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>NaSSA</td>
<td>Noradrenergic and specific serotonergic antidepressant</td>
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<tr>
<td>NBRSA</td>
<td>Neurobehavioral Rating Scale - Agitation subscale</td>
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<tr>
<td>NINCDS</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke</td>
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<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communications Disorders and Stroke-Alzheimer Disease and Related Disorders Association</td>
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<tr>
<td>NNH</td>
<td>Number needed to harm</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<td>NPS</td>
<td>Neuropsychiatric symptoms</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SIB</td>
<td>Severe Impairment Battery</td>
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<tr>
<td>SNRI</td>
<td>Serotonin-norepinephrine reuptake inhibitor</td>
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<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<tr>
<td>STOPP/START</td>
<td>Screening Tool of Older People's Prescriptions / Screening Tool to Alert to Right Treatment</td>
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<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
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Executive Summary

Key messages
1. Those with frailty and/or dementia are commonly diagnosed with depression, however it may be difficult to differentiate the symptoms of depression from the physical decline of frailty or symptoms of dementia.
2. Antidepressants are widely prescribed in long-term care (approximately 60% of residents in Canada), where many frail older adults with and without dementia reside.
3. Based on our systematic review and meta-analyses, we conclude there is considerable uncertainty about the benefit of antidepressants for depression in frail, older adults with and without dementia or the neuropsychiatric symptoms of dementia compared to placebo. However, there are individual patients who might benefit from antidepressants.
4. Patients started on antidepressants for depression should be reassessed after 8 to 12 weeks and 9 weeks for those using antidepressants for neuropsychiatric symptoms.
5. Fatigue, nausea, constipation, dizziness, and diarrhea were significantly more frequent in those taking antidepressants and may be burdensome side effects in advanced frailty.

Evidence Gap Addressed by Systematic Review
- Polypharmacy, the use of more medications than is clinically necessary, is a significant problem among frail, older adults.
- With this in mind, we appraised the evidence for the efficacy and safety of antidepressants in frail, older adults, as they appear to be commonly prescribed to older adults who are frail. For example, in long-term care, where many frail, older adults reside, antidepressants are the second most commonly prescribed medication, with 60% of residents using an antidepressant and 36% using a selective serotonin reuptake inhibitor (SSRI).
- Although antidepressants may be prescribed for several conditions, this review focused on depression and the neuropsychiatric symptoms (NPS) of dementia, as these are frequent conditions in frailty. NPS refers to behavioural and affective symptoms commonly experienced in dementia (e.g., depression, wandering, resistance, agitation, aggression, sexually inappropriate behaviour, and change in sleep patterns).
- The use of antidepressants for NPS of dementia is an off-label indication, however, there has been increasing interest in the efficacy and safety of antidepressants for NPS due to concerns about the risks of stroke and death from antipsychotics.

Uncertainty about the diagnosis of depression
- Those with frailty and/or dementia are commonly diagnosed with depression. For instance, the prevalence of depression in hospitalized geriatric populations is over 30%.
Comorbidities that are commonly associated with frailty—such as stroke, heart disease, and cancer—may be associated with rates of depression over 40%. Likewise, the diagnosis of depression is common in long-term care, where between 44 to 54% of residents may have a diagnosis and/or symptoms of depression.

- However, the diagnosis of depression is complicated by significant overlap in the signs and symptoms among depression, frailty, dementia and NPS of dementia (Table 1).

Table 1. Similarities among the characteristics of depression, frailty, dementia and NPS

<table>
<thead>
<tr>
<th>Deposition (DSM-5)*</th>
<th>Frailty</th>
<th>Dementia</th>
<th>NPS</th>
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<tbody>
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<td>Depressed mood/irritability</td>
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<td>Loss of interest</td>
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<td>Suicidality</td>
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*DSM-5 criteria: Requires that five or more of the symptoms have been present during the same two-week time frame and represent a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Additionally, symptoms cause clinically significant distress or impairment in functioning and are not attributable to the physiological effects of a substance or to another medical condition.

**Review Methodology**

- In 2013, a network of stakeholders with an interest in reducing polypharmacy in frail, older adults used a Delphi process to select antidepressants, among a list of 32 other medications, as a priority topic for a systematic review.

- The systematic review was completed by a team of clinical and academic professionals in geriatric medicine, family medicine, pharmacy and research from September 2015 through March 2016.

- The goal of the review was to assess the efficacy and safety of antidepressants for frail, older adults with (1) depression; (2) depression and dementia and (3) neuropsychiatric symptoms of dementia. The evidence for non-drug (psychosocial) interventions was not assessed in this review.

- We engaged the Canadian Agency for Drugs and Technologies in Health (CADTH) to conduct a rapid review for each clinical question to inform the systematic review.

- We reviewed meta-analyses, systematic reviews and randomized controlled trials that were published between 1997 and 2016.

- Relevant Canadian and international clinical practice guidelines were identified and references to support recommendations reviewed.
Patients were from long-term care, outpatient clinics or community dwelling. The level of depression reported by many trials was moderate to severe (based on standardized scale ratings) and the level of dementia was mild to moderate. Trials assessing antidepressants for NPS included frail populations with Alzheimer Disease or other forms of dementia.

We included trials on selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and noradrenergic and specific serotonergic antidepressants (NaSSAs). We also conducted a sensitivity analysis with tricyclic antidepressants (TCAs) for depression with and without dementia.

We conducted meta-analyses on the trials of antidepressants for depression using random effects models. We were unable to conduct a meta-analysis for antidepressants for NPS due to variation in study methods, however, we provide a narrative synthesis.

Key Findings

1. Antidepressants for Depression in Frail, Older Adults
   - As we found no trials that evaluated antidepressants in frail older adults, we analyzed data from nine double-blind randomized controlled trials (n=2641 patients) that compared antidepressants to placebo to treat older adults with depression (65 years of age or older) using age as a surrogate marker for frailty [SSRIs (n=5 trials), SNRI (n=3 trials) and bupropion (n=1 trial)].
   - Meta-analysis results showed no overall statistically significant benefit for antidepressants over placebo (Table 2). Results were not substantially different with the inclusion of one study (n=120) of clomipramine, a TCA.
   - Further review of antidepressants for depression in adults with comorbid conditions that typically lead to frailty, such as post-stroke, Parkinson’s disease and heart failure, found no definitive evidence of efficacy.
   - After non-response to the first antidepressant, we found uncertain benefit for most medication related strategies that are used to manage treatment-resistant depression. The evidence was limited to populations of middle aged adults, where adding an antipsychotic or lithium to an antidepressant may improve response or remission, but at the risk of significant adverse effects that may limit their usefulness in frail older adults. Other strategies to manage treatment resistant depression had uncertain efficacy.

2. Antidepressants for Depression in Dementia
   - We analyzed data from six double-blind randomized controlled trials (n=597 patients) that compared antidepressants to placebo [SSRIs (n=5 trials), SNRI (n=2 trials – one trial included an SSRI and SNRI)] for depression in adults with mild to moderate stage dementia (MMSE 17 -23).
Meta-analysis results showed no overall statistically significant benefit for antidepressants over placebo (Table 2). Results were not substantially different with the inclusion of one small study (n=21) of clomipramine, a TCA.

### Table 2. Meta-analysis of response and remission rates for antidepressants for depression

<table>
<thead>
<tr>
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<th>Response</th>
<th>Remission</th>
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<tr>
<td></td>
<td>ADs</td>
<td>PBO</td>
</tr>
<tr>
<td>Frail older adults</td>
<td>45%</td>
<td>38%</td>
</tr>
<tr>
<td>9 studies, n=2641</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frail older adults</td>
<td>45%</td>
<td>37%</td>
</tr>
<tr>
<td>with dementia, 6 studies, n=597</td>
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</table>

ADs= Antidepressants; PBO = Placebo; RR = Relative Risk; 95% CI = 95% Confidence Interval. 1Response defined as ≥ 50% decrease in depression scores or Clinical Global Impression rating of symptoms as “better” or “much better”); 2Remission defined as depression scores above cut-off criteria on scales (e.g., Hamilton Depression Rating Scale, Cornell Scale for Depression in Dementia and the Montgomery-Åsberg Depression Rating Scale).

3. Antidepressants for NPS

- We reviewed studies of patients with neuropsychiatric symptoms (NPS) related to dementia. Studies compared an SSRI to either placebo or an active comparator (1st/2nd generation antipsychotics). We were unable to conduct a meta-analysis due to variation in study methods, however, a narrative synthesis can be found in the full review document.

- Based on a Cochrane review of nine trials, and two additional RCTs (n=918 patients in total), we conclude that there is considerable uncertainty about the benefit of antidepressants to treat NPS of dementia.
  - The Cochrane review found few high-quality studies examining antidepressants for agitation and psychosis in dementia but reported a 0.90-point decrease in agitation for SSRIs versus placebo (203-point scale, n=250). We question the clinical significance of this difference, although this finding was statistically significant.
  - A recent study, which was higher quality than the studies in the Cochrane review and provided more weight in our assessment of the evidence found better odds of being ‘marked or much improved’ for citalopram (30mg) versus placebo (OR 2.13; 95% CI 1.21-3.54), however, the clinical relevance of these findings were uncertain because:
    - There was only a 1-point decrease in agitation for citalopram versus placebo (18 point scale), although this finding was statistically significant.
    - 60% of patients using citalopram did not demonstrate a notable improvement.
    - The difference in the percent of responders between citalopram and placebo was 14%, not statistically significant.
The trial used a higher dose of citalopram (30mg) than is recommended (max. daily dose 20mg) along with an intensive psychosocial intervention in both the treatment and placebo arms.

- There was no difference between groups in the use of “rescue lorazepam.”
- Adverse effects were higher for citalopram (diarrhea, worsening cognition, and cardiac side effects such as Qt prolongation).

Adverse Effects of Antidepressants in Frail, Older Adults

- Adverse events were poorly reported in many of the trials and our review of antidepressant safety was limited to the data presented by the study authors.
- In the studies we reviewed, fatigue, nausea, constipation, dizziness, and diarrhea were significantly more frequent in those taking antidepressants. For example, in the CitAD trial, diarrhea was twice as likely to be reported among those taking antidepressants (28% vs 14%, NNH = 7), which may be a serious side effect in advanced frailty.
- Overall, the rate of withdrawal was twice as high for antidepressants as placebo (13% versus 6%, NNH = 13). Numbers Needed to Harm for other adverse effects were nausea 12, fatigue 19, constipation 22, and dizziness 31.

Recommendations for Practice

- For frail older adults, we recommend more judicious prescribing of antidepressants for depression (with and without dementia) and/or neuropsychiatric symptoms of dementia. A reduction in the use of antidepressants in frail older adults could decrease the risk of polypharmacy and medication side effects.
- However, the evidence does not exclude that antidepressants could provide benefit for some individuals.
- Families, patients and care givers need to be aware of the limited potential for benefit based on the numbers that will not likely benefit, and balance this with the potential for adverse effects from antidepressants.
- If a trial of antidepressant medication is considered, response should be carefully evaluated at:
  - 8 to 12 weeks for depression
  - Approximately 9 weeks for neuropsychiatric symptoms (based on the duration of CitAD trial)
- Antidepressants should be discontinued if benefit is not achieved. Treatment with antidepressants is not appropriate as a sole agent for acute agitation requiring immediate response.
• If patients with depression do not respond to the first antidepressant, alternate approaches (such as switching to another antidepressant or augmenting the first antidepressant with another medication) are not likely to be effective.

Questions and Uncertainties
• It is unclear if there was any difference in efficacy depending on history of recurrent depression, duration of depression, baseline depression severity (most had moderate to severe depression). In addition, patients at risk for suicide were excluded from most studies.
• Since most studies were 13 weeks or less in duration, the long-term efficacy and tolerability of antidepressants for average antidepressant use in LTC (12 to 36 months) is uncertain.
• It is unclear why there was a high response and remission rate in the placebo groups.
• There was a moderate to high level of heterogeneity found in many analyses. This may be related to different scales used, different patient populations, and different methods of assessment and levels of non-pharmacologic support provided during the study.
• For most outcomes, differences between antidepressant and placebo groups were based on total scale scores and improvements in specific symptoms are unknown.

Remaining Knowledge and Research Gaps
• The efficacy and safety of pharmacological and non-pharmacological interventions for depression and neuropsychiatric symptoms in frail, older adults with and without dementia needs further study.
• There is a need for validated tools/approaches to differentiate the symptoms of depression from those of dementia, frailty, and neuropsychiatric symptoms of dementia.
• Accepted standards of minimal clinically important differences (MCID) in measurement scales are required to aide in the interpretation of clinical relevance as MCID are not defined for all scales.
Background
As the population ages and the number of frail older adults increase, optimizing drug treatment and avoiding polypharmacy will be an increasingly important mandate. Polypharmacy can be defined as prescribing more medications than is clinically indicated. Frail individuals, in particular, are at increased risk of polypharmacy, as they often have multiple chronic illnesses that not only impair physiologic resilience, but also increase the likelihood of prescribing many medications. As the number of medications increase, the probability of adverse effects also increases, which may shift the risk-to-benefit balance of treatment. In 2012, the Canadian Institute of Health Information reported that over 60% of elderly in LTC used 10 or more prescription drugs.

Several groups, including the Beers (3) and STOPP/START(4) criteria, tackle “deprescribing” for older adults by identifying potentially inappropriate medications. In contrast, our approach relies on critical appraisal of evidence to inform prescribing decisions for common medical conditions in frailty, as Canadian Clinical Practice Guidelines (CPGs) seldom consider the applicability of their recommendations for frail older adults. Frailty-specific guidance should be based on the best evidence, but also consider the increased vulnerability to adverse drug reactions and shortened life expectancy associated with advancing age and frailty.

Since 2009, Dalhousie University Continuing Professional Development, the Palliative and Therapeutic Harmonization Clinic, the Nova Scotia Health Authority Drug Evaluation Unit and related organizational partners have conducted evidence appraisals on the benefits and harms of therapy in frail elderly adults. Guidelines for the frail elderly include the appropriate use of statins, appropriate hypertension, diabetes targets and the management of asymptomatic bacteriuria.

The inappropriate use of antidepressant medications could add to existing polypharmacy. As such, the purpose of the current antidepressant review was to appraise the evidence for the efficacy and safety of antidepressant medications for the management of depression and neuropsychiatric symptoms in the frail elderly, with and without dementia.

Antidepressants are used to treat a range of conditions, including anxiety, chronic pain, insomnia, depression, and neuropsychiatric symptoms of dementia (NPS). However, this review is limited to the use of antidepressants for depression and NPS because of their high prevalence in older adults with and without dementia, particularly those who reside in LTC.
Rationale for a focus on antidepressants

Antidepressants are commonly prescribed to older adults who are frail. For example, the Canadian Institute of Health Information report that antidepressants were the second most common medication used in long term care (LTC), after proton pump inhibitors, with 58% having one or more drug claims for an antidepressant and 36% using an SSRI.

Prevalence of depressive and neuropsychiatric symptoms in long term care

Depression and dementia are common conditions in LTC. In 2012, the Canadian Institute of Health Information, using data from the Residential Assessment Instrument Minimum Data Set (RAI MDS) 2.0, reported that among Canadian LTC residents, 44% had a diagnosis and/or symptoms of depression and 45% of those with dementia had a diagnosis and/or symptoms of depression. They also reported that antidepressant use was very common among residents diagnosed with depression and/or the symptoms of depression (79% and 39% respectively).

Hoover et al reviewed data from 634,060 LTC residents in the U.S. and found that:

- 54.4% of LTC residents had depression diagnosed over the first year; 32.8% at admission and a further 21.6% subsequently during the first year.

Both depression at admission and new depression over the first year rose over time, with 42.3% found to be depressed in 1999 versus 54.4% in 2005 at year one. The authors suggest that the increasing trend of diagnosing and treating depression in LTC may “reflect a spiraling trend of over-diagnosis of depression and treating with therapy while ignoring other depression treatment options.”

Neuropsychiatric Symptoms of Dementia

The neuropsychiatric symptoms (NPS) of dementia, also known as ‘behavioural and psychological symptoms of dementia’ (BPSD) or responsive behaviours, are common among the elderly in LTC and occur in 61 to 92% of individuals with dementia. NPS comprise a number of non-cognitive symptoms such as agitation, wandering, verbal and physical aggression, and sleep alterations. In 2014, the Canadian Institute of Health Information, using data from Prince Edwards Island, New Brunswick, Ontario, Manitoba, and British Columbia reported that among elderly in LTC:

- 39% had used at least one antipsychotic over the course of the previous year
- 22% were chronic users (two or more prescriptions over 180 days)
  - Nearly two-thirds of chronic antipsychotic users also used an antidepressant

The increasing awareness of the risks of antipsychotics in dementia have led to a modest, but significant decrease in their use, but it may be possible that clinicians are exploring antidepressants as an alternative to manage NPS.
The Symptoms of Depression, Dementia, Frailty and NPS

As there is no objective test to diagnose depression, we rely on symptoms and observations from patients, caregivers and family members. The diagnosis of depression in the elderly with advancing frailty and/or dementia is complicated by the overlap in symptoms among these conditions. For example, elderly with advancing frailty and/or dementia, often develop weight loss, reduced activity and other symptoms that may make them more likely to be diagnosed with depression, as described below.

Table 1. Similarities among the characteristics of depression, frailty, dementia and NPS

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</table>

*DSM-5 criteria: Requires that five or more of the symptoms have been present during the same two-week time frame and represent a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Additionally, symptoms cause clinically significant distress or impairment in functioning and are not attributable to the physiological effects of a substance or to another medical condition.

Frailty describes the health of older adults with physiologic deficits that increase vulnerability to adverse outcomes and compromises their ability to live independently. (15) Although there are several measures of frailty, one way to identify frailty is based on the Clinical Frailty Scale (CFS), which describes frailty as the accumulation of health issues that result in declining function, mobility, or cognition. (16) Accordingly, frailty manifests as dependency, but the etiology can be related to physical or cognitive disorders. Given the cognitive and functional deficits associated with dementia, there is a close correlation between frailty and dementia and individuals with dementia would be frail by definition. In fact, the CFS categories of frailty stage are meant to be concordant with dementia stage, so that an individual with moderate stage dementia will be moderately frail.

Current Guidelines for the Use of Antidepressants in Depression and NPS

The national guidelines for the assessment and treatment of mental health issues in long-term care homes from the Canadian Coalition for Seniors Mental Health (CCSMH) state that: (17)

* Treatment for residents with severe major depression should include an antidepressant. Residents with less severe depression should receive psychosocial interventions as a first step. If the depression persists, an antidepressant should be considered. [Grade A evidence]
The CCSMH guideline recommendation for behavioural symptoms related to the use of antidepressants states that: (17)

*Appropriate first-line pharmacologic treatment of residents with severe behavioural symptoms without psychotic features can include (a) atypical antipsychotics [Grade B evidence] and (b) antidepressants such as trazodone or selective serotonin reuptake inhibitors (e.g., citalopram or sertraline) [Grade C evidence].*

The guideline emphasizes that antipsychotics should only be used if there is marked risk, disability or suffering and that LTC homes should develop quality improvement initiatives to optimize prescribing of psychotropic medications. The guideline also suggests that clinicians may prefer to initially prescribe an SSRI, as serious adverse effects appear less likely than with antipsychotics, although an increased risk of injurious falls with SSRIs was acknowledged.

**Objectives and research questions**

This comprehensive document provides detailed results from the systematic reviews and meta-analyses of the evidence for the benefits and harms of antidepressants for depression with and without dementia and a complete narrative synthesis of the evidence of antidepressants for the neuropsychiatric symptoms of dementia.

**Clinical Questions**

1. What is the efficacy and safety of antidepressants for depression in frail older adults?
   a. What is the efficacy and safety of antidepressants for depression in adults ≥ 65 years with depression but without dementia, using age as a marker for potential frailty? What is the efficacy of antidepressants for depression in chronic conditions such as post-stroke, heart failure and Parkinson’s as a marker of frailty?
   b. After non-response to the first antidepressant, is there benefit to further pharmacotherapy?
2. What is the efficacy and safety of antidepressants for depression in the elderly with dementia?
3. What is the efficacy and safety of antidepressants for the neuropsychiatric symptoms in the elderly with dementia?

**Target Users**

The findings from this review are intended for physicians, pharmacists, nurses, and other healthcare professionals who care for the frail elderly to help them make evidence-informed decisions about prescribing antidepressants for their patients. This includes information on the characteristics of patients in the clinical studies for antidepressants, the expected levels of benefit, the relevancy of trial outcomes in frailty, adverse events related to antidepressant use and uncertainties in the evidence.
Methodology

A summary chart of the review process is organized by four phases below. The work was completed between June 2015 and April 2016.

Figure 1. Overview of review process

PHASE I (JUNE 2015-AUG 2015): DEFINE REVIEW
- Finalize team members, assign roles and tasks
- Generate and refine review questions (PICO-ST), study inclusion/exclusion criteria
- Meeting with project partners
- Collaboration with Canadian Agency for Drugs and Technology in Health (CADTH) to conduct rapid review based on clinical questions and inclusion/exclusion criteria

PHASE II (SEPT 2015 - DEC 2015): CRITICAL APPRAISAL
- Augment CADTH literature review
- Finalize data extraction tool
- Biweekly team meetings to review findings
- Meeting with statistician
- Meetings with project partners
- Two-day writing workshop
- Meeting with local Seniors Mental Health team (Jan 12 2016)

PHASE III (JAN 2016 - APRIL 2016): FINALIZE REVIEW
- Refine review, conduct appraisal of chronic conditions literature, augmentation/switching literature
- Biweekly team meetings to review findings
- Meetings with statistician (2)
- Finalize review document
- Two half-day writing workshops
- Develop decision aid template based on clinical question 2 and conduct evaluation

PHASE IV (MAY 2016 AND ONWARD): DISSEMINATION
- Meeting with project partners to discuss plans for dissemination
- Present review findings via physician/health professional education programs offered with Dalhousie University Continuing Professional Development (e.g., physician conferences, webinars, Community Hospital Program)
- Apply for funding for a large-scale multifaceted intervention and evaluation program for frailty-specific medication use the Maritimes.
Eligibility criteria for included studies

Table 2. Inclusion criteria for studies to address the three Clinical Questions

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Antidepressants for depression in frailty/chronic conditions</td>
<td>Age: Older adults (≥65 years of age) *include age range, mean age</td>
</tr>
<tr>
<td></td>
<td>Dementia: N/a</td>
</tr>
<tr>
<td></td>
<td>Depression: Diagnosed according to DSM criteria and or achieving pre-specified rating on depression scale.</td>
</tr>
<tr>
<td></td>
<td>Setting: LTC, outpatient clinics, community dwelling</td>
</tr>
<tr>
<td></td>
<td>Intervention: SSRIs, TCAs, SNRIs, NaSSAs</td>
</tr>
<tr>
<td></td>
<td>Comparison: Placebo (+/- counselling/support)</td>
</tr>
<tr>
<td></td>
<td>Outcomes: Change in scores on depression measure Response defined as ≥ 50% decrease in depression scores Remission defined as achieving pre-specified score on depression scale</td>
</tr>
<tr>
<td></td>
<td>Study design: DBRCT</td>
</tr>
<tr>
<td>Q2. Antidepressants for depression in dementia</td>
<td>Age: *No age criteria but studies must report age range, mean age</td>
</tr>
<tr>
<td></td>
<td>Dementia: Adults with probable or possible forms of dementia as per DSM-IV, NINCDS/ADRDA for probable Alzheimer’s disease. Most common criteria was MMSE ≥ 10 – 26.</td>
</tr>
<tr>
<td></td>
<td>Depression: Diagnosed according to DSM criteria and or achieving pre-specified rating on depression scale.</td>
</tr>
<tr>
<td></td>
<td>Setting: LTC, outpatient clinics, community dwelling</td>
</tr>
<tr>
<td></td>
<td>Intervention: SSRIs, TCAs, SNRIs, NaSSAs</td>
</tr>
<tr>
<td></td>
<td>Comparison: Placebo (+/- counselling/support)</td>
</tr>
<tr>
<td></td>
<td>Outcomes: Change in scores on depression measure Response defined as ≥ 50% decrease in depression scores Remission defined as achieving pre-specified score on depression scale</td>
</tr>
<tr>
<td></td>
<td>Study design: DBRCT</td>
</tr>
<tr>
<td>Q3. Antidepressants for NPS of dementia</td>
<td>Age: *No age criteria but studies must report age range, mean age</td>
</tr>
<tr>
<td></td>
<td>Dementia: Cognitive status assessed using scales such as the ADAS-cog, MMSE or NINCDS-ADRDA</td>
</tr>
<tr>
<td></td>
<td>Depression: n/a</td>
</tr>
<tr>
<td></td>
<td>Setting: LTC, outpatient clinics, community dwelling</td>
</tr>
<tr>
<td></td>
<td>Intervention: SSRIs, TCAs, SNRIs, NaSSAs</td>
</tr>
<tr>
<td></td>
<td>Comparison: Placebo or active comparator (+/- counselling/support)</td>
</tr>
<tr>
<td></td>
<td>Outcomes: Change in scores on neuropsychiatric scales</td>
</tr>
<tr>
<td></td>
<td>Study design: DBRCTs</td>
</tr>
</tbody>
</table>
Information sources
We searched PubMed, Cochrane Library, reference lists from meta-analyses and other relevant publications (hand searching).

Study selection
We read the study titles and abstracts to first screen studies for eligibility. We included studies in the meta-analysis that provided response data. See Table 1 above for a description of inclusion criteria for each clinical question.

Data extraction
We developed the data extraction tables in Microsoft Excel™ to collect data from individual studies. One member of the review team extracted data from each study into the data extraction Excel sheet. Another member of the team reviewed each study and checked for inaccuracies in data extraction and assessment of bias and quality of evidence. Inconsistencies were resolved by discussion. We collected information on citation, goal of study, design/year/setting; drug mean dose of those staying on medication; number of participants per study group; duration of the trial; risk of bias (see below); study withdrawals, inclusion and exclusion criteria; assessment procedures (e.g., psychiatrist evaluation using MADRS, not described); participants baseline demographics (e.g., age, gender, setting, MMSE scores, depression scores); statistical adjustments (e.g., baseline, marital status); study results on primary and secondary outcome measures; adverse events; serious adverse events; mortality; relevance to frailty; subgroup analyses; reviewer conclusions. We also included a section for categories on comments/interpretation/notes to capture reviewer interpretation of the trial.

Assessment of study quality and clinical relevance
We assessed study quality and the clinical relevance of the evidence using the following appraisal questions:

1. What is the quality of the evidence? (see further details under assessment of bias)
2. What is the applicability of the evidence to the frail elderly patient population?
3. What is the potential benefit and are the outcomes clinically relevant to those who are frail?
4. Is the timeframe appropriate to achieve benefit or to reliably evaluate adverse events?
5. What are the potential harms of antidepressants?

Assessment of bias
We assessed risk of bias in individual studies using the Cochrane risk of bias criteria, including random sequence generation, allocation concealment, blinding of participants and researchers, incompleteness of outcome data, selective reporting, and other bias.
In addition to the Cochrane risk of bias criteria, we evaluated the quality of the evidence using the criteria established by GRADE:

- High quality: Systematic reviews, well conducted RCTs
- Moderate quality: RCTs with important limitations
- Low quality: RCTs with multiple serious limitations

We also considered other indicators of study quality, including:

- Sample size
- Consistency of results
- Directness of evidence (applicability to frail elderly)
- Precision of results
- Appropriateness of statistical analysis methods
- Applicability of drug dose
- Duration of study/time to benefit

We provided an overall score for the quality of evidence using the following rubric as a guide:

- High: Rigorous RCTs
- Moderate: RCTs with important limitations such as small sample size
- Low: RCTs with multiple and/or serious limitations

We note that publication bias has been identified by others as a problematic source of bias in antidepressant clinical trials. For example, Turner et al found that the inclusion of unreported FDA antidepressants trials dropped the percentage of positive trials from 94% to 51%. (19)

**Synthesis of results**

For clinical questions 1 and 2 we conducted meta-analyses of response and remission rates to update existing meta-analyses (20, 21) with new studies and conduct sensitivity analyses without TCAs. For these analyses, we used Comprehensive Meta-Analysis v 1.2.064 and a random-effects model to calculate pooled effect sizes and confidence intervals. We used a random effects model for two reasons:

1. The published meta-analyses we reanalyzed and data from other studies also used random effects models.
2. The random effects model assumes that the studies included will differ from each other in ways that could influence the treatment effect, and takes into account differences between drugs used, study populations, duration, and depression scales. (22)
3. As suggested by Marx and Bucher we calculated NNH by applying the pooled estimate of relative risk to the pooled event rate in the placebo group. While this gives a general estimate of the NNHs, these values should be applied to individual patients with caution because that patient’s risk may be larger or smaller than the pooled event rates in the
placebo group in the studies. In addition, data on adverse events may be inconsistently reported among the studies. (23)

We set alpha for statistical significance at alpha level 0.05.

For clinical question 3, we conducted a narrative synthesis of the evidence which included a detailed appraisal of existing meta-analyses and high quality randomized controlled trials not included in the meta-analyses. We were unable to conduct an updated meta-analysis of the trials involving antidepressants for NPS due to variability in study outcomes.

**Determining summary statements**

Final recommendations were derived from team consensus regarding the meta-analytic findings in conjunction with the assessment of study quality and clinical relevance questions which addressed study quality, clinical relevance, potential benefits/harms, and the timeframe to benefit.
Question 1a. What is the efficacy and safety of antidepressants for depression in adults ≥ 65 years with depression but without dementia, (using age as a marker for potential frailty)?

SUMMARY

- We found no DBRCTs that evaluated the effect of antidepressants in frail older adults with depression but without dementia. Our review was limited to studies of adults ≥ 65 years with depression but without dementia (10 studies, N=2761).
- Patients in the studies we reviewed were somewhat younger and healthier than the frail elderly and had moderate to severe depression.
- Our primary analysis excluded TCAs because they are not recommended for the frail elderly. Antidepressants were associated with greater rates of response and remission but the results were not statistically significant benefit.
  - Response: 45% vs 38%; RR 1.17 (95% CI 0.97 – 1.38)  p=0.106
  - Remission: 33% vs 29%; RR 1.11 (95% CI 0.93 – 1.33)  p=0.267
- Including one study of imipramine led to a statistically significant benefit in response but had no effect on remission.
  - Response: 45% vs 39%; RR 1.20 (95% CI 1.00 – 1.42); p=0.045 NNT 13 (95% CI 6 – 658)
- The withdrawal rate for adverse events was higher with antidepressants than placebo.
  - 13% vs 5.8%; RR 2.30 (95% CI 1.46 – 3.62); NNH 13 (95% CI 7 – 37)
- Fatigue, nausea, constipation and dizziness were more frequent with antidepressants than placebo.
- Further review of antidepressants for depression in individuals with comorbid conditions that typically lead to frailty, such as post-stroke, Parkinson’s disease and heart failure, found no definitive evidence of efficacy.
- When thinking about prescribing antidepressants for depression in the frail elderly, clinicians should be aware of these considerations:
  - It may be difficult to differentiate the symptoms of depression from the physical decline of frailty.
  - Reflect on patient circumstances and carefully assess whether changes in mood are situational. Make a concerted effort to address situational factors that may be responsible for or contributing to symptoms.
  - Evidence for the efficacy of antidepressants is uncertain; there may be no therapeutic response. Patients started on antidepressants should be reassessed after 8 to 12 weeks and, if there is no response, the drug should be discontinued over 2 to 4 weeks.
  - Adverse events may be more frequent in the frail elderly than in the population in the studies we reviewed.
1. What is the quality of the evidence?

Results of literature search

- The literature search did not identify any studies that address the benefits of treating depression with antidepressants for frail older adults without dementia. Therefore, we reviewed the evidence from studies that enrolled a younger, healthier population and examined whether the evidence could be applied to those who are frail.

- The following search trial characteristics were used as inclusion criteria:
  - Patient age of ≥ 65 years
  - Outcomes included response and remission rates.
  - Duration of therapy ≥ 4 weeks.
  - Parallel design. (not crossover studies)
  - Double blind randomized trials that compared active treatment to placebo. Open label trials and those that compared two or more drugs without a placebo arm were excluded.

- The search revealed two recent meta-analyses that address the use of antidepressants for depression in older patients:
  - Kok 2012(24) focused on patients ≥ 55 years old, but did not report separately on those ≥ 65 years old; therefore this publication was excluded.
  - Tedeschini 2011 (21) focused on patients ≥ 55 years old, and reported separately on those ≥ 65 years old. Six studies (N=1840) included only patients ≥ 65 years old. (25–30) These same six studies were included in the Kok meta-analysis.
    - Table 1 summarizes the 6 relevant studies from the Tedeschini meta-analysis.

- The literature search identified four additional studies. (31–34) Two of the four studies were published at the time of the Tedeschini meta-analysis, but were not included for unknown reasons. (32,34)
  - Table 2 summarizes the four additional studies.

- In total, ten placebo-controlled DBRCTs were identified for analysis (N=2761).

- The data-set from the Tedeschini meta-analysis was expanded by adding results from the four additional studies.

- The ten studies were critically appraised using the Cochrane risk of bias criteria and were of variable quality. Study quality is indicated in Tables 1 and 2.
  - Generally, blinding and allocation concealment were inadequately described.
  - Eight studies were 8 weeks in duration, one was 10 weeks, and one was 12 weeks with a 24-week extension.
  - Six of the ten studies used an intention-to-treat analysis (ITT), (25,27–31) while the other four stated they used an ITT analysis that was not borne out by close analysis of the numbers of subjects included in the results.
  - Eight of the ten studies had over 100 subjects and two studies were small (fewer than 100 subjects).
- No studies adjusted p-values for multiple comparisons.
  - There were moderate to high levels of heterogeneity ($I^2$) for most outcomes, including remission, response, and adverse effects. $I^2$ was 72% for response and 57% for remission.
  - All studies, except one small study from Brazil (32), were funded by industry and five of the ten studies were either carried out by industry or included industry employees in the list of authors.
Table 3. Studies of patients ≥ 65 years included in the Tedeschini meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Daily dose</th>
<th>Duration (wks)</th>
<th>N</th>
<th>Mean Age</th>
<th>Quality</th>
<th>Funding</th>
<th>Scale</th>
<th>Primary outcome</th>
<th>Stat sig benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer</td>
<td>1998</td>
<td>Imipramine</td>
<td>50-100 mg</td>
<td>8 + 44 extension</td>
<td>120</td>
<td>72</td>
<td>Moderate</td>
<td>Industry</td>
<td>HDRS-17 CGI-S CGI-I</td>
<td>Change from baseline Response/remission</td>
<td>Yes</td>
</tr>
<tr>
<td>Raskin</td>
<td>2008</td>
<td>Duloxetine</td>
<td>60 mg</td>
<td>8</td>
<td>311</td>
<td>73</td>
<td>Low</td>
<td>Industry</td>
<td>GDS, HDRS, CGI-S</td>
<td>Change from baseline Response/remission</td>
<td>Yes</td>
</tr>
<tr>
<td>Kasper</td>
<td>2005</td>
<td>Escitalopram</td>
<td>10 mg</td>
<td>8</td>
<td>517</td>
<td>75</td>
<td>Moderate</td>
<td>Industry</td>
<td>HDRS-17 CGI-S CGI-I</td>
<td>Change from baseline Response/remission</td>
<td>No</td>
</tr>
<tr>
<td>Roose</td>
<td>2004</td>
<td>Citaloprine</td>
<td>10-20 mg</td>
<td>8</td>
<td>174</td>
<td>80</td>
<td>High</td>
<td>Industry</td>
<td>HDRS</td>
<td>Response/remission</td>
<td>No</td>
</tr>
<tr>
<td>Schatzberg</td>
<td>2006</td>
<td>Fluoxetine</td>
<td>40 or 60 mg</td>
<td>8</td>
<td>300</td>
<td>71</td>
<td>High</td>
<td>Industry</td>
<td>HDRS-21</td>
<td>Change from baseline Response/remission</td>
<td>No</td>
</tr>
<tr>
<td>Hewett</td>
<td>2010</td>
<td>Bupropion</td>
<td>150-300 mg</td>
<td>10</td>
<td>418</td>
<td>71</td>
<td>Low</td>
<td>Industry</td>
<td>HDRS</td>
<td>Change from baseline Inconsistent</td>
<td></td>
</tr>
</tbody>
</table>

* Quality based on Cochrane risk of bias criteria
* Primary outcome was four cognitive tests - Verbal Learning and Recall Test; Symbol Digit Substitution Test; Two-Digit Cancellation Test; Letter-Number Sequencing Test. Secondary outcomes were measures of depression and pain, which included the Geriatric Depression Scale; HDRS (HDRS) Visual Analogue Scale for pain; and Clinical Global Impression severity scale.
* Industry employees were among study authors
* The pre-specified ANCOVA analysis was not statistically significant (p=0.085). Post-hoc rank-based ANCOVA analysis was statistically significant (p=0.033). Response was statistically significant (p=0.014), but remission was not statistically significant (p=0.167).

Table 4. Studies of patients ≥ 65 years not included in the Tedeschini meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Daily dose</th>
<th>Duration (wks.)</th>
<th>N</th>
<th>Mean Age</th>
<th>Quality</th>
<th>Funding</th>
<th>Scale</th>
<th>Primary outcome</th>
<th>Stat sig benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katona</td>
<td>2012</td>
<td>Duloxetine</td>
<td>60 mg</td>
<td>8</td>
<td>452</td>
<td>71</td>
<td>High</td>
<td>Industry</td>
<td>HDRS-24</td>
<td>Change from baseline</td>
<td>Yes</td>
</tr>
<tr>
<td>Fraguas</td>
<td>2009</td>
<td>Citalopram</td>
<td>20-40 mg</td>
<td>8</td>
<td>37</td>
<td>74</td>
<td>Low</td>
<td>Public</td>
<td>HDRS-17</td>
<td>Response</td>
<td>No</td>
</tr>
<tr>
<td>Robinson</td>
<td>2014</td>
<td>Duloxetine</td>
<td>60 mg</td>
<td>12 + 24 extension</td>
<td>370</td>
<td>73</td>
<td>Low</td>
<td>Industry</td>
<td>HDRS-17 Maier subscale</td>
<td>Change from baseline</td>
<td>No</td>
</tr>
<tr>
<td>Evans</td>
<td>1997</td>
<td>Fluoxetine</td>
<td>20 mg</td>
<td>8</td>
<td>62</td>
<td>82</td>
<td>Low</td>
<td>Industry</td>
<td>HDRS-17</td>
<td>Response</td>
<td>No</td>
</tr>
</tbody>
</table>

* Patients had heart failure
* Industry employees were among study authors
2. What is the applicability of the evidence to the frail elderly patient population?

Patient Characteristics

- Frail older adults are almost always excluded from large-scale clinical trials, (35) which generates uncertainty about the applicability of trial conclusions in advanced frailty. Since frailty is highly associated with age,(36,37) we evaluated studies that included older adults to better understand their response to antidepressants. We also considered the characteristics of subjects enrolled in trials and how these subjects compare to those who are frail.

- The six relevant publications from the Tedeschini meta-analysis and the four additional trials generally used the following inclusion/exclusion criteria:
  - Diagnosis of Major Depressive Disorder (MDD) according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III, DSM-III Revised, DSM-IV, Research Diagnostic Criteria, or Feighner Diagnostic Criteria.
  - Excluded patients with treatment resistant depression or other depressive disorders, including bipolar disorder, depression with psychotic features, dysthymic disorder, neurotic depression, or minor depression.
  - Excluded MDD in patients with comorbid alcohol disorders, substance abuse disorders, or a specific comorbid medical condition; thus, the patients in these studies may not be representative of the frail, who typically have multiple co-morbid medical conditions.
  - Used the Hamilton Depression Rating Scale (HDRS), Montgomery–Åsberg Depression Rating Scale (MADRS), or Clinical Global Impression (CGI-I) as outcome measures.

- Patients were, on average, healthier and younger than those who are frail.
  - In particular, patients with dementia, a key indicator of frailty, were excluded in 7 of 10 studies. Due to the variable response to those with dementia compared to those without dementia, the efficacy and harms of antidepressants for those with concomitant depression and dementia was reviewed separately (Clinical Question 2).
  - The frail elderly are usually much older than 65 years of age.
    - One study, Roose 2008 (28) included only patients ≥ 75 years old. The inclusion age for the other studies was ≥ 65 years. The range of mean ages in the studies was 71 to 82 years with 8 studies in the low 70s as per table 1 and 2.
  - Eight of ten studies excluded patients with unstable medical conditions and other psychiatric syndromes.
  - Two studies allowed inclusion of patients with concomitant medical conditions, which may more closely represent our population of interest, frail older adults.
    - Fraguas et al studied patients with stable heart failure. (32)
    - Evans et al included patients with other medical conditions. Most patients had least one acute and one or more chronic health problem including cognitive impairment.(34)
Eight of ten studies excluded patients at risk for suicide. The range of mean ages in the studies was 69 to 82 years as per tables 1 and 2. Most studies included outpatients only, although this was not always specified. One study, Evans 1997, enrolled only inpatients admitted under the care of a geriatrician or family physician. (34)

Baseline depression scores were as follows:
- HDRS-17: 16 to 23 (moderate to severe depression)
- MADRS: 21 to 30 (moderate depression)
- GDS: 17 to 18 (mild depression). Used in two studies that also had baseline scores of 19 on HDRS-17 indicating severe depression (26,33)

Bottom Line:
- Patients in the studies we reviewed were somewhat younger and healthier than the frail elderly and had moderate to severe depression.

3. What is the potential benefit from treatment? Are the outcomes clinically relevant to those who are frail?

Results
- The outcomes in the Tedeschini meta-analysis included response rates, defined as a 50% or greater decrease in depression scores or a CGI-I ≤ 2 at the final visit, which indicate improvement in symptoms rated as “better” or “much better.” Remission rates were not reported.
- The Tedeschni meta-analysis reported results in several age sub-groups:
  - Older late-life (≥ 65 years): RR 1.13 (95% CI 0.93 – 1.37) p 0.27.
  - Adult (55 to 64 years): RR 1.42 (95% CI 1.35-1.49) p<0.001.
  - Late-life (≥ 55 years): RR 1.30 (95%CI 1.15-1.48) p<0.001.
    - The six studies of the older late life population (≥ 65 years) did not show a statistically significant benefit in response from treatment with antidepressants.
    - This result was significantly different from the response demonstrated in adults 55 to 64 years of age and in those ≥ 55 years (the full study population), where there was benefit.

Statistical Analysis of 10 relevant studies
- We conducted a meta-analysis to calculate the remission and response rates using data from the 10 relevant trials.
- We validated our statistical methods by replicating the Tedischeini meta-analysis (N=6 studies, N=1836 subjects). The publication did not provide numbers of events and we did not receive a response to our request for this data. Therefore, our meta-analysis
sometimes required an estimation of numbers of responders from figures and percentages. Our calculated estimate of the relative risk of response was almost identical to the relative risk published in the Tedeschini meta-analysis.

- Tedeschi: RR 1.13 (95% CI 0.93–1.37) p 0.27
- Calculated estimate: RR 1.13 (95% CI 0.94–1.27) p 0.21

➢ To align with the Tedeschini meta-analysis, response was defined as a 50% or greater decrease in depression scores or a CGI-I ≤ 2.

➢ Remission was scored using the definition in the included studies:
  - HDRS-24 score ≤ 10
  - HDRS-17 score ≤ 7
  - MADRS score ≤ 11 or ≤ 12 (see Clinical Question#3 for a description of the scales)
    ▪ For both response and remission, if more than one scale was reported, we gave priority to the HDRS data to maintain consistency with the Tedeschini meta-analysis.

➢ The results of our meta-analysis of the 10 studies are statistically significant for response, but not remission.

<table>
<thead>
<tr>
<th>N Studies</th>
<th>N Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response: RR 1.20 (1.00–1.42) p 0.045</td>
<td>10 2670</td>
</tr>
</tbody>
</table>
  ▪ Number needed to treat 13 (95% CI 6–658). The wide confidence intervals indicate the imprecision for this result.
| Remission: RR 1.12 (0.93–1.33) p 0.267 | 8 2348 |

➢ The Schweizer study used imipramine, a tricyclic antidepressant (TCA). (25) Given the widespread caution against using TCAs for older adults, (3,4,38) it may be clinically relevant to exclude this trial from the meta-analysis. First, TCA’s have different pharmacology from other antidepressants. In addition, they are associated with adverse events that may be problematic in frailty as reflected in current guidelines, such as the Beers criteria and STOPP/START criteria. (3,4,38)

➢ As the Schweizer study did not report on remission, excluding this data changes only the results for response, which no longer showed statistically significant benefit.

<table>
<thead>
<tr>
<th>N Studies</th>
<th>N Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response: RR 1.16 (0.97–1.38) p 0.106</td>
<td>9 2550</td>
</tr>
</tbody>
</table>

➢ Consideration of mean change in depression score from baseline, rather than percent of patients who responded or who achieved remission, does not change the overall picture. The studies that showed a positive result in response or remission also showed a positive result in mean change from baseline score. Similarly, negative studies were negative in all analyses.

➢ There is inconclusive evidence for benefit in a population over 65 years of age.
For response, there was statistically significant benefit if one study of imipramine is included but not statistically significant if this study is excluded. (25)

For remission, there was no statistically significant benefit of second generation antidepressants; the imipramine study did not report remission. (25)

Placebo was associated with high rates of response and remission, 38% and 29% of patients respectively.

Table 7 and Figures 1 and 2 summarize the results of the meta-analysis for response and remission.

Results of studies that included patients with concomitant medical conditions

- Two studies allowed inclusion of patients with concomitant medical conditions. (32,34) Both studies showed no statistically significant benefit from treatment with antidepressants. This finding might be significant to our review, as the patients in this study may more closely represent our population of interest, frail older adults.
Figure 2. Outcome: Response. Treatment effects of second-generation antidepressants vs placebo for older adults (≥ 65 years)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Antidepressant</th>
<th>Placebo</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin 2007 DUL</td>
<td></td>
<td>1.985</td>
<td>1.291</td>
<td>3.052</td>
<td>0.002</td>
<td>79 / 207</td>
<td>20 / 104</td>
<td>7.6</td>
</tr>
<tr>
<td>Kasper 2000 ESC</td>
<td></td>
<td>0.979</td>
<td>0.784</td>
<td>1.224</td>
<td>0.854</td>
<td>80 / 173</td>
<td>85 / 180</td>
<td>11.4</td>
</tr>
<tr>
<td>Kasper 2000 FLU</td>
<td></td>
<td>0.788</td>
<td>0.612</td>
<td>1.013</td>
<td>0.063</td>
<td>61 / 164</td>
<td>85 / 180</td>
<td>10.8</td>
</tr>
<tr>
<td>Roose 2004 CIT</td>
<td></td>
<td>1.071</td>
<td>0.739</td>
<td>1.553</td>
<td>0.715</td>
<td>34 / 84</td>
<td>34 / 90</td>
<td>8.6</td>
</tr>
<tr>
<td>Schatzberg 2006 VEN</td>
<td></td>
<td>1.062</td>
<td>0.771</td>
<td>1.462</td>
<td>0.715</td>
<td>46 / 104</td>
<td>40 / 96</td>
<td>9.5</td>
</tr>
<tr>
<td>Schatzberg 2006 FLU</td>
<td></td>
<td>0.912</td>
<td>0.646</td>
<td>1.287</td>
<td>0.600</td>
<td>38 / 100</td>
<td>40 / 96</td>
<td>9.1</td>
</tr>
<tr>
<td>Hewett 2010 BUP</td>
<td></td>
<td>1.225</td>
<td>1.000</td>
<td>1.501</td>
<td>0.050</td>
<td>111 / 210</td>
<td>88 / 204</td>
<td>11.7</td>
</tr>
<tr>
<td>Katona 2012 DUL</td>
<td></td>
<td>1.751</td>
<td>1.358</td>
<td>2.258</td>
<td>0.000</td>
<td>93 / 151</td>
<td>51 / 145</td>
<td>10.8</td>
</tr>
<tr>
<td>Fraguas 2009 CIT</td>
<td></td>
<td>1.368</td>
<td>0.786</td>
<td>2.381</td>
<td>0.267</td>
<td>13 / 19</td>
<td>9 / 18</td>
<td>5.9</td>
</tr>
<tr>
<td>Robinson 2014 DUL</td>
<td></td>
<td>0.911</td>
<td>0.703</td>
<td>1.180</td>
<td>0.481</td>
<td>90 / 204</td>
<td>46 / 95</td>
<td>10.7</td>
</tr>
<tr>
<td>Evans 1997 FLU</td>
<td></td>
<td>1.929</td>
<td>0.909</td>
<td>4.096</td>
<td>0.087</td>
<td>14 / 39</td>
<td>8 / 43</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.157</td>
<td>0.970</td>
<td>1.380</td>
<td>0.105</td>
<td>659 / 1455</td>
<td>506 / 1251</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BUP buproprion; CIT citalopram; DUL duloxetine; ESC escitalopram; FLU fluoxetine; VEN venlafaxine
The plot demonstrates no overall statistically significant benefit for antidepressants over placebo.
Figure 3. Outcome: Remission. Treatment effects of second-generation antidepressants vs placebo for older adults (≥ 65 years)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Remitters / Total</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Raskin 2007 DUL</td>
<td>1.842</td>
<td>1.095</td>
<td>3.099</td>
</tr>
<tr>
<td>Kasper 2000 ESC</td>
<td>0.945</td>
<td>0.735</td>
<td>1.213</td>
</tr>
<tr>
<td>Kasper 2000 FLU</td>
<td>0.708</td>
<td>0.529</td>
<td>0.946</td>
</tr>
<tr>
<td>Roose 2004 CIT</td>
<td>1.036</td>
<td>0.684</td>
<td>1.568</td>
</tr>
<tr>
<td>Schatzberg 2006 VEN</td>
<td>1.124</td>
<td>0.698</td>
<td>1.810</td>
</tr>
<tr>
<td>Schatzberg 2006 FLU</td>
<td>0.835</td>
<td>0.491</td>
<td>1.418</td>
</tr>
<tr>
<td>Hewett 2010 BUP</td>
<td>1.160</td>
<td>0.893</td>
<td>1.506</td>
</tr>
<tr>
<td>Katona 2012 DUL</td>
<td>1.749</td>
<td>1.172</td>
<td>2.611</td>
</tr>
<tr>
<td>Fragas 2009 CIT</td>
<td>1.368</td>
<td>0.786</td>
<td>2.381</td>
</tr>
<tr>
<td>Robinson 2014 DUL</td>
<td>1.127</td>
<td>0.802</td>
<td>1.584</td>
</tr>
</tbody>
</table>

0.1 0.2 0.5 1 2 5 10

BUP buproprion; CIT citalopram; DUL duloxetine; ESC escitalopram; FLU fluoxetine; VEN venlafaxine
The plot demonstrates no overall statistically significant benefit for antidepressants over placebo.
Relevance of outcomes

The gold standard for describing and diagnosing depression is the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM), therefore the scales used to diagnose depression should reflect the criteria defined in DSM. We examined the HDRS, MADRS and GDI and found their questions did reflect DSM-IV criteria with the exception that the GDS does not include questions about suicidal ideation and reduced sleep and appetite.

- It may be difficult to differentiate depression from the common manifestations of frailty, as some DSM-5 criteria overlap with the common manifestations of frailty, including depressed mood, irritability, decreased interest or pleasure, appetite/weight change, change in activity, fatigue/loss of energy, diminished concentration, and change in sleep.
  - Frailty is associated with significant losses in independence, function, cognition, and mobility, which commonly results in feelings of sadness and loss. In addition, older age is frequently associated with other difficult circumstances, such as the loss of a spouse or changes in financial security, all of which can lead to feelings of despondency.
    - It is reasonable to question whether these types of life challenges will respond to pharmacotherapy.
  - For example, heart failure may cause decreased energy or fatigue, trouble sleeping, social isolation and thoughts of death.
  - As such, it may be difficult to determine if the symptoms included on screening tools accurately differentiate depression from frailty. This is not to say that a major depressive disorder cannot co-exist with frailty, but the overlap in symptoms may make it difficult to differentiate the two conditions.
  - It is possible that the lack of response to antidepressants in studies of older adults is because the depression scales are identifying aspects of health that may not be related to depression.
  - Second, the physical challenges of frailty may mimic symptoms of depression. For example, heart failure may cause decreased energy or fatigue, trouble sleeping, social isolation, and thoughts of death.
  - This is not to say that a major depressive disorder cannot co-exist with frailty, however, the overlap in symptoms may make them difficult to differentiate.

Depression scales used to assess initial severity of depression and response to therapy

- The scales used to rate depression in the studies reviewed include:
  - Hamilton Depression Rating Scale (HRDS or HDRS or HAMD)
    - The original scale had 21 items, but only the first 17 items are scored because the additional items do not affect severity.
    - Some studies use total scores on all 21 items and some add 3 extra questions.
    - Scoring 17 items:
<table>
<thead>
<tr>
<th>Normal</th>
<th>0 – 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild depression</td>
<td>8 – 13</td>
</tr>
<tr>
<td>Moderate depression</td>
<td>14 – 18</td>
</tr>
<tr>
<td>Severe depression</td>
<td>19 – 22</td>
</tr>
<tr>
<td>Very severe depression</td>
<td>&gt; 23</td>
</tr>
</tbody>
</table>

- **Montgomery–Åsberg Depression Rating Scale (MADRS)**
  - 10 questions scored 0 – 6; maximum score 60
    | Normal | 0 – 6 |
    |-------|-------|
    | Mild depression | 8 – 19 |
    | Moderate depression | 20 – 34 |
    | Severe depression | >34 |

- **Geriatric Depression Scale (GDS)**
  - Does not address suicidality, appetite loss, or sleep disturbances.
  - Thirty questions answered yes/no; maximum score 30. There is also short 15-question version. On the 30 question version:
    | Normal | 0 – 9 |
    |-------|-------|
    | Mild depression | 10 – 19 |
    | Severe depression | 20 – 30 |

The bottom line:
- It may be difficult to differentiate the symptoms of depression from the physical decline of frailty. As such, the depression scales included in the trials may not be clinically relevant to those who are frail.
- Meta-analysis results show a statistically significant benefit in response not remission if a study of imipramine is included; however excluding this study (as TCAs are seldom prescribed in the frail elderly) yields a non-significant result. In either case, the potential benefit from antidepressants is modest.

4. Is the timeframe appropriate to achieve benefit or for adverse events to appear?
- Major depression should be treated with antidepressants for 6 to 12 weeks before deciding whether a regimen is beneficial. (39) The majority of studies included were 8 to 10 weeks in length so the timeframe to achieve benefits is reasonable. Raskin (duloxetine) showed benefit in the CGIS at 2 weeks and the HDRS at 4 weeks. Katona (duloxetine) showed benefit at 6 weeks and Hewett (bupropriion) showed benefit at 8 weeks. (31)
In reference to the frail elderly, the 10 studies are of short duration. Many patients use antidepressant medications for an extended period. The studies do not address questions about the sustainability of response and the likelihood of developing adverse effects as frailty increases over time. In the one study that reported adverse events at 12 and 24 weeks, (33) falls were more frequent with duloxetine vs placebo in the continuation phase (24% vs 14% p = 0.04), but not in the first 12 weeks (16% vs 10% p = 0.15). There was no statistically significant difference in orthostatic hypotension between treatment and placebo at either 12 or 24 weeks.

5. What are the potential harms from antidepressants?

- There is inconsistency between studies as to the adverse events reported. To obtain an overall estimate of common adverse events, we combined those that were most frequently reported in a meta-analysis.
- The primary analysis included only studies that provided data on second-generation antidepressants. One study (N=120) compared imipramine, a TCA, to placebo (25) and we conducted a sensitivity analysis in which we included this study.
- Seven studies (N = 2384 subjects) recorded withdrawals due to adverse events, which occurred more frequently with antidepressants compared to placebo (13% vs 5.8%, p 0.0001, NNH 13 (95% CI 7 – 37)).
- Fatigue, nausea, constipation, and dizziness were all reported more frequently in the antidepressant group (Table 7).
- The most commonly reported adverse event in the antidepressant group was nausea. Event rates for nausea with medication and placebo were 14% and 6.8%, p = 0.001, NNH 12 (95% CI 5 – 35).
- Adverse events reported were generally minor and would be expected to reverse upon discontinuation of the medication.
- It is important to consider serious adverse events related to antidepressants. One study, Kasper 2005 (27) reported there were no instances of hyponatremia in either study group, which is a known adverse effect of SSRIs. No studies reported information on QTc prolongation, however, Robinson reported there were no electrocardiographic changes in either study group.

Sensitivity analysis

- Dry mouth was the only outcome substantially affected by the sensitivity analysis in which the data from the study of imipramine were included.
  - The rate of dry mouth in the drug group increased from 9.4% to 13.9% while the rate in the placebo group increased from 5.6% to 6.1%. The relative risk increased from 1.63 to 1.83 and this increase was statistically significant (RR 1.83, 95% CI 0.99 – 3.36; p=0.05).
Long-term adverse events

- The studies reviewed so far are of short duration and provide data on short term adverse effects of antidepressants. Since there don’t appear to be long-term RCTs, we must turn to observational studies for long term effects. We have not conducted a thorough review of such observational studies but a recent retrospective cohort study conducted by Coupland et al. in 2011 does provide some information. (40)

- Using data from the QResearch primary care database in the UK, this study followed 60,746 patients over 65 with depression for a mean of 5.0 years (305,188 person-years). The study compared several clinical outcomes for patients not treated with antidepressants with those treated with TCAs, SSRIs or other antidepressants. The median duration of treatment with antidepressants was 364 days (interquartile range 91-1029).

- After adjusting for numerous factors SSRIs were associated with greater rates of several outcomes compared to TCAs. (Table 3)

Table 5. Adverse events associated with SSRIs (Coupland et al.)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.32</td>
<td>1.26 to 1.39</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>1.15</td>
<td>1.05 to 1.26</td>
</tr>
<tr>
<td>Falls</td>
<td>1.27</td>
<td>1.20 to 1.35</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.26</td>
<td>1.15 to 1.37</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.80</td>
<td>1.32 to 1.37</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1.44</td>
<td>1.19 to 1.75</td>
</tr>
</tbody>
</table>

- Some of these outcomes were more frequent with all classes of antidepressants compared to no antidepressant.

Table 6. Comparison of adverse events associated TCAs and SSRIs versus no antidepressant (Coupland et al.)

<table>
<thead>
<tr>
<th></th>
<th>No Antidepressant</th>
<th>TCA</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7.04</td>
<td>8.12</td>
<td>10.61</td>
</tr>
<tr>
<td>Falls</td>
<td>3.46</td>
<td>4.49</td>
<td>5.67</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.76</td>
<td>2.18</td>
<td>2.74</td>
</tr>
</tbody>
</table>

- Thirty-two percent of prescriptions were for TCAs. However they were prescribed at lower than usual doses (70% of prescriptions were for ≤ 0.5 defined daily dose).

- The outcomes reported in this study are different from those reported in short term studies in that they are clinical outcomes rather than symptomatic ones.
This study suggests that for these clinical outcomes, SSRIs may not be associated with fewer events than TCAs.

Questions and uncertainties

Several areas of uncertainty remain after this review. For instance, is there any difference in efficacy depending on:

- Duration of depression. Four studies reported the duration of depression upon study entrance, and the shortest duration reported was 34 weeks. (Table 5)

<table>
<thead>
<tr>
<th>Study benefit</th>
<th>Antidepressants</th>
<th>Duration of depression</th>
<th>Statistically significant benefit?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schatzberg (^{30})</td>
<td>Venlafaxine, fluoxetine</td>
<td>198 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Raskin (^{28})</td>
<td>Duloxetine</td>
<td>~56 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Katona (^{34})</td>
<td>Duloxetine</td>
<td>34 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Evans (^{33})</td>
<td>Fluoxetine</td>
<td>~50% longer than 12 months</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- History of recurrent depression
  - There was inconsistent evidence, summarized in the table below, to determine if a history of recurrent depression was related to outcomes. (Table 6)

<table>
<thead>
<tr>
<th>Study</th>
<th>Antidepressants</th>
<th>History of Recurrent depression</th>
<th>Sign.benefit?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hewett (^{26})</td>
<td>Bupropion</td>
<td>67% had prior episodes of MDD, mean number ~3.5</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Raskin (^{28})</td>
<td>Duloxetine</td>
<td>Mean no. prior episodes = 5</td>
<td>Yes</td>
</tr>
<tr>
<td>Robinson (^{43})</td>
<td>Duloxetine</td>
<td>All subjects had recurrent MDD (inclusion criteria)</td>
<td>No</td>
</tr>
<tr>
<td>Roose (^{29})</td>
<td>Citalopram</td>
<td>Recurrent unipolar depression, avg. 1(^{st}) episode was 11 years prior</td>
<td>No</td>
</tr>
</tbody>
</table>

- Baseline severity of depression
  - Based on the mean scores on the depression scales used in the studies included in our analysis, the patients had moderate to severe depression.
A systematic review (42) addressing this question found that although the response of both drug and placebo groups in “late-life” depression was greater with more severe baseline depression, there was no overall difference between the groups. In contrast, a meta-regression found that the higher the baseline severity of depression, the greater the antidepressant efficacy. (41)

Another area of uncertainty is the high level of heterogeneity found in our analysis. This may be related to different scales used, different patient populations, different methods of assessment, different levels of non-pharmacologic support provided during the study or other factors.

Summary of findings

We were interested in learning about how people who are frail (but without dementia) respond to antidepressants. As is typical of most studies, frail patients were underrepresented in these studies and so we reviewed studies of the elderly, which we defined as ≥ 65 years.

- The population of patients enrolled in the studies were generally in their 70s, non-frail with moderate to severe depression.

There is uncertain evidence regarding the efficacy of first line pharmacotherapy with antidepressants for the treatment of depression in the elderly. The majority of studies reviewed do not show a statistically significant benefit.

- Of the two studies that showed benefit, one was high quality (31) and the other was of low quality, which considered response only as a secondary outcome. (26)

- All other studies demonstrated inconsistent (30) or negative results. (27–29,32–34)

Two studies were high quality (28,29) one was moderate quality (27) and three were low quality. (32–34)

Meta-analysis results show a statistically significant benefit in response not remission if a study of imipramine is included; however excluding this study (as TCAs are seldom prescribed in the frail elderly) yields a non-significant result. In either case, the potential benefit from antidepressants is modest.

When thinking about prescribing antidepressants for depression in the frail elderly, clinicians should be aware of these considerations:

- It may be difficult to differentiate the symptoms of depression from the physical decline of frailty.

- Reflect on patient circumstances and carefully assess whether changes in mood are situational. Make a concerted effort to address situational factors that may be responsible for or contributing to symptoms.

- Evidence for the efficacy of antidepressants is uncertain; there may be no therapeutic response. Patients started on antidepressants should be reassessed after 8 to 12 weeks and, if there is no response, the drug should be discontinued over 2 to 4 weeks.
• Adverse events may be more frequent in the frail elderly than in the population in the studies we reviewed.

- Patients under 65 years of age show more significant benefit for treatment with antidepressants compared to those who are older than 65. The overall evidence for benefit in previous reviews of patients with late-life depression may be powered by results from younger healthier patients.

- Thirteen percent of subjects over age 65 on monotherapy withdrew because of adverse events (NNH=16). Nausea was the most frequently reported adverse event (NNH=11).

- Both placebo and treatment groups improve with time. As such, when patients treated with antidepressants have a reduction in symptoms, we cannot reliably conclude that this is a result of the medication.

- There could be risks associated with under treatment of depression. Notably, most studies reviewed excluded patients at risk of suicide.

- There are several unanswered questions that need attention.
  - Were the results of studies negative due to lack of power?
  - Advancing age is associated with an increasing risk of frailty (43), however none of the studies reviewed involved frail older adults. Therefore, we also reviewed the evidence for antidepressants for depression with co-morbid conditions that impair cognition, function or mobility as surrogate markers of frailty. We found a similar lack of effect for the use of antidepressants over placebo for depression in heart failure, stroke and Parkinson’s Disease.

- In summary, the population of elderly subjects enrolled in studies did not appear to be frail. As such, although the evidence suggests declining benefit of antidepressants for older adults above age 65, the efficacy of antidepressants for frail elderly individuals with depression is uncertain. The evidence, thus, does not exclude the possibility of benefit or non-benefit, but it is reasonable to contemplate the special circumstances of frailty, as follows:
  - First, frailty is associated with significant losses in independence, function, cognition, and mobility. In addition, older age is frequently associated with other difficult circumstances, such as the loss of a spouse or changes in financial security, all of which can lead to feelings of despondency. It is reasonable to question whether these types of life challenges will respond to pharmacotherapy.
  - Second, the physical challenges of frailty may mimic symptoms of depression. For example, heart failure may cause decreased energy, trouble sleeping and thoughts of death. Illnesses that cause fatigue may make it more difficult to leave the house to socialize, which can be considered a manifestation of frailty, when in fact it may be due to physical limitations.
  - Finally, frail patients are at greater risk of experiencing medication adverse events.
Discussion

- Many commentaries highlight the notion that late-life depression is underdiagnosed and inadequately treated. (44) Our results call attention to another possibility— that depression may well be over treated with pharmacotherapy. Accordingly, for frail, older adults, we recommend the following:
  - Reflect on patient circumstances and carefully assess whether changes in mood are situational. Make a concerted effort to address situational factors that may be responsible for or contributing to symptoms.
  - Antidepressants should be used judiciously, with awareness that there is limited evidence for their efficacy. If antidepressants are trialed, adequate dose and treatment time should be assured before making a conclusion about efficacy. On the other hand, continuation of antidepressants past therapeutic indication contributes to polypharmacy.
- Despite this recommendation, we recognize that there are likely varied responses and patient populations and, as such, antidepressants may be beneficial for some older adults who are frail.
- When treatment is initiated, provide careful and ongoing follow up to assess treatment response, with the aim of stopping medications when no benefit is observed. Stopping medications should be done carefully, typically over a period of four weeks.
- Long-term use of antidepressants should be regularly re-evaluated.
- This review also raises a call to action for experts in the field to consider further criteria that could identify symptoms that will respond to pharmacotherapy and to help prescribers better understand the available evidence.
Table 9. Random effects meta-analysis of efficacy and safety outcomes for studies comparing second-generation antidepressants to placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number studies/subjects</th>
<th>Event Rate (%)</th>
<th>Relative Risk</th>
<th>NNT/NNH for 8-12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ADX</td>
<td>Placebo</td>
<td>RR</td>
</tr>
<tr>
<td><strong>Efficacy Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 / 2550</td>
<td>45</td>
<td>38</td>
<td>1.16</td>
</tr>
<tr>
<td>Remission</td>
<td>8 / 2348</td>
<td>33</td>
<td>29</td>
<td>1.11</td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal for AEs</td>
<td>7 / 2384</td>
<td>13</td>
<td>5.8</td>
<td>2.30</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 / 1079</td>
<td>9.4</td>
<td>4.6</td>
<td>2.12</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 / 2016</td>
<td>14</td>
<td>6.8</td>
<td>2.26</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 / 2384</td>
<td>9.5</td>
<td>4.2</td>
<td>2.09</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 / 2466</td>
<td>7.3</td>
<td>5.6</td>
<td>1.57</td>
</tr>
<tr>
<td>Dry mouth&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7 / 2384</td>
<td>9.4</td>
<td>5.6</td>
<td>1.63</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 / 1598</td>
<td>4.9</td>
<td>2.4</td>
<td>2.28</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 / 1409</td>
<td>5.3</td>
<td>3.8</td>
<td>1.49</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 / 1957</td>
<td>9.2</td>
<td>6.1</td>
<td>1.27</td>
</tr>
<tr>
<td>Headache</td>
<td>6 / 1785</td>
<td>11.7</td>
<td>11.7</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<sup>a</sup> If Schweizer (imipramine) is included in analysis event rates in anti-depressant and placebo groups are unchanged but the result becomes statistically significant: RR = 1.20 95% CI 1.00 to 1.42; p =0.045; NNT = 13 (95% CI 6 to 658)

<sup>b</sup> NNT and NNH not calculated if relative risk is non-significant

<sup>c</sup> a If Schweizer (imipramine) is included in analysis event rates are higher in the antidepressant group (14% vs 6.9%) and the result approaches statistical significance: RR = 1.83 95% CI 0.999 to 3.36; p =0.05
**ADX Antidepressants**

Case: An 89 year-old woman Mrs. H., comes to her physician’s office complaining of feeling sad and lonely. She is relatively well, but has remained persistently distressed over the death of her husband, 4 years ago. She describes a great marriage, with few other friendships, both before and following her husband’s death. Mrs. H. is more or less housebound, due to trouble walking following a hip fracture and chronic back pain. She has not been able to improve her socialization and has no interest in physiotherapy, as it did not help in the past. Her physician prescribes an SSRI, which does not help, despite a 6 week course at adequate dose. He subsequently switches antidepressants, also without effect. Given Mrs. H.’s ongoing complaints of sadness, lack of energy, long-term trouble sleeping, decreased interest, and feelings of guilt, an antipsychotic medication is added for augmentation. It would be reasonable to consider, based on the evidence in this review, whether one would expect treatment response with pharmacotherapy for these types of problems.

*This patient description represents the challenge of differentiating difficult life experiences from depression that is likely to respond to pharmacotherapy.*
Question 1a. What is the efficacy of antidepressants for depression in chronic conditions such as post-stroke, heart failure and Parkinson’s as a marker of frailty?

The prevalence of frailty increases with age, but also with chronic illness. (43) Thus, we also sought to evaluate antidepressant response with concomitant depression and chronic illness, such as stroke, heart failure and Parkinson’s disease. This approach uses chronic illness as a surrogate marker for frailty. In addition, the presence of one or more of these conditions in the frail elderly may provide an indication for prescribing an antidepressant if there is evidence of efficacy. While it is beyond the scope of this review to conduct an extensive evidence appraisal of the use of antidepressants in chronic conditions, we do note the following:

Post-stroke depression

- We assessed a 2008 Cochrane review on the effects of pharmacotherapies on stroke patients with depression. (45)
  - The primary outcome was the proportion of participants who met the diagnostic, or scoring, categories for depression at the end of follow up (remission).
  - Meta-analysis of 7 studies (789 patients) showed a statistically significant benefit for pharmacotherapy with substantial heterogeneity:
    \[ \text{OR } 0.467, \ 95\% \ CI \ 0.223 \ - \ 0.975; \ I^2 \ 74\%; \ p=0.043 \]
  - However, this analysis included a Japanese study using aniracetam which is a cognitive enhancer (not an antidepressant) and is not approved for use in North America.(46) Repeating the analysis without this drug still indicates a benefit from pharmacotherapy but the result is not statistically significant:
    \[ \text{OR } 0.459, \ 95\% \ CI \ 0.171 \ - \ 1.231; \ I^2 \ 79\%; \ p=0.122 \]
  - The six remaining studies in this analysis contained 583 patients. One study was from the USA, one from China, and four from Europe. The mean age in 5 studies was between 61 and 67 and the mean age in the remaining study was 71.
    - Of these six studies, one was a TCA (nortriptyline)(47) and the rest were SSRIs. Repeating the analysis excluding the TCA study lowers the odds ratio but the result is still not statistically significant.
      \[ \text{OR } 0.398, \ 95\% \ CI \ 0.130 \ - \ 1.2205; \ I^2 \ 82\%; \ p=0.107 \]
  - These analyses indicate that the efficacy of antidepressants in treating post-stroke depression is uncertain. We did not explore the use of antidepressants for the prevention of post-stroke depression. In addition, the age range of the patients studied is younger than would be expected of the frail elderly.

- A 2012 Cochrane review examined the efficacy of SSRIs in treating post-stroke depression.(48)
This review included many Chinese studies. Analysis of 31 studies (N=2256 patients) that reported data as continuous outcomes showed there was a statistically significant benefit from SSRIs with a large effect size.

**Standardized mean difference -2.07, 95% CI -2.55 to -1.58 \( \chi^2 = 96\% \), p <.0001

In many studies the risk of bias of several criteria in the risk of bias tool was unclear because of inadequate reporting. We conducted an analysis of only the studies in which 4 of the 7 criteria were judged to be at low risk of bias (6 studies, N = 432 patients) which showed a smaller and non-significant benefit from SSRIs.

**Standardized mean difference -0.32, 95% CI -0.81 to 0.175 \( \chi^2 = 84\% \), p <0.206

The mean age in 5 studies was in the 50s, in 18 studies was in the 60s and in 5 studies was in the 70s, with the oldest mean age being 75.

In eight studies patients were randomized within 30 days of their stroke. In another eight studies patients were randomized less acutely, up to 1 year following their stroke. The remaining studies did not specify the timing of randomization in relation to stroke.

**Parkinson’s Disease**

- Two recent meta-analyses had similar findings about the efficacy of antidepressants for depression in patients with Parkinson’s disease. (49,50)
  - A meta-analysis of 5 placebo-controlled RCTs with 264 patients and 8 comparisons (3 RCTs had included 2 antidepressants) found that the effect size of TCAs and SSRIs combined was moderate but not statistically significant.(49)
    - In a subgroup analysis, the effect was statistically significant for TCAs but not for SSRIs.
  - When considering TCAs and SSRIs together, there was a large degree of heterogeneity (\( \chi^2 = 69\% \)), but little when considering TCAs and SSRIs separately, suggesting the overall heterogeneity was attributable to different drug classes. (Table 8)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect size (d)</th>
<th>95% CI</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs and SSRIs combined</td>
<td>0.71</td>
<td>-1.33 to 3.08</td>
<td>69%</td>
</tr>
<tr>
<td>TCAs</td>
<td>1.35</td>
<td>0.19 to 2.52</td>
<td>21%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>0.57</td>
<td>-1.33 to 2.47</td>
<td>0%</td>
</tr>
</tbody>
</table>

A network meta-analysis similarly found no statistically significant improvement in depression scores with SSRIs versus placebo.(50)

**OR 1.60; 95% CI 0.87 to 2.97**

- There was a statistically significant benefit for TCAs

**OR 4.85; 95% CI 1.63 to 14.37**
Indirect comparison also showed that TCAs were more efficacious than SSRIs

**OR 2.77; 95% CI 0.75 to 7.75**

- These meta-analyses generally used the same studies, so it is not surprising that results are similar. A limitation of the analyses is that there were only two placebo-controlled trials of TCAs (N=63). Overall, there is insufficient data to definitively conclude whether antidepressants are or are not effective, in treating depression associated with Parkinson’s disease.

**Depression and Heart Failure**

- Both depression (51) and frailty (52) are common in heart failure.
- The Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) was a DBRCT that evaluated the response to an antidepressant for patients with major depression and heart failure.(53)
  - The study included 469 subjects with a mean age of 62 years.
  - Based on changes in the Hamilton Depression Rating Scale total score, there was no difference in depression severity at 12 weeks between sertraline and placebo.
- The DBRCT, Mortality, Morbidity, and Mood in Depressed Heart Failure Patients (MOOD-HF) trial, enrolled 372 patients with heart failure and depression and found no difference in depression symptom scores based on the MADRS after 12 weeks of receiving escitalopram or placebo.(54)
  - The study also found no difference in all-cause mortality or hospitalizations for patients taking escitalopram versus placebo.
- A small DBRCT of paroxetine for patients with depression and heart failure (N=28, mean age=62 yrs.) resulted in statistically significant reductions in depression based on the Beck Depression Inventory (p=.018) and improvements in psychological aspects of quality of life after 12 weeks.(55)
- While more studies should be conducted, current evidence suggests antidepressants are not efficacious for depression in heart failure.

**Conclusion**

- Our review of the current evidence found that antidepressants do not improve depression for those with chronic conditions such as stroke, Parkinson’s disease and heart failure. There was limited evidence to suggest that TCAs improve depression in Parkinson’s disease.
Question 1b. After non-response to the first antidepressant, is there benefit to further pharmacotherapy?

For severe or resistant depression, alternative pharmacological approaches may be considered. In these situations, clinical practice guidelines typically recommend (56) switching to a different antidepressant; or (57) augmenting the antidepressant with additional pharmacotherapy (also known as combination therapy). (56–58) In this section, we review the evidence for these recommendations.

- We found limited information about the efficacy of these approaches for older adults. Only one DBRCT enrolled patients over age 60 to evaluate the benefit of augmenting an antidepressant with the antipsychotic aripiprazole (see results below).
  - We found no information for frail older adults or for those with dementia.
- Due to the limited information about the benefit of switching or augmenting antidepressants in elderly non-responders, we reviewed the evidence of benefit for younger populations. To do so, we relied on meta-analyses (59–63) and our review of clinical trials.
- In the studies we reviewed, we considered how the characteristics of enrolled subjects compared to those who are frail.
  - Studies of treatment-resistant depression enrolled relatively young populations (usually middle age adults or younger).
  - Studies included a preponderance of subjects with multiple past depressive episodes and unsuccessful treatment trials.
  - Thus, the generalizability of these findings to people over 65 years of age may be limited, especially for those who are frail and without previous episodes of depression. Nevertheless, understanding the efficacy of treating non-responders, albeit in a younger population, provides a useful preliminary exploration.
- The evidence for three different approaches - switch to a different antidepressant; combination therapy with two antidepressants; or combination with a second drug that is not an antidepressant - is described below.

1. SWITCH TO A DIFFERENT ANTIDEPRESSANT

- After a lack of response or intolerable adverse effects to the first antidepressant, this strategy involves trying a different antidepressant, either of the same or different class. Most studies of this approach do not include a placebo arm or are open-label. (64,65) The DBRTs that are available (without a placebo arm) come to divergent conclusions, which makes it difficult to draw firm conclusions about efficacy. The following three double-blind, randomized trials compare one antidepressant to another but lack a placebo arm:
  - One trial of 122 patients (mean age 43 and 44 years) who did respond to two previous antidepressants (e.g., SSRI and/or TCA) were switched to either venlafaxine or paroxetine. At 4 weeks, remission rate (defined as a HDRS < 10) was 42.3% in the venlafaxine group compared to 20.0% in the paroxetine group (P = 0.001). (66)
Another trial of 406 SSRI non-responders (mean age 42 and 43 years) compared venlafaxine XR to citalopram and found no difference between the two. (67)

An eight-week double-blind RCT of 105 patients (mean age = 41) who had failed two or more adequate treatments with different classes of antidepressants compared switching to either venlafaxine extended release, mirtazapine, or paroxetine and found that remission was comparable at 42%, 36%, and 47%, respectively, with no statistically significant differences between treatment arms. (68)

The STAR*D studies, (64,65) are commonly cited to support the benefit of switching to another after treatment failure, but the studies were not blinded and are therefore not reviewed here.

One systematic review and meta-analysis of switching antidepressants after the failure of a first SSRI (69) included both open-label and double-blind trials and concluded that, due to the paucity of high-level studies, “no unequivocal evidence is available to prove an advantage to a between class switch.”

2. COMBINATION THERAPY USING A SECOND ANTIDEPRESSANTS FROM A DIFFERENT CLASS

After the failure of the first antidepressant, another strategy is to add a second antidepressant. There are limited data to support this approach, with the few trials conducted showing inconsistent results, and have methodological flaws, or enroll small numbers of subjects: (59,70)

A systematic review by Rocha (59) evaluated five trials that compared two antidepressant medications (combination therapy) to an antidepressant plus placebo for depressed patients with an incomplete response (mean age of included studies ranged between 39 and 47 years).

Two of five trials found benefit from an antidepressant combination, (71,72) but three did not. (73–75)

One example of a positive trial is the Carpenter study, which included 26 non-responders (mean age = 46), who were randomized to either mirtazapine augmentation or placebo augmentation following an adequate trial of an antidepressant. After four weeks, remission rates were greater with mirtazapine (45%) versus placebo (13%). (72)

The second positive study was a 6-week double-blind study of 104 patients (mean age = 34, 38, and 32) with major depression who had not responded to previous fluoxetine treatment, subsequently treated with mianserin (an alpha-2 antagonist similar to mirtazapine), mianserin plus fluoxetine, or continuation of fluoxetine. Intent-to-treat analysis showed that the decrease in the Hamilton Depression rating scale score was significantly greater in the mianserin plus fluoxetine group compared to the fluoxetine group. Switching from fluoxetine to mianserin gave intermediate results. Complete remission was 44% for the mianserin plus fluoxetine combination, 36% for mianserin, and 18% for fluoxetine; P=0.06). (71)
Based on this review, the authors conclude that the “practice of using a combination of two antidepressants for those with major depression and an incomplete response to monotherapy “is not warranted by the literature” due to the small number of trials, methodological drawbacks, and conflicting results.

- A DBRCT (n = 46, mean age = 35 and 43, duration = 4 weeks) published after the Rocha systematic review compared duloxetine plus bupropion to duloxetine plus placebo in patients with a history of treatment resistant depression and found that response was similar for monotherapy compared to combination therapy. (76)
- Studies of antidepressant combinations in incomplete responders were also conducted as part of the STAR*D series. These studies are frequently cited as providing evidence of efficacy for augmentation, but the lack of placebo control and open-label design prevent definitive conclusions.
  - One study from the STAR*D series compared bupropion SR/citalopram to buspirone/citalopram (n=595, mean age = 27 years, mean duration of treatment = 7 weeks). Symptom reduction was greater with the bupropion SR/citalopram combination compared to buspirone/citalopram, (77) but the lack of a monotherapy placebo group and open-label design hampers interpretation.
  - A second study compared mirtazapine/venlafaxine extended release with tranylcypromine (MAO inhibitor) monotherapy (n =109, mean age = 46 years, mean duration of treatment = 9 weeks). (78) Remission rates were modest for both the tranylcypromine group (6.9%) and mirtazapine/venlafaxine extended release (13.7%), with no statistically significant difference between groups.

3. COMBINATION THERAPY USING A SECOND DRUG THAT IS NOT AN ANTIDEPRESSANT

After failing monotherapy, a second medication, such as an antipsychotic, lithium, psychostimulant (i.e. methylphenidate and triiodothyronine), or anticonvulsant (i.e. lamotrigine) can be added to an antidepressant for augmentation.

Antipsychotic medications

- Multiple placebo-controlled trials of augmentation using antipsychotics show efficacy (79)
- A recent study of older adults over age 60 (mean age approximately 66 years) evaluated augmentation with aripiprazole. (80) Patients with dementia were excluded.
  - Subjects were enrolled in a pre-trial for at least 12 weeks using venlafaxine extended-release (150–300 mg/day), with four weeks at the highest dose.
  - Those who did not achieve remission (MADRS score of ≥15) were randomized to receive the addition of aripiprazole (target dose 10 mg [maximum 15 mg] daily) or placebo for 12 weeks.
  - Of 468 eligible participants, 181 (39%) did not remit and were randomly assigned to aripiprazole (n=91) or placebo (n=90).
Remission was higher with aripiprazole (44%) compared to placebo (29%); OR 2.0 (95% CI 1.1–3.7), p=0.03; NNT 7 (95% CI 4-82), but most adverse events were higher in the aripirazole group. (Table 1)

Table 11. Comparison of adverse effect rates by aripiprazole and placebo

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Aripiprazole (n=91)</th>
<th>Placebo (n=90)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>26%</td>
<td>12%</td>
<td>9 (4-35)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>17%</td>
<td>2%</td>
<td>7 (4-16)</td>
</tr>
<tr>
<td>Dream activity</td>
<td>27%</td>
<td>14%</td>
<td>7 (4-89)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>20%</td>
<td>9%</td>
<td>9 (5-442)</td>
</tr>
<tr>
<td>Tremor</td>
<td>6%</td>
<td>0%</td>
<td>17 (9-215)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>21%</td>
<td>29%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Aripiprazole was not associated with an increase in cardiometabolic risk, as measured by changes in whole body adiposity, plasma lipids, glucose, or insulin.

Lithium

A meta-analysis of nine double-blind placebo controlled trials found lithium to be an effective adjunctive treatment for major depressive disorder when added to either TCAs or SSRIs (N = 237, the mean age of included studies ranged between 37 and 54 years). (20) The odds ratio for response to lithium compared placebo was 2.89 (95%CI 1.65, 5.05, p = 0.0002). Heterogeneity was very low, I² = 0%. There was no evaluation of remission. Despite this evidence, lithium may be challenging for frail older adults to tolerate due to the risk of toxicity and the need for monitoring.

Triiodothyronine

A 1996 meta-analysis evaluated the efficacy of T3 (triiodothyronine) augmentation for patients who had not responded to TCAs. (81)

There were eight studies included with a total of 292 patients (mean age of the included studies ranged from 35 to 56 years). Five of the study were double-blind, while three were unblinded and historical controls.

Patients treated with triiodothyronine augmentation were twice as likely to respond compared to controls (relative response, 2.09; 95% CI 1.31 - 3.32; P = .002). However, among the four randomized, double-blind studies, pooled effects were not significant (relative response, 1.53; 95% CI, 0.70 to 3.35; P=.29).

The authors concluded, “the total number of patients randomized was small, and additional placebo-controlled data are required for a definitive verdict.”
Psychostimulants (e.g., methylphenidate)

- A systematic review by the Cochrane group failed to establish definitive efficacy for psychostimulants, such as dexamphetamine, methylphenidate, and methylamphetamine. (82)

Anticonvulsants (e.g., lamotrigine)

- Two small randomized, placebo-controlled trials (N = 96 and 34) show that augmentation of antidepressants with lamotrigine for treatment-resistant depression is not beneficial. (83,84)

CONCLUSIONS

Few placebo-controlled trials evaluate the effectiveness of second-line treatment for treatment-resistant late-life depression. As such, we reviewed evidence of benefit for younger populations. Beyond issues of generalizability, even in younger cohorts, there is an uncertain benefit for most strategies that are used to manage treatment-resistant depression. Antipsychotics and lithium may improve response or remission but at the expense of significant adverse effects or tolerability that will limit the usefulness of these medications for individuals who are frail.
Question 2. What is efficacy and safety of antidepressants for the treatment of depression in older adults with dementia?

SUMMARY

- We found no DBRCTs that evaluated the effect of antidepressants in frail older adults with depression and dementia. Our efficacy review was limited to studies of adults ≥ 65 years with depression and dementia (8 studies, N=646).
- Patients in the studies we reviewed were representative of adults with frailty. The mean MMSE scores ranged between 17 and 23, which indicates mild to moderate degrees of dementia. In addition, most studies included patients with co-morbid conditions and the average age ranged from 71-89 years old.
- Our primary analysis excluded TCAs because they are not recommended for the frail elderly. Antidepressants were associated with greater rates of response and remission but the results were not statistically significant.
  - Response 45% vs 37%; RR 1.08 (95% CI 0.80 – 1.46) p=0.606
  - Remission 42% vs 38%; RR 1.10 (95% CI 0.79 – 1.55) p=0.571
    - Response defined as:
      - 50% improvement on the Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Scale (MADRS), or Cornell Scale for Depression in Dementia (CSDD).
      - Much or very much improved on the modified Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC).
    - Remission defined as:
      - HDRS score ≤ 7
      - CSDD ≤ 6
      - MADRS ≤ 10
- Results were not substantially different with the inclusion of one small study of clomipramine a TCA.
- Adverse events are generally minor, but are troublesome enough to lead to approximately 11% of patients withdrawing from treatment versus 6% in the placebo group and may worsen quality of life.
  - 10.9% vs 6.1%; RR 1.63 (95% CI 1.03 – 2.57); NNH 26 (95% CI 10 – 546) p=0.037
- Dizziness and diarrhea were more frequent with antidepressants than placebo.
- The evidence reviewed indicates that frail elderly patients with depression and dementia are unlikely to benefit from antidepressants. Therefore, the use of antidepressants should be the exception rather than the norm. If antidepressants are used, they should be given over a discrete timeframe (e.g., 8 to 12 weeks), with evaluation of effectiveness before continuation.
1. What is the quality of the evidence?

Results of literature search

- The literature search revealed one recent systematic review and meta-analysis on the use of antidepressants in older adults with concomitant depression and dementia (20) and one subsequent randomized control trial (85).

- Inclusion criteria were:
  - Acute-phase, parallel-group, double-blind, random-assignment, placebo-controlled trials of antidepressants marketed in the United States.
  - Participants had a diagnosis of dementia and depression according to established criteria.
  - The studies reported on outcomes based on objective measures, and the number of participants discontinuing treatment.

- The reported outcomes included response and remission:
  - **Response**, defined as:
    - 50% improvement on the Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Scale (MADRS), or Cornell Scale for Depression in Dementia (CSDD). Much or very much improved on the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC).
  - **Remission** defined as:
    - HDRS score ≤ 7
    - CSDD ≤ 6
    - MADRS ≤ 10

- The systematic review included 7 DBRCTs with a total of 320 subjects (Table 1). (86–92)

- The Nelson meta-analysis was published before the Banerjee trial. Banerjee et al compared sertraline and mirtazapine to placebo over 13 weeks, with an extension to 39 weeks. This trial was publicly funded, high quality and had slightly more subjects than all previous studies combined (326 vs 320).

- After including Banerjee, we had 8 DBRCTs (n=646) for consideration in our evidence review (Table 1). (85–92)

- We used the Cochrane risk of bias criteria to help appraise the quality of the studies. The studies were mostly low quality, with the exception of Banerjee which was high quality, however:
  - None of the studies adjusted p-values for multiple comparisons.
  - In three studies, blinding and allocation concealment were adequate. (85,86,88) In the other studies, these criteria were inadequately described. (87,89–92)
  - Three studies were 6 weeks in duration, (87,89,90) two were 8 weeks, (91,92) two were 12 weeks (86,88) and one was 13 weeks with extension to 39 weeks. (85)
o Four of the 8 studies used an intention-to-treat analysis (ITT) (86,88,89,91), while close analysis of the numbers of subjects included in the results of other studies indicated that the analysis was not fully ITT. (85,87,90,92)

o Two studies had more than 100 subjects (85,88), while the others had between 21 and 44 subjects.

- One study was funded by industry (87) and one study did not disclose funding (89), the rest were publically funded.
- There was a moderate degree of heterogeneity found in the Nelson meta-analysis ($I^2=56\%$ for response; $I^2=49\%$ for remission).
**Table 12. Studies of patients with dementia and depression in the Nelson meta-analysis plus Banerjee 2011 which was published subsequently**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Duration (wks)</th>
<th>N</th>
<th>Mean Age</th>
<th>Mean MMSE</th>
<th>Quality</th>
<th>Funding</th>
<th>Scale</th>
<th>Primary Outcome</th>
<th>Stat Sig Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyketsos<strong>a</strong> 86</td>
<td>2003</td>
<td>Sertraline</td>
<td>Up to 150 mg Mean 95 mg</td>
<td>12</td>
<td>44</td>
<td>78</td>
<td>17</td>
<td>Moderate</td>
<td>NIMH HDRS</td>
<td>Response</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Petracca<strong>b</strong> 87</td>
<td>1996</td>
<td>Clomipramine</td>
<td>100 mg</td>
<td>6</td>
<td>21</td>
<td>72</td>
<td>21</td>
<td>Low</td>
<td>Industry HDRS-D 17</td>
<td>Not defined – HDRS reported first</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rosenberg<strong>a</strong> 88</td>
<td>2010</td>
<td>Sertraline</td>
<td>50 – 100 mg Mean 93 mg</td>
<td>12</td>
<td>124</td>
<td>77</td>
<td>20</td>
<td>High</td>
<td>NIMH mADCS-CSDD</td>
<td>Ratings on mood domain mADCS-CGIC</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>de Vasconcelos Cunha<strong>a</strong> 89</td>
<td>2007</td>
<td>Venlafaxine</td>
<td>37.5 – 131.25 mg Mean 75 mg</td>
<td>6</td>
<td>31</td>
<td>78</td>
<td>No data</td>
<td>Low</td>
<td>Not disclosed MADRS</td>
<td>Change from baseline</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Petracca<strong>90</strong></td>
<td>2001</td>
<td>Fluoxetine</td>
<td>40 mg</td>
<td>6</td>
<td>41</td>
<td>71</td>
<td>23</td>
<td>Low</td>
<td>CONICET + research foundations HDRS-D17</td>
<td>Not defined Response, remission and mean change reported</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Magai<strong>91</strong></td>
<td>2000</td>
<td>Sertraline</td>
<td>100 mg</td>
<td>8</td>
<td>31</td>
<td>89</td>
<td>No data</td>
<td>Low</td>
<td>Pfizer, NY DoH, NIA CSDD</td>
<td>Not defined Mean difference and response reported</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Reifler<strong>b,c,92</strong></td>
<td>1989</td>
<td>Imipramine</td>
<td>Mean 83 mg</td>
<td>8</td>
<td>28</td>
<td>73</td>
<td>17</td>
<td>Low</td>
<td>NIMH HDRS-17</td>
<td>Not defined Mean difference reported</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Banerjee<strong>a,d</strong> 85</td>
<td>2011</td>
<td>Sertraline Mirtazapine</td>
<td>SER up to 150 mg – mean 95 MIR up to 45 mg – mean 30</td>
<td>13 + 39 extension</td>
<td>326</td>
<td>79</td>
<td>18</td>
<td>High</td>
<td>UK NIHR HTA CSDD</td>
<td>Reduction CSDD score</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

a Studies included in our meta-analysis  
b Studies excluded from our meta-analysis because they involved TCAs  
c Study did not report response or remission and was included in Nelson systematic review but not meta-analysis  
d Study published after Nelson meta-analysis and was included in our meta-analysis
2. What is the applicability of the evidence to the frail elderly patient population?

Patient Characteristics
- Due to the diagnosis of dementia, the study population was representative of adults with frailty. The mean Folstein MMSE scores ranged between 17 and 23, which indicates mild to moderate degrees of dementia. In addition,
  - Most studies included patients with co-morbid conditions.
  - The average age ranged from 71-89 years old.
- Only one study by de Vasconcelos Cunha et al., 2007 (89) had an inclusion criterion based on age (≥ 60). The other studies specified that enrolled subjects have probable Alzheimer’s disease or another type of dementia, regardless of age. However, the ages of the study populations are congruent with the age at which frailty typically occurs.
- Five studies excluded patients who were taking psychotropic or cognition-enhancing drugs. (145–149) As such, it is unknown if patients taking such drugs would be more likely to respond to antidepressants.
- Two studies excluded patients if they had unstable comorbidities. (86, 89)

The long-term care (LTC) population was not well represented in these studies. Only one study enrolled patients residing solely in a LTC setting. (91) Less than 20% of subjects in the Banerjee study were enrolled in LTC. (85) The other subjects included in the studies were either from outpatient clinics or living at home. (89)

3. What is the potential benefit from treatment? Are the outcomes clinically relevant to those who are frail?

Results
- The results of the Nelson meta-analysis showed no significant benefit in response or remission after using antidepressants in patients with concomitant depression and dementia. However, for both outcomes, the point estimate of the odds ratio was approximately 2, in favour of antidepressants.

<table>
<thead>
<tr>
<th></th>
<th>N Studies</th>
<th>N Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>OR 2.12</td>
<td>(0.95 – 4.70)</td>
</tr>
<tr>
<td>Remission</td>
<td>OR 1.97</td>
<td>(0.85 – 4.55)</td>
</tr>
</tbody>
</table>

- The study by Banerjee et al did not show a statistically significant difference between treatment and placebo for the primary outcome of reduction in CSDD score from baseline. Mean change in CSDD score (and standard deviation) at 13 weeks was:
  - Sertraline      -3.9 (5.1)  p vs placebo = 0.10
  - Mirtazapine    -5.0 (4.9)  p vs placebo = 0.99
  - Placebo        -5.6 (4.7)

Results were similar at 39 weeks.
Statistical Analysis

- We obtained data on response and remission rates from the authors of the Banerjee study. Values at 13 weeks are shown. Since this analysis was not included in the Banerjee publication, we calculated P values using chi-square tests.

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Sertraline</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>p vs placebo</td>
<td>0.039</td>
<td>0.189</td>
</tr>
<tr>
<td>O Mirtazapine</td>
<td>34%</td>
<td>36%</td>
</tr>
<tr>
<td>p vs placebo</td>
<td>0.892</td>
<td>0.666</td>
</tr>
<tr>
<td>O Placebo</td>
<td>35%</td>
<td>33%</td>
</tr>
</tbody>
</table>

- Results were similar at 39 weeks, except for the fact that there was no longer a significant difference between sertraline and placebo in response rate. (Response in the sertraline group was no longer lower than in the placebo group (sertraline 24% vs placebo 31%; p = 0.295)).

- We added the response and remission data from Banerjee into Nelson’s meta-analysis. The results showed point estimates closer to a null result with narrower confidence intervals:

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>p</th>
<th>I²</th>
<th>N Studies</th>
<th>N Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Response</td>
<td>1.41</td>
<td>0.26</td>
<td>65%</td>
<td>7</td>
<td>625</td>
</tr>
<tr>
<td>O Remission</td>
<td>1.37</td>
<td>0.28</td>
<td>59%</td>
<td>6</td>
<td>594</td>
</tr>
</tbody>
</table>

- In this analysis we used 13-week data from Banerjee because that was the primary outcome and it is closer to the duration of the other studies.

- The Petracca study used clomipramine, a tricyclic antidepressant (TCA). (90) We performed an analysis without this study for the following reasons:

  - TCAs are less likely to be used in older adults with dementia due to their anticholinergic properties and are not recommend by the Beers and STOPP/START criteria.
  - It is a small with only 11 patients in the drug group and 10 in the placebo group, with a crossover design
  - The results for response used in the Nelson meta-analysis came from the number of patients who achieved remission at the end of the first 6-week phase, before the crossover.

- If this trial is excluded from the analysis, the results become:

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>p</th>
<th>I²</th>
<th>N Studies</th>
<th>N Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Response</td>
<td>1.20</td>
<td>0.52</td>
<td>61%</td>
<td>6</td>
<td>604</td>
</tr>
<tr>
<td>O Remission</td>
<td>1.18</td>
<td>0.52</td>
<td>50%</td>
<td>5</td>
<td>573</td>
</tr>
</tbody>
</table>

- Without the Petracca study, the point estimate of the odds ratio is lower at 1.2 vs 1.4.

- In summary, the above evidence does not show a statistically significant benefit for treatment of depression in dementia with antidepressants vs placebo (see Figures 1 and 2).
### Figure 4. Outcome: Response. Treatment effects of second-generation antidepressants vs placebo for older adults (≥ 65 years) with dementia

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Responders / Total</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyketsos 2003 SER</td>
<td>2.381</td>
<td>1.276</td>
<td>4.441</td>
<td>0.006</td>
<td>20 / 24</td>
<td>12.6</td>
</tr>
<tr>
<td>Rosenberg 2010 SER</td>
<td>1.075</td>
<td>0.699</td>
<td>1.652</td>
<td>0.743</td>
<td>27 / 67</td>
<td>17.7</td>
</tr>
<tr>
<td>de Vasconcelos Cunha 2007 VEN</td>
<td>0.883</td>
<td>0.498</td>
<td>1.567</td>
<td>0.671</td>
<td>8 / 14</td>
<td>13.8</td>
</tr>
<tr>
<td>Petracca 2001 FLU</td>
<td>1.412</td>
<td>0.662</td>
<td>3.012</td>
<td>0.372</td>
<td>8 / 17</td>
<td>10.0</td>
</tr>
<tr>
<td>Magai 2000 SER</td>
<td>1.318</td>
<td>0.555</td>
<td>3.129</td>
<td>0.532</td>
<td>8 / 17</td>
<td>8.4</td>
</tr>
<tr>
<td>Banerjee 2011 SER</td>
<td>0.638</td>
<td>0.414</td>
<td>0.985</td>
<td>0.043</td>
<td>24 / 107</td>
<td>17.6</td>
</tr>
<tr>
<td>Banerjee 2011 MIR</td>
<td>0.975</td>
<td>0.678</td>
<td>1.403</td>
<td>0.892</td>
<td>37 / 108</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>1.082</td>
<td>0.802</td>
<td>1.458</td>
<td>0.606</td>
<td>132 / 354</td>
<td></td>
</tr>
</tbody>
</table>

FLU fluoxetine; MIR mirtazapine; SER sertraline; VEN venlafaxine

This plot demonstrates no overall statistically significant benefit for antidepressants over placebo.
Figure 5. Outcome: Remission. Treatment effects of second-generation antidepressants vs placebo for older adults (≥ 65 years) with dementia

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Remitters / Total</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Lyketsos 2003 SER</td>
<td>1.875</td>
<td>0.678</td>
<td>5.186</td>
</tr>
<tr>
<td>Rosenberg 2010 SER</td>
<td>1.751</td>
<td>0.947</td>
<td>3.237</td>
</tr>
<tr>
<td>de Vasconcelos Cunha 2007 VEN</td>
<td>0.607</td>
<td>0.271</td>
<td>1.361</td>
</tr>
<tr>
<td>Petracca 2001 FLU</td>
<td>1.412</td>
<td>0.662</td>
<td>3.012</td>
</tr>
<tr>
<td>Banerjee 2011 SER</td>
<td>0.757</td>
<td>0.498</td>
<td>1.151</td>
</tr>
<tr>
<td>Banerjee 2011 MIR</td>
<td>1.083</td>
<td>0.753</td>
<td>1.558</td>
</tr>
</tbody>
</table>

FLU fluoxetine; MIR mirtazapine; SER sertraline; VEN venlafaxine

This plot demonstrates no overall statistically significant benefit for antidepressants over placebo.
Considering mean changes in depression scale scores from baseline, rather than percent of patients who responded or who achieved remission, does not change the overall picture. The studies that showed a statistically significant benefit in response or remission based on percent response also showed a statistically significant result in mean change from baseline score. Similarly, non-significant outcomes based on percent response were negative in all analyses.

An improvement in response and remission rates is seen in both groups: placebo and antidepressant, but there is no statistical difference between groups. Approximately 40% of placebo and 45% of anti-depressant patients respond to treatment, defined as a ≥ 50% reduction in depression scale.

- Table 2 summarizes data on response and remission. Data is shown as relative risk for consistency with the data reported for Clinical Question 1, use of antidepressants in the elderly.

Relevance

- Given that all patients in these studies had dementia, the patient population would be representative of those who are frail. There are many ways to define frailty. One recognized approach is based on the Clinical Frailty Scale, (15, 36) which characterizes frailty based on the accumulation of deficits in cognition, function, and mobility. Given that individuals with dementia have impaired cognition and function, they would be considered frail.

Depression scales used to assess initial severity of depression and response to therapy

As in Question 1, which addressed the use of antidepressants in the elderly without dementia, studies rely on scales that reflect the Diagnostic and Statistical Manual of Mental Disorders-V (DSM) criteria for depression to identify treatment benefit.

- One potential problem with these scales is that the items used by the scale to identify depression are common characteristics of dementia. For example, the Cornell Scale rates anxiety, lack of reactivity to pleasant events, irritability, agitation, retardation, loss of interest, loss of appetite, weight loss, lack of energy, and sleep disturbance, all of which are common manifestations of dementia.

- In addition to the HDRS and MADRS described in clinical question 1, the studies we reviewed used two other scales to rate depression:
  - Cornell Scale for Depression in Dementia (CSDD)
    - Information elicited from an informant and the patient
    - Focuses on symptoms the week before the interview
    - Scoring: 19 questions rated 0 – 2 (0= absent; 1= mild/intermittent; 2= severe); maximum score 38
    - Absence of significant depressive symptoms <6
    - Probable major depression 10 – 18
Definite major depression >18

- Modified Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change index (mADCS-CGIC)
  - Requires a clinical assessment of the study participant with input from the caregiver
  - Seven-point scale ranging from 7 “much worse”, to 4 “no change,” to 1 “much better.”

4. Is the timeframe appropriate to achieve benefit or for adverse events to appear?

- Depression should be treated for 8 to 12 weeks before assessing for benefits of treatment.
- Studies generally ranged from 6 to 13 weeks in duration. One study had an extension to 39 weeks. (85)
- In the Banerjee study the results of mean changes in CSDD, response and remission were similar at 13 and 39 weeks.
- A separate study, not included in our analysis, performed an extension of the Rosenberg study (151) to 24 weeks
  - Similar to the results at 12 weeks, Weintraub found no statistically significant difference between placebo and sertraline in remission rates, change in CSDD, activities of daily living or MMSE at 24 weeks.
  - The adverse effects of dizziness, diarrhea, and dry mouth were also similar at 12 and 24 weeks.
- In general, the studies were of short duration. In clinical practice some patients may be prescribed antidepressants for an extended time and this meta-analysis does not address long-term efficacy or tolerability of antidepressants.

5. What are the potential harms from antidepressants?

- Many studies report adverse events, but there is inconsistency among studies as to the events reported.
- Eight studies (N = 819 subjects) reported withdrawals due to adverse events, which occurred more frequently with antidepressants compared to placebo (10.9% vs 6.1%, p 0.037, NNH 20 (95% CI 12 – 56).
- The Porsteinsson study reported that citalopram was associated with a greater cognitive worsening compared to placebo of – 1.05 points on the MMSE (95% CI -1.97 to -0.13, p = 0.026).
- To make a comprehensive estimate of common adverse events, we combined those that were most frequently reported in a meta-analysis.
- To further increase the sample size, we included information on adverse events from three placebo-controlled trials that used antidepressants in patients with dementia for the treatment of NPS.
The primary analysis included only studies that provided data on second-generation antidepressants. One small study (N=42) compared clomipramine, a TCA, to placebo and we conducted a sensitivity analysis in which we included this study.

The studies which contributed most to these analyses were the largest studies Rosenberg 2010 and Porsteinsson 2014. Both found high rates of adverse events in both the drug and placebo groups. All adverse events in our meta-analyses contained data from these two studies.

Dizziness and diarrhea occurred more frequently in the antidepressant group compared to placebo, which was a statistically significant difference (Table 13). For both outcomes the NNH was 7.

Sensitivity analysis

- The adverse events reported in the TCA study were withdrawals, dry mouth, dizziness, insomnia, headache, and nausea.
- Dry mouth and insomnia were the only outcomes substantially affected by the sensitivity analysis.
  - The rate of dry mouth in the drug group increased from 32% to 41% while the rate in the placebo group remained unchanged at 27%. The relative risk increased from 1.19 to 1.50 and the risk difference increased from 2.9% to 17%. However, the difference in rates of dry mouth between the drug and placebo groups was not statistically significant.
  - In the primary analysis insomnia occurred less frequently in the antidepressant group than the placebo group (33% vs 39%) which led to risk difference of -9.4 indicating a benefit from antidepressants. Insomnia was more frequent in the antidepressant group in the TCA study (43% vs 10%) and with inclusion of this study the benefit disappeared.
- Banerjee 2011 reported adverse events at 39 weeks, but categorized them by system and found no statistically significant differences between antidepressant and placebo in neurological, psychiatric, urinary tract, cardiovascular, respiratory, musculoskeletal, dermatological, infectious, hematological, endocrine, or otolaryngeal adverse events.
- Adverse events were generally minor and probably reversible if patients decide to stop taking the antidepressant.
- We compared adverse events for those with dementia to those found in older adults without dementia (Question 1). Results are shown in Q1 - Table 7.
  - The rate of many adverse events was several times higher in both the antidepressant and placebo groups for subjects with dementia and depression compared to those with depression but without dementia. This may reflect the vulnerability related dementia or the difficulty extracting meaningful information from elderly patients with dementia and their caregivers.
Questions and uncertainties

- Does the baseline severity of depression influence the efficacy of antidepressants? The study that included patients with the most severe depression was one of the two studies that showed a benefit from antidepressants. (86)
- Three studies excluded patients at risk for suicide,(85,86,89) so it is uncertain if the overall findings apply to such patients.
- Our analysis focused on depressive symptoms in the patients themselves and did not consider caregivers. The one study that evaluated the effect of antidepressants on caregiver distress found no statistically significant difference between placebo and sertraline as measured by the Non-Mood Neuropsychiatry Inventory.(86)
- In the guidelines we reviewed, albeit not an extensive search, none cautioned about the potential over use of antidepressant medications. For example, the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia states [Moore 2012] states, “A trial of antidepressant medications could be considered if the patient has an inadequate response to nonpharmacologic interventions or has a major depressive disorder, severe dysthymia, or severe emotional lability (grade 2A).” In making this statement, the document refers to two large RCTs, DIADS-2 and HTA-SADD, to describe that antidepressants have “shown benefit equivalent to placebo,” although at the expense of increased adverse events in the group treated with medication.

Conclusions

- We conducted a review of the evidence for the use of antidepressants to treat depression in the frail elderly with dementia.
- Two high quality studies were both negative, providing moderate to strong evidence that antidepressants do not show benefit in improving symptoms of depression in patients with dementia. The evidence reviewed excluded patients thought to be at risk of suicide.
- The evidence does not show a significant difference between antidepressants and placebo in the treatment of depression. On average, patients who received either treatment showed similar response in depression scores, which was not statistically different.
- Placebo and drug groups improve with time, perhaps because of support they get during the study. Approximately 40% of placebo and 45% of anti-depressant patients respond to treatment, defined as a ≥ 50% reduction in depression scale.
- This evidence does not exclude the possibility that that some patients may show benefit from antidepressants in depression.
- Adverse events are generally minor, but are troublesome enough to lead to approximately 10% of patients withdrawing from treatment versus 6% in the placebo group (NNH=20), and may worsen quality of life.
- People with dementia may seem to be depressed because many of the manifestations of dementia overlap with symptoms of depression.
Discussion

- There is limited evidence that antidepressants will have a significant effect in the frail elderly with dementia.
- In some situations, an antidepressant may be an appropriate treatment approach. Clinicians should expect that treatment benefit, if any, will be modest. Treatment could be considered:
  - If a patient has severe depressive symptoms.
  - A patient has responded to antidepressant treatment in the past.
- If antidepressants are used, they should be given over a discrete timeframe (e.g., 4 to 8 weeks) with evaluation of effectiveness before continuation. Careful follow up is needed so that medications can be stopped if there is no benefit.
- Long-term use of antidepressants should be regularly re-evaluated.
- Most reviews comment on the lack of evidence for treating depression with dementia using antidepressants, but then comment that antidepressants could be trialed. In the guidelines we reviewed, albeit not an extensive search, none cautioned about the potential over use of antidepressant medications. For example, the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia states, “A trial of antidepressant medications could be considered if the patient has an inadequate response to non-pharmacologic interventions or has a major depressive disorder, severe dysthymia, or severe emotional lability (grade 2A).”(94) In making this statement, the document refers to two large RCTs, DIADS-2 and HTA-SADD, to describe that antidepressants have “shown benefit equivalent to placebo,” although at the expense of increased adverse events in the group treated with medication.
- Families and caregivers should receive education about the manifestations of dementia and how they can mimic symptoms of depression. Some changes in mood may be caused by situational and psychosocial factors. Treatment approaches should include non-pharmacologic approaches.
  - We don’t have a gold standard diagnosis of depression in dementia. People with dementia may seem to be depressed, because many of the manifestations of dementia overlap with symptoms of depression. This evidence review is a call to action to experts to more carefully consider the limitations of diagnosing depression when there is concomitant dementia.
- Screening for depression, which has become a suggested standard of care in nursing homes, has the potential to over diagnose depression and potentiate inappropriate use of antidepressants.
- There may be a propensity to overestimate the benefit of antidepressants.
  - Families should receive education about the manifestations of dementia and how they can mimic symptoms of depression.
Table 13. Random effects meta-analysis of efficacy and safety outcomes for studies comparing second-generation antidepressants to placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number studies/subj.</th>
<th>Event Rate (%)</th>
<th>Relative Risk</th>
<th>NNT/NNH for 8-12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADX</td>
<td>Placebo</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Efficacy Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>6 / 604</td>
<td>45</td>
<td>37</td>
<td>1.08</td>
</tr>
<tr>
<td>Remission</td>
<td>5 / 573</td>
<td>42</td>
<td>39</td>
<td>1.10</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals</td>
<td>8 / 819</td>
<td>10.9</td>
<td>6.1</td>
<td>1.63</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 / 475</td>
<td>30</td>
<td>14</td>
<td>2.08</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 / 348</td>
<td>30</td>
<td>17</td>
<td>1.83</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>4 / 684</td>
<td>13</td>
<td>12</td>
<td>1.21</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4 / 431</td>
<td>32</td>
<td>27</td>
<td>1.19</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 / 421</td>
<td>46</td>
<td>41</td>
<td>1.09</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 / 390</td>
<td>54</td>
<td>62</td>
<td>0.92</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 / 348</td>
<td>11</td>
<td>9.1</td>
<td>1.38</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 / 317</td>
<td>64</td>
<td>64</td>
<td>0.97</td>
</tr>
<tr>
<td>Falls</td>
<td>4 / 392</td>
<td>16</td>
<td>13</td>
<td>1.38</td>
</tr>
<tr>
<td>Headache</td>
<td>3 / 359</td>
<td>32</td>
<td>26</td>
<td>1.21</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 / 348</td>
<td>33</td>
<td>39</td>
<td>0.83</td>
</tr>
</tbody>
</table>

a NNT and NNH not calculated if relative risk is non-significant. ADX antidepressants; NNT number needed to treat; NNH number needed to harm; NS not statistically significant.
Table 14. Adverse event rates (percentages) in placebo and antidepressant groups of studies of elderly patients without dementia and patients with dementia

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Antidepressant</th>
<th>Placebo</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elderly without dementia</td>
<td>Patients with dementia</td>
<td>Elderly without dementia</td>
<td>Patients with dementia</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9.3</td>
<td>32</td>
<td>5.6</td>
<td>27</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.6</td>
<td>30</td>
<td>5.5</td>
<td>14</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.9</td>
<td>46</td>
<td>2.2</td>
<td>41</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.3</td>
<td>33</td>
<td>3.6</td>
<td>39</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.4</td>
<td>54</td>
<td>4.7</td>
<td>62</td>
</tr>
<tr>
<td>Headache</td>
<td>11.7</td>
<td>32</td>
<td>12.4</td>
<td>26</td>
</tr>
</tbody>
</table>
Question 3. What is the efficacy and safety of antidepressants for the neuropsychiatric symptoms of dementia?

SUMMARY

- We included one Cochrane Review of nine RCTs plus two additional RCTs in our assessment of the efficacy and safety of antidepressants for NPS related to dementia.
  - Studies primarily compared an SSRI to either placebo or an active comparator (e.g., 1st or 2nd generation antipsychotics).
  - Study populations in all trials were highly relevant to the frail elderly (e.g., mostly Alzheimer disease with NPS).
- The Cochrane review, published in 2011, concluded there were few high-quality studies examining the efficacy and safety of antidepressants for the treatment of agitation and psychosis in dementia and, at the time, there was limited evidence to support the use of antidepressants for these indications.
- One of the more recent studies by Porsteinsson et al. (CitAD) is of higher quality than the nine studies included in the Cochrane Review and provides more weight in our assessment.
- Important features of CitAD include the following:
  - Citalopram 30 mg/day was compared with placebo yet the maximum daily dose in Canada for citalopram is 20 mg/d. The effect of citalopram 20 mg/day for the treatment of agitation/aggression in dementia is unknown.
  - An intensive psychosocial intervention was provided to all patients.
- The CitAD study (citalopram vs. placebo) found a statistically significant benefit for both co-primary outcomes; however, the clinical relevance is uncertain.
- For example:
  - The difference in the NBR-S-A, an assessment of agitation was less than 1 point on an 18 point scale.
  - The odds of being in a better CGIC category were higher for citalopram; however, the trial did not report statistical differences between the individual categories of the mADCS-CGIC.
  - Most participants receiving citalopram did not demonstrate a notable improvement in their NPS compared to placebo.
  - Assessment of caregiver distress (NPI) showed a statistically significant improvement in the CitAD trial; we questioned the clinical relevance as it was a small change (2.7 on a 60 point scale).
  - Agitation (measured on NPI subscale) showed no significant differences between treatment arms after 9 weeks of treatment.
- Adverse effects were poorly reported in many of the trials. Small numbers in the trials and high withdrawal rates from all treatment groups complicate interpretation.
SSRIs increased the rate of diarrhea and there was worsening of cognition in the citalopram treated group in the CitAD trial.

- Our review has shown there is considerable uncertainty about the efficacy of antidepressants for those with behavioural symptoms of dementia.
- Families and patients should be aware of the limited potential for benefit based on the numbers that will not likely benefit.
- When treatment is initiated response should be assessed and medications stopped if benefit is not achieved. As was studied in the CitAD trial, 9 weeks of treatment is required to adequately assess response.
- Treatment with antidepressants is not appropriate for acute agitation requiring immediate response.
- The evidence for non-drug (psychosocial) interventions has not been assessed in this review; however, the current Canadian Senior’s Mental Health guidelines recommend non-pharmacological approaches prior to a trial of drugs for the treatment of NPS in dementia and emphasize the need to rule out underlying medical problems and consider potential benefits with harms prior to the use of pharmacotherapy for NPS.
1. **What is the quality of the evidence?**

**Results of literature search**

- The literature search for Question 3 identified one systematic review and two randomized controlled trials that matched our inclusion criteria (see Table 1 for study characteristics).
  - One Cochrane review,(95) consisting of nine randomized controlled trials (RCTs) representing a total of 692 patients. The authors suggest that the included studies represent the best evidence currently available on this topic. (96–104)
  - Two randomized controlled trials that were published after the Seitz review:
    - Barak et al. 2011 – compared escitalopram vs. risperidone (n=40). (105)
    - Porsteinsson et al. 2014 – compared citalopram to placebo, the Citalopram for Agitation in Alzheimer Disease Study (CitAD) trial (n=186). (106) Two other publications related to CitAD were also reviewed:
      - CitAD design and methods. (107)
      - Time to response. (93)
  - Other published meta-analyses were excluded if they included the same studies as in the Seitz Cochrane Review and did not offer alternative analysis or results (e.g., Wang et al). (108)
- Each of the trials included in the Seitz meta-analysis were examined individually and the additional studies were appraised to determine the quality, validity and clinical relevance of the results and are discussed below. (See Table 1)
- There is confidence in the results of the literature search, as they matched recent guidelines and reviews on the topic identified after the search was performed.

**Description of Seitz Cochrane Review**

- The systematic review considered studies of any type of antidepressant (SSRIs, TCAs or others) compared with placebo, typical or atypical antipsychotics, anticonvulsants, benzodiazepines, cholinesterase inhibitors, memantine or other medications for the treatment of agitation or psychosis in older adults with dementia.
  - Nine RCTs were included in the systematic review, which evaluated either an SSRI or trazodone compared with either placebo or an active comparator. Five studies compared SSRIs with placebo, three compared SSRIs with typical antipsychotics (haloperidol, perphenazine) and one trial compared the SSRI, citalopram with the atypical antipsychotic, risperidone.
  - Antidepressants studied included: sertraline (2 studies), fluvoxamine (1 study), citalopram (3 studies), trazodone (2 studies) and fluoxetine (1 study). Of the three trials that included trazodone, one trial compared trazodone with placebo, and two trials compared trazodone with haloperidol.
- Both inpatient (N=285) and outpatient (N=407) participants were enrolled in the studies.
Study size ranged from 15 to 244 patients and study length ranged from 17 days to 16 weeks. Only 3 of the 9 studies included > 100 patients and four of the studies included < 50 patients.

- Efficacy was measured as the mean change in neuropsychiatric symptom scores (such as agitation and psychosis), as measured by various neuropsychiatric and global scales.
  - Clinical Global Impression Scale (CGI).
  - Neuropsychiatric Inventory (NPI).
  - Gottfried, Brane, and Steen Scale (GBS)
  - Cohen Mansfield Agitation Inventory (CMAI).
  - Behavioural Pathology in Alzheimer’s disease (BEHAVE AD).
  - Neurobehavioral Rating Scale (NBRS)
  - Behavioural Rating Scale for Dementia (BRSD).
  - And the subscales of the above scales.

- Cognitive status was assessed using the Alzheimer’s disease Assessment Scale cognitive subscale (ADAS-cog), the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating sum of the boxes (CDR) and the Severe Impairment Battery (SIB). (See Table 6 p. 79 for description of NPS scales).

- Caregiver distress was also measured.

- The results of the meta analyses were presented as weighted mean differences (WMD) and standard deviations (SD) using a random effects model. For binary outcomes, meta analyses results are presented as risk ratios (RR) and 95% confidence intervals (CI).

- Safety and tolerability was assessed as:
  - Overall rates of trial withdrawal.
  - Withdrawals due to adverse events or worsening of symptoms.
  - Reports of adverse events including: falls, headache, gastrointestinal upset, worsening of dementia, anxiety, headache, bleeding, extrapyramidal symptoms, and hyponatremia.

Quality Assessment of Seitz Cochrane Review

- All trials included in the systematic review and meta-analysis were of randomized, controlled design (See Table 1). The Cochrane Risk of Bias Tool was used to assess study quality. None of the included studies in the systematic review were rated of low risk of bias on all quality domains. The potential risk of bias for many studies was unclear from information reported in the study publication. One study by Pollock, 2007 was rated as “low risk of bias” for all domains except blinding. (100)
  - Authors suggest that all studies were included regardless of potential risk of bias to reflect the best evidence currently available on this topic.

- Nine studies, with relatively small sample sizes were identified for the review.
- Limitations of the studies
  - Lack of detailed description of study methods to determine the potential risk of bias resulting in unclear risk of bias for most items.
  - Withdrawal rates varied, but were as high as 40% to 60% in some studies.
  - Relatively small studies.
  - Adverse events were not well reported and in some studies not reported at all.

Description of Barak 2011 (105)
- The Barak study was not included in the Seitz Cochrane Review. This study reports the results of a six-week randomized, double-blind, controlled trial of inpatients (n = 40), randomized to either a fixed dose of risperidone 1 mg or escitalopram 10 mg once daily, following a week of each at 0.5 mg or 5 mg respectively. Patients were hospitalized due to behavioural symptoms.
- The study was conducted in Israel.

Quality Assessment of Barak Trial
The study design was rated as low to moderate risk based on the following characteristics:
- Computer generated randomization list and randomization series were sealed in opaque envelopes.
- Double blinding: both pills were identical, researchers and patients were blinded for the duration of study.
- ITT analysis using last observation carried forward for missing data.
- No apparent selective reporting identified.
- Authors state no conflict of interest and all authors contributed to and have approved the final paper.
- A board-certified psychiatrist blinded to medication status performed the Neuropsychiatric Inventory (NPI) assessments at baseline and weekly for the duration of the study, which contributes to consistency in the evaluations.

However,
- There was no placebo arm and fixed doses of the medications prevent knowing if dose escalation or decrease could result in greater or similar response.
- Small sample size; N = 40 and single centre design.
- Completion rate: 16 (75%) in the escitalopram group and 11 (55%) in the risperidone group completed the study. This withdrawal rate resulted in a lack of power to detect the predefined 5-point difference in the NPI score.
- The study lasted only one week, which is not enough time to achieve full response from citalopram.
- Funded by Lundbeck, the manufacturer of escitalopram.
Description of the CitAD Trial (93,106,107)

- The CitAD study was a multicentre, double blind, 9 week, RCT designed to evaluate the efficacy of citalopram in patients with Alzheimer’s disease and clinically significant agitation, but without major depression. The trial lasted from 2009 to 2013 and involved 8 US and Canadian centres.
- The trial compared citalopram 30 mg/day plus a psychosocial intervention to placebo plus a psychosocial intervention.
  - The psychosocial interventions included provision of educational materials; 24 hour availability for crisis management; and a 20-30 minute counselling session at each scheduled visit.
  - Counselling sessions included a review and adjustment of the supportive care plan; emotional support; counseling regarding specific care giving skills; assistance with specific issues brought up by the caregiver or study participant; discussion of the educational materials.
- Lorazepam 0.5 mg daily was permitted as a rescue medication for clinically significant agitation and a maximum of 50 mg of trazodone was used to treat sleep disturbance.
- Two primary outcomes were evaluated: (See Table 6 p. 79 for description of scales)
  - The NBRS-A
    - The treatment effect was based on the difference in NBRS-A scores at 9 weeks. A statistical analysis controlled for differences between citalopram and placebo groups in baseline MMSE and NBRS-A scores.
  - The modified ADCS-CGIC
    - In the CitAD trial, the ADCS-CGIC was modified by the addition of items specific to agitation in AD in order to produce a global rating of change in agitation over time.
- Secondary efficacy outcomes included the following: (See Table 2)
  - NPI Total
  - Individual NPI domain ratings
  - NPI caregiver distress ratings
  - CMAI
  - ADCS-ADL (activities of daily living)
  - Cumulative lorazepam dose
- Secondary adverse events were also measured, including divergent scores on the MMSE and the Get up and Go (assessing mobility and gait).

Quality Assessment of CitAD

- The CitAD trial represents a well-designed, placebo controlled analysis of an antidepressant for the neuropsychiatric symptoms of dementia; and therefore, should provide greater weight in developing guidance compared to the Seitz meta-analysis.
The CitAD trial has a low risk of bias, according to the Cochrane Risk of Bias Tool. For example, patients were randomized in a 1:1 ratio by a coordinating centre, independent of the trial team.

- The trial was double blind. Masking was accomplished by over encapsulating citalopram tablets and creating matching placebos.
- ITT analysis was completed using appropriate statistical methods.
- No apparent selective reporting was identified in the main trial publication.
- The trial was funded by the National Institute on Aging and the National Institute of Mental Health.

We identified a number of limitations to the study:

- The total number of subjects screened to enroll the 186 study participants was not described and the reason why fewer than the intended 200 patients were recruited was not explained. In addition, each of the eight centers appeared to have enrolled a small number of patients. For example, if subjects were equally distributed across the 8 centers, each center would have enrolled 23 patients over 4 years, or approximately 6 patients per year. Thus, the patients enrolled may not represent the typical patient with neuropsychiatric symptoms.

- There were differences between groups for several baseline characteristics, suggesting the populations may have been unmatched; however, statistical analysis of the differences was not reported.
  - The placebo group had lower MMSE scores (2.6 point difference) and ADCS-ADL scores (3.5 point difference), and higher NBRS-A scores (0.4 point difference).
    - This difference suggests that the placebo group had more impaired cognition (MMSE score), function (ADCS-ADL score) and behavior (NBRS-A scores) compared to the citalopram group.
    - Efficacy outcomes were statistically adjusted for baseline differences in MMSE scores and NBRS-A scores, but not for differences in ADCS-ADL scores.

- The percentage of patients receiving lorazepam at baseline was higher in the placebo arm (10%) than the citalopram group (6%), which may also indicate that patients in the placebo group exhibited greater agitation.

This trial was undertaken before Health Canada established a maximum recommended dose of 20 mg of citalopram in patients 65 years of age or older. In the trial, doses were titrated to 30 mg of citalopram and too few patients received the 20 mg dose to evaluate the efficacy of this strength.
Table 15. Summary of studies included in Question 3 analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Daily dose</th>
<th>No. Weeks</th>
<th>N</th>
<th>Mean Age</th>
<th>Quality</th>
<th>Funding</th>
<th>Assessment Scales</th>
<th>Primary outcome</th>
<th>Statistically Sign. Benefit?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkel96</td>
<td>2004</td>
<td>Sertraline PBO</td>
<td>Subjects received donepezil</td>
<td>12</td>
<td>244</td>
<td>77</td>
<td>Unclear</td>
<td>Pfizer</td>
<td>NPI total b CGI (impact and severity) BEHAVE-AD CMAI</td>
<td>Change in NPI</td>
<td>No</td>
</tr>
<tr>
<td>Nyth77</td>
<td>1990</td>
<td>Citalopram PBO</td>
<td>20 to 30 mg/d</td>
<td>4</td>
<td>98</td>
<td>78</td>
<td>Unclear</td>
<td>No info</td>
<td>CGI Gottfrie, Brane, Steen (GBS) c UKU side-effect scale</td>
<td>Not specified</td>
<td>No</td>
</tr>
<tr>
<td>Olafsson98</td>
<td>1992</td>
<td>Fluvoxamine PBO</td>
<td>50 to 150 mg/d (gradual increase-no mean dose presented)</td>
<td>6</td>
<td>46</td>
<td>81 median</td>
<td>Unclear</td>
<td>No info</td>
<td>GWB Neuropsychological tests Multiple Neuropsychological tests</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>A chuck99</td>
<td>1997</td>
<td>Fluoxetine Haloperidol PBO</td>
<td>Fluoxetine (20mg/d) Haloperidol (3mg/d) Fixed doses</td>
<td>6</td>
<td>15</td>
<td>76</td>
<td>Unclear</td>
<td>Pilot study</td>
<td>National Institute on Aging CMAI BEHAVE-AD sections C,D,E adverse events</td>
<td>Change in CMAI</td>
<td>No</td>
</tr>
<tr>
<td>Pollock101</td>
<td>2002</td>
<td>Citalopram Perphenazine PBO</td>
<td>Citalopram 20 mg/d Perphenazine 0.1mg/kg/d</td>
<td>17 days</td>
<td>85</td>
<td>80</td>
<td>Unclear</td>
<td>NIMH, NIH</td>
<td>NBRS Side Effect Rating Scale MMSE</td>
<td>NBRS</td>
<td>Yes</td>
</tr>
<tr>
<td>Pollock100</td>
<td>2007</td>
<td>Citalopram Risperidone</td>
<td>Citalopram 20 - 40mg/d Risperidone 1 - 2 mg/d Mean (SD) final doses mg/d Citalopram: 29.4 (9.9) Risperidone: 1.25 (0.51)</td>
<td>12</td>
<td>103</td>
<td>82</td>
<td>Most items rated good quality except blinding</td>
<td>US Public Health and Sandra Rotman Program Authors declare COI</td>
<td>NBRS NPI Cornell scale UKU side effect MMSE Severe Impairment Battery</td>
<td>NBRS agitation and psychosis scores</td>
<td>No difference between active comparators – both improved from baseline</td>
</tr>
<tr>
<td>Sultzer102</td>
<td>1997</td>
<td>Trazodone Haloperidol</td>
<td>Trazodone 50 - 250 mg/d</td>
<td>9</td>
<td>28</td>
<td>72</td>
<td>3 of six variable</td>
<td>Non industry</td>
<td>CMAI, CGI Overt Aggression Scale</td>
<td>CGI CMAI TOTAL</td>
<td>No difference between active</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Drug</td>
<td>Daily dose</td>
<td>No. Weeks</td>
<td>N</td>
<td>Mean Age</td>
<td>Quality a</td>
<td>Funding</td>
<td>Assessment Scales</td>
<td>Primary outcome</td>
<td>Statistically Sign. Benefit?</td>
</tr>
<tr>
<td>--------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Teri3</td>
<td>2000</td>
<td>Trazodone Haloperidol PBO Behavioral mgt.</td>
<td>Trazodone 50-300 mg/d Haloperidol (0.5 - 3mg/d)</td>
<td>16</td>
<td>148</td>
<td>75</td>
<td>Unclear</td>
<td>National Institute on Aging</td>
<td>CGI BRSD (CERAD) CMAI</td>
<td>ADCS-CGIC</td>
<td>No</td>
</tr>
<tr>
<td>Gaber4</td>
<td>2001</td>
<td>Sertraline Haloperidol</td>
<td>Sertraline (25 to 50 mg/d) Haloperidol (1- 2 mg/d) Mean not reported</td>
<td>10</td>
<td>23</td>
<td>82</td>
<td>Unclear</td>
<td>Not stated</td>
<td>CMAI</td>
<td>CMAI</td>
<td>No difference between active comparators – both improved from baseline</td>
</tr>
<tr>
<td>Barak5</td>
<td>2011</td>
<td>Escitalopram Risperidone</td>
<td>Escitalopram: 5 mg daily x 7 d then 10 mg/d Risperidone 0.5 mg daily x 7 d then 1 mg/d</td>
<td>6</td>
<td>40</td>
<td>78</td>
<td>Most items low risk, industry funded, LOCF for missing data</td>
<td>Mfr of escitalopram</td>
<td>NPI BEHAVE-AD CSI ADCS-CGIC – post hoc</td>
<td>NPI</td>
<td>No difference between active comparators – both improved from baseline</td>
</tr>
<tr>
<td>Porstiensson6</td>
<td>2014</td>
<td>Citalopram Placebo</td>
<td>Citalopram 30 mg/d starting at 20 mg/day titrated to 30 mg/day over 3 weeks</td>
<td>9</td>
<td>186</td>
<td>78</td>
<td>Most items rated good quality</td>
<td>National Institute on Aging and National Institute of Mental Health</td>
<td>mADCS-CGIC NBRS-A NPI total NPI individual domains NPI caregiver distress CMAI ADCS-ADL MMSE GUG</td>
<td>mADCS-CGIC (modified to assess items specific to agitation) NBRS-A</td>
<td>Yes</td>
</tr>
</tbody>
</table>

a Quality based on Cochrane risk of bias criteria, b NPI 12 domains rated by caregiver interview frequency (0-4) and severity (0-3) Total score 0-144, c GBS rating scale is a quantitative rating scale for dementia syndromes; divided into 4 subscales measuring motor, intellectual and emotional functioning and symptoms common in dementia.
2. What is the applicability of the evidence to the frail elderly patient population?

Seitz Cochrane Review (95)

- The studies included in the systematic review were highly relevant to the frail population. Subjects were enrolled with a diagnosis of dementia, diagnosed according to standard diagnostic criteria including ICD-9, ICD-10, DSMIII, DSM-IV, NINCDS-ADRDA, NINDS/AIREN or DLB and included those with Alzheimer disease (AD), vascular dementia, mixed dementia, dementia with Lewy bodies (DLB), or dementia not otherwise specified.
  - Those with fronto-temporal dementia, Parkinson’s related dementia, dementia with concomitant major depressive disorder, and dementia with depressive symptoms but without mention of agitation or psychosis were not included in the analysis. Patients with other psychiatric disorders were generally excluded. These exclusions may limit the generalizability of results.

- Subjects ranged in mean age from 72-82.
- In 6/9 studies reporting MMSE measures, baseline scores ranged from 6.4 – 19 (mean approximately 13), indicating moderate to severe cognitive impairment. One study excluded patients with severe dementia. (97)
- The settings of the studies appear appropriate, 3 of 9 studies took place in the outpatient setting, with the remaining participants from either hospital or nursing home settings.
- Baseline assessment of neuropsychological symptoms used scales such as NBRSA, NBRSTotal, BEHAVE AD and CMAI. Four of 9 trials did not report values for baseline neuropsychiatric symptom scores. In the studies that did report on baseline symptom scores, approximate values had the following ranges in scores: NBRSA: 7 to 10; BEHAVE AD: 5.6 to 11.8; CMAI: 35 to 120; NPI total: 17-37.
  - Based on these scores it appears the severity of agitation was low to moderate. See Table 6 for description of scales.

Barak 2011 (105)

Characteristics of patients in this study are highly representative of a frail elderly population, with neuropsychological symptoms of dementia that required hospitalization.

- Inpatients were included if there was a diagnosis of dementia of the Alzheimer type (DSM IV) and admitted for signs and symptoms of psychosis, agitation, or aggression that occurred nearly daily in the week prior to enrollment. MMSE had to be between 5 and 24.
  - Baseline mean MMSE and NPI scores were approximately 14 and 19, respectively.
- Subjects suffered from delusions, hallucinations, aggression or agitation, which developed after the onset of dementia and were severe enough to disrupt function and justify treatment with antipsychotic medications, in the opinion of the study physicians.
- Patients were excluded if there was a diagnosis of a primary psychotic disorder (e.g. schizophrenia) or delirium, psychosis, agitation or aggression that could be better
accounted for by another medical condition; alcohol or substance abuse; or if there was previous treatment with the drugs under study, or contraindications to the study drugs.

- Mean age was 78 years old and approximately 50% were women.

**CitAD 2014 (106)**

- The participants enrolled in the CitAD trial were representative of a frail elderly population.
- Participants had probable Alzheimer disease, as determined by the National Institute of Neurological and Communications Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA).
- Most subjects were community dwelling (89%), with MMSE scores ranging from 5 to 28 (mean score 15.7), which given the correlation between dementia and frailty suggests the population in the study were frail.(16)
- In order to be enrolled in the trial, subjects were required to have clinically significant agitation, for which a physician determined that medication was appropriate.
- The presence of agitation was based on the ratings on the Neuropsychiatric Inventory (NPI) for items pertaining to agitation/aggression; these had to occur either:
  - very frequently
  - frequently with moderate or marked severity
- The severity of agitation for the participants at the beginning of the CitAD trial is unclear. The mean baseline score on the NPI subscore for agitation was 7.8 for citalopram and 8.0 for placebo (range of possible score is 0 to 12), indicating that participants predominantly experienced either severe agitation that occurred less than once per week, or moderate agitation occurring daily or several times per week.
  - The trial excluded patients with major depressive disorder (MDD), psychosis requiring antipsychotic treatment, adequate previous treatment with citalopram, or contraindications to citalopram.
    - In 2011, following the FDA advisory regarding a dose-dependent risk of QT prolongation with citalopram therapy, the CitAD steering committee amended their protocol to exclude individuals with a QTc greater than 450 ms for men and greater than 475 ms for women.

3. What is the potential benefit of antidepressants for NPS, and are the outcomes clinically relevant to those who are frail?

**Seitz Cochrane Review (95)**

The Seitz systematic review performed meta-analyses of results on seven comparisons (4 on efficacy outcomes and 3 on safety). Other results are reported for single studies, as noted by author names and dates of publications in the evidence table below.
### Table 16. Efficacy outcomes from Seitz Cochrane review

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI vs. PBO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAI Total</td>
<td>Meta analysis of 2 studies (sertraline and fluoxetine), N=250&lt;sup&gt;96&lt;/sup&gt;, MD -0.89, 95% CI -1.22 to -0.57, p&lt;0.00001 I²= 0%</td>
<td>Statistically significant but not likely clinically relevant as there was only a one point difference in a 203 point scale</td>
</tr>
<tr>
<td>NPI Total</td>
<td>One study N=240&lt;sup&gt;96&lt;/sup&gt; Sertraline -4.7 (SD 17.6): PBO -6.5 (SD 12) MD 1.80, 95% CI -2.01 to 5.61, p=0.35</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>BEHAVE-AD Total</td>
<td>One study N=240&lt;sup&gt;96&lt;/sup&gt; Sertraline -1.5 (SD 5.5): PBO -0.8 (SD 4.4) MD -0.70, 95 CI, -1.95 to 0.55, p=0.27</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>NBR Total</td>
<td>One study N=52&lt;sup&gt;101&lt;/sup&gt; Citalopram -10 (13.62): PBO -2.3 (17.46). Unadjusted MD -7.7, 95 CI -16.57 to 1.17, p=0.09</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td><strong>SSRIs vs. Atypical Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBR Total</td>
<td>One study N=103&lt;sup&gt;100&lt;/sup&gt; Citalopram -1.26 (SD 4.58) : Risperidone -0.73 (SD 4.91) MD -0.53, 95 CI -2.37 to 1.31, p=0.57</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>NBRS Psychosis Subscale</td>
<td>One study N=103&lt;sup&gt;100&lt;/sup&gt; Citalopram -1.9 (4.49): Risperidone -2.16 (4.68) MD 0.26, 95 CI, -1.51 to 2.03, p=0.77</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>CMAI Total</td>
<td>Meta analysis of 2 studies. N=33&lt;sup&gt;99,104&lt;/sup&gt; Fluoxetine or sertraline vs. haloperidol: MD 4.66, 95% CI, -3.58 to 12.9, p=0.27, I² =0%</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>NBRS</td>
<td>One study, N=64&lt;sup&gt;101&lt;/sup&gt; Citalopram -10 (SD 13.62) : Perphenazine -7.2 (SD 17.05) MD -2.80, SD -10.34 to 4.74 p=0.47</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td><strong>Trazodone vs. PBO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAI Total</td>
<td>One study, N=73&lt;sup&gt;103&lt;/sup&gt; Trazodone -0.76 (SD 16.76) : PBO -5.35 (SD 18.5). MD 5.18, 95% CI, -2.86 to 13.22, p=0.21</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td><strong>Trazodone vs. Typical Antipsychotic (haloperidol)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAI Total</td>
<td>Meta analysis of 2 studies, N=99&lt;sup&gt;102,103&lt;/sup&gt; Trazodone vs. haloperidol: MD 3.28, 95% CI, -3.28 to 15.74, p=0.33)</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>Clinical Global Impression</td>
<td>Meta analysis of two studies N=99&lt;sup&gt;102,103&lt;/sup&gt; Much or very much improved Trazodone vs. haloperidol: RR 1.25, 95%CI, 0.82 to 2.34, p=1.00</td>
<td>Not statistically significant</td>
</tr>
</tbody>
</table>

<sup>1</sup>The maximum recommended dose of Citalopram for those ≥65 years is 20mg/day due to prolonged QT interval risk.  
<sup>2</sup>Risperidone in dementia has been restricted to the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia such as vascular and mixed types of dementia.

- One outcome in the Cochrane Review demonstrated a statistically significant difference for antidepressants compared with placebo.
  - CMAI Mean Difference -0.89, 95% CI -1.22 to -0.57, p<0.00001 I²= 0%
A one point difference on a 203 point scale is likely of minimal clinical relevance.

All other comparisons did not demonstrate statistically significant differences as shown in Table 2 above.

Several comparisons were between active comparators. While there were no differences between them, without a placebo comparison, the clinical relevance is uncertain as most agents used to treat NPS of dementia have limited efficacy.

Barak 2011 (105)

The primary efficacy outcome in this study was change in the mean NPI scores from baseline.

NPI scores decreased significantly from baseline in both treatment groups over six weeks. Baseline NPI scores: escitalopram 21.3 (SD 11.8) and risperidone 17.4 (SD 4.5)

Mean (SD) change from baseline at Week 6:

- Escitalopram: -4.7 (7.3), p=0.02
- Risperidone: -7.7 (6.8), p=0.004

Between group difference in mean change from baseline was not statistically significant (p = 0.28).

Post-hoc analysis for changes from baseline in the “delusions, hallucinations, agitation/aggression” cluster on NPI were: (mean, standard deviation):

- Escitalopram: Baseline 4.4 (SD 1.8) reduced to 2.5 (SD 1.7)
- Risperidone: Baseline 4.7 (SD 2.1) reduced to 1.8 (SD 2.3)

CitAD 2014: Primary efficacy outcomes (106)

NBRS-A (range 0-18)

At 9 weeks, the mean unadjusted NBRS-A scores were 4.1 for the citalopram group and 5.4 for the placebo group.

Crude difference of 1.3 points (95% CI 2.6 to 3.5) between treatment and placebo groups.

The mixed effects regression model, resulted in an estimated difference on the NBRS-A between treatment group of -0.93 points at 9 weeks (95% CI -1.80 to -0.06).

The clinical relevance of less than a 1-point difference on the 18 point NBRS-A scale is not established.

In the methodological paper and in follow-up communication with one of the trial authors, a 3- to 5-point difference between treatment and placebo was thought to be clinically meaningful when the power calculation was performed. This is much greater than the results found in the trial.
mADCS-CGIC

- A total of 167 of the original 186 patients had week 9 results for the mADCS-CGIC and were categorized as indicated in Table 3 below:

<table>
<thead>
<tr>
<th></th>
<th>Citalopram N=86</th>
<th>Placebo N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked improvement</td>
<td>12 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>22 (26%)</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td>25 (29%)</td>
<td>20 (25%)</td>
</tr>
<tr>
<td>No change</td>
<td>17 (20%)</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>Minimal worsening</td>
<td>6 (7%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Moderate worsening</td>
<td>3 (4%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Marked worsening</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

- When patients with week 9 data were evaluated using a proportional odds model it was found that the odds of being in a better CGIC category were 2.13 times more likely with citalopram compared to placebo (OR 2.13; 95% CI 1.21-3.54).
- A sensitivity analysis included imputed values for missing data at 9 weeks. This analysis resulted in a similar odds ratio (OR 2.10; 95% CI 1.21-3.64).
- Forty percent of individuals in the citalopram group achieved marked to moderate improvement compared to 26% in the control group.
  - The trial did not report statistical differences between individual categories of the mADCS-CGIC however, according to our calculations the difference between groups is not statistically significant, likely due to the small sample size. (Katie clinical significance calculator http://medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service/AC-Service-Resources.html)
- To put results in another perspective the majority of participants experienced minimal to no change or worsening on the CGIC scale even on the background of an intensive psychosocial intervention.
  - 60% in the citalopram group and 74% in the placebo group.
- The trial did not report/evaluate statistical differences between individual categories of the mADCS-CGIC.
- The following questions were raised by us in relation to the CGIC analysis:
  - Baseline differences for the MMSE and the NBRS-A indicate the placebo arm had worse function and cognition. These variances may have impacted the response to medication.
  - Details on how the ADCS-CGIC was modified in the trial are not included in the trial publications.
- The clinical relevance of the CitAD primary outcome results is uncertain.
One co-primary outcome measure, NBRS-A, although statistically significant, is of questionable clinical significance (<1 point difference on an 18-point scale).

Interpreting the results of the mADCS-CCIG is difficult. The trial did not report/evaluate statistical differences between the individual categories of the mADCS-CGIC.

Most people will not demonstrate a benefit in their NPS by taking citalopram compared to placebo, however, a minority may benefit.

Although more patients respond to citalopram compared to placebo, the reality of these results is that the majority of patients do not respond or respond minimally, even on the background of counselling.

Secondary Efficacy Outcomes

- Relative to placebo, citalopram was associated with improved scores on:
  - NPI total score (range 0 to 144) (MD of -6.03; 95% CI -10.75 to 1.32, p=0.01).
  - NPI caregiver distress scale (range 0 to 60) (MD of -2.7; 95% CI -4.95 to -0.47, p=0.02)
    - The clinical relevance of less than a 3 point difference on the 60 point NPI caregiver distress scale is uncertain. Caregiver distress is an important outcome to study, as the impact of NPS can be significant for family members and caregivers.
  - CMAI (range 14 to 70) (MD of -2.38; 95% CI -4.13 to 0.63; p=0.008)

- There were no significant differences between citalopram and placebo at endpoint in the following measures:
  - ADCS-ADL scale
  - NPI agitation subscale:
    - Use of rescue lorazepam.
      - Notably, although there was no difference in use of lorazepam between citalopram and placebo groups, use was higher by the end of the study than at baseline in both groups, which may be an indication of escalating behaviours during the study.
        - 6% in the citalopram group and 10% in the placebo group used lorazepam at baseline.
        - 19% in the citalopram group and 23% in the placebo group used rescue lorazepam during the study.
  - The NPI agitation subscale was used to establish the presence and severity of agitation/aggression for study entry.
    - The clinical importance of failing to find a difference on the agitation scale, which was used for study inclusion, is not known.
    - The clinical relevance of finding improvement on one agitation scale (NBRS-A), but not another (NPI agitation subscale) is also not clear.
While trazodone 50 mg/day was permitted in the trial to manage sleep disturbances, the use of trazodone during the trial was not reported.

There are a number of features of the CitAD trial that may influence the generalizability of its results.

- The target dose of citalopram in CitAD was 30 mg, and 78% of patients achieved this dose.
- Health Canada recommends that the maximum prescribed dose of citalopram be 20 mg/day in patients’ ≥ 65 years of age.
- It was not possible to assess the efficacy of the 20 mg dose, as too few patients were maintained on this dose.

It is possible that some of the benefit in both groups could be attributed to psychosocial interventions, which included the provision of educational materials, 24 hour availability for crisis management, and a 20-30 minute counseling session at each study visit.

- The response rate in programs without an intensive psychosocial intervention is not known; however, it is likely the response would be lower than what was found in the CitAD trial.

Despite randomization, there were a number of baseline differences between the citalopram and placebo groups for cognition, function and agitation.

- Statistical analysis accounted for these differences for several of the efficacy outcomes, although not for the primary outcomes of CGIC.
- It is possible that other unaccounted differences also exist between the treatment groups.

It should be noted that citalopram was compared only to placebo, no other commonly prescribed drug was used as a comparator.

4. Is the timeframe appropriate to achieve benefit or for adverse events to appear?

Seitz Cochrane Review (95)

- Trials included in the systematic review lasted between 17 days to 16 weeks, with no discussion of time to effect.
- Behavioural symptoms of agitation and aggression often require treatments with quick onset. The trials in the review do not provide sufficient information to determine the timeframe for onset of action for antidepressants.
- The high withdrawal rates also complicate the assessment of time to benefit. Withdrawals due to any cause ranged from 12% to 53% for SSRIs, 41 to 60% for antipsychotics and 27% to 31% in placebo groups. See Table 18 below.

Barak 2011 (105)

- Results in this study are presented as changes from baseline to week 6 on the NPI scale. There are no analyses at other times during the trial.
Patients in this trial suffered delusions, hallucinations, aggression or agitation, which were severe enough to disrupt their functioning and to justify treatment with antipsychotic drugs. Six weeks may be too long a timeframe for medications to have effect in patients with these symptoms.

Secondary analysis of CitAD Study 2015 (109)

An analysis of time to response to citalopram during the 9-week study was performed and presented in a subsequent publication.

The time to effect analysis found:
- There was no difference in response rates between active and placebo treatments groups during the first 3 weeks of study.
- Approximately half of citalopram responders achieved their response after 3 weeks of treatment.
- Approximately 15% of responders showed a response at 3 weeks, but not at 9 weeks.

This analysis suggests that citalopram may not be a reasonable treatment option in Alzheimer’s disease patients with agitation who require more immediate management of their symptoms.

The treatment effect should be evaluated after 9 weeks of therapy.
- It may take up to 9 weeks to respond to treatment.
- Some individuals who show a response at 3 weeks will not maintain their response by 9 weeks.

5. What are the potential harms of antidepressants?

Seitz Cochrane Review (95)
Safety was evaluated in studies by the following outcomes: (see Table 4)
- Trial withdrawals due to adverse events
- Overall rates of trial withdrawal due to any cause
- Trial withdrawal due to worsening of symptoms
- Deaths during treatment
- Rates of specific side-effects such as somnolence, insomnia, headache, nausea, diarrhea, falls, bleeding, extrapyramidal symptoms, and hyponatremia.

Adverse events
- There was limited reporting of adverse events in the Cochrane Review and in the individual study publications.
- The studies had relatively high rates of trial withdrawal, as high as 40-60% in some studies which may limit the interpretability of the results.
Table 18. Withdrawals due to adverse events or due to any cause (Seitz meta-analysis)

<table>
<thead>
<tr>
<th>Withdrawals</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI vs. PBO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals - adverse events</td>
<td>Meta analysis of four studies(^{96-99})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>SSRI 24/200 (12%) vs. PBO 21/199 (11%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 1.07 (95% CI, 0.55 to 2.11), p=0.84.</td>
<td></td>
</tr>
<tr>
<td>Withdrawals - any cause</td>
<td>Meta analysis of three studies(^{96,98,101})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>SSRI 25% vs. PBO 27%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.91, (95% CI, 0.65 to 1.26), p=0.56</td>
<td></td>
</tr>
<tr>
<td><strong>SSRIs vs. Atypical Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals - adverse events</td>
<td>One study(^{100})</td>
<td>Small number of events in both groups.</td>
</tr>
<tr>
<td></td>
<td>Citalopram 4/53 (8%) vs. Risperidone 9/50 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.88 (95 CI, 0.63 to 1.24) p=0.46</td>
<td></td>
</tr>
<tr>
<td>Withdrawals - any cause</td>
<td>One study(^{100})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Citalopram 28/53 (53%) vs. Risperidone 30/50 (60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.37 (95 CI, 0.11 to 1.30) p=0.12.</td>
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</tr>
<tr>
<td><strong>SSRIs vs. Typical Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals - adverse events</td>
<td>One Study(^{99})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine 0/5 (0%) vs. Haloperidol 2/5 (40%)</td>
<td></td>
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<tr>
<td></td>
<td>RR 0.13 (95 CI, 0.00 to 3.52) p=0.22</td>
<td></td>
</tr>
<tr>
<td>Withdrawals - any cause</td>
<td>One study(^{101})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Citalopram 16/31 (52%) vs. perphenazine 18/31 (58%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.89 (95 CI, 0.33 to 2.37) p=0.81</td>
<td></td>
</tr>
<tr>
<td><strong>Trazodone vs. PBO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals - any cause</td>
<td>One study(^{103})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Trazodone 12/37 (32%) vs. Placebo 11/36 (31%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 1.06 (95 CI, 0.54 to 2.09) p=0.86</td>
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<tr>
<td><strong>Trazodone vs. Typical Antipsychotic (haloperidol)</strong></td>
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<td></td>
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<tr>
<td>Withdrawals - any cause</td>
<td>One study(^{103})</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Trazodone 12/37 (32%) vs. Haloperidol 14/34 (41%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.79 (95 CI, 0.43 to 1.46) p=0.40</td>
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</table>

Additional adverse events reported in the Cochrane Review or individual trials

SSRIs were associated with:

- A higher rate (20%) of diarrhea compared to placebo (8%): RR 2.37 (1.35 to 4.15). This outcome is a meta-analysis of 2 studies with a total of 342 participants.
- Less fatigue compared to the typical antipsychotic, haloperidol RR 0.19 (0.07 to 0.51)
- Fewer side effects than atypical antipsychotics (UKE Side Effect Scale total score MD -2.82 (-4.94 to -0.70)). This outcome was reported in one study with 103 participants.(100)
  - Pollock 2007 et al attributed the difference in UKE Side effect scale to the differences in sedation with a 26.2% decrease in sedation with citalopram and an 83.3% increase with risperidone.(100)
  - Comparable increases in EPS were seen with citalopram and risperidone.
Trial completion rates: escitalopram 75% (n = 16) and risperidone 55% (n = 11)

Reasons for patient discontinuation were:
- Escitalopram: Two patients transferred to a nursing home and two patients withdrew consent. No adverse events reported.
- Risperidone: one patient transferred to nursing home, two patients withdrew consent, two patients suffered from severe EPS and recurrent falls and four patients suffered from an acute physical illness necessitating transfer to a general hospital (myocardial infarction, pneumonia and two patients with urosepsis).

Safety was assessed by adverse events and cognitive ability based on MMSE scores.
- The MMSE score decreased at 9 weeks in those receiving citalopram, while the MMSE scores improved slightly in the placebo group from baseline.
- The difference between the two treatment groups at study endpoint was statistically significant in favour of placebo (estimated mean treatment effect −1.05; p=0.03).
  - The clinical significance of the small reduction in the mean MMSE scores in the citalopram arm is uncertain, although the mean drug-placebo differences for 10 mg donepezil was 1.36 in a 24 week trial. (110)
  - The authors conclude that the decline in MMSE scores with citalopram treatment should remain a consideration in patients with dementia until more research is conducted.
- Anorexia, diarrhea, and fever were all more common in the citalopram group and the rates of insomnia were higher with placebo. (Table 5)

Diarrhea may be a bothersome symptom, particularly for patients with dementia and their caregivers.

Withdrawals due to adverse events were similar in each treatment group (13.8% with citalopram vs. 14.1% with placebo).

Electrocardiogram monitoring results were available for 48 trial participants (24 in each treatment group). Citalopram was associated with a greater increase in QTc-interval than placebo (18.1 ms; 95% CI 6.1 - 30.1; p=0.004). More patients treated with
citalopram showed a QTc increase of greater than 30 ms from enrollment to week 3 than in patients taking placebo (7 vs. 1; p=0.05). Three people taking citalopram and 1 person taking placebo showed QTc prolongation >450 ms for men and >475 ms for women.

- The authors of the study conclude that the cognitive worsening and QTc interval prolongation observed in the citalopram group raised concern about the 30 mg per day dose used in this study and may limit the clinical utility of the findings.

Summary of Findings

- Our literature search identified one Cochrane Review of nine RCTS plus two additional RCTs evaluating the efficacy and safety of antidepressants for the treatment of NPS related to dementia. The majority compared an SSRI to either placebo or an active comparator (e.g., antipsychotics).
- None of the studies were rated as low risk of bias in the Cochrane Review primarily due to lack of detailed description of study methods or poor design.
- The additional two studies have low to moderate risk of bias on quality assessment but are not without limitations.
  - The Barak et al. trial lacked power to detect treatment difference due to size and withdrawal rates, and did not include a placebo arm. (105)
  - The Porsteinsson et al. CitAD trial was larger than most other studies and well designed; however, at baseline the placebo group had lower cognition and function scores which may have influenced results, despite analyses that attempted to correct for some of the baseline differences. (106)
- The majority of studies included in our analysis were not industry funded or the source of funding was unclear.
- The populations evaluated in the clinical trials were highly relevant to the frail elderly population with diagnoses of NPS associated with moderate to severe dementia, predominantly of the Alzheimer’s type.
  - Subjects with major depression or other psychiatric disorders were excluded.
  - Mean ages ranged between 72-82 years and included both community, nursing home, or hospitalized patients.
- Prior to the publication of the CitAD trial, studies did not provide sufficient evidence to support treating the neuropsychiatric symptoms of dementia with an antidepressant.
- In the Seitz Cochrane Review, only the Pollok et al. (2002) trial, of several reported, resulted in a statistically significant benefit in favor of SSRIs (sertraline and fluoxetine) compared to placebo. (101)
  - This outcome was the mean difference in CMAI (MD -0.89, 95% CI -1.22 to -0.57, p<0.00001).
  - The small difference of less than one point on a 203 point scale is of questionable clinical relevance.
The authors of the Seitz Cochrane Review state “at the present time, there is limited evidence to support the use of antidepressants for this indication.” (95)

Barak et al. studied an SSRI compared to a second generation antipsychotic in a population of patients with higher levels of agitation and psychosis than in other studies. (105)
- Both citalopram and risperidone improved the NPI scores to a similar extent over a 6 week period.
- Without a placebo control group it is difficult to suggest that either treatment is efficacious for treating the NPS of dementia, since a high placebo response is frequently demonstrated in these trials.

The CitAD study evaluated citalopram vs. placebo and provides evidence of a statistically significant benefit for several outcomes; however, the clinical relevance of the CitAD results is uncertain. (106)
- One co-primary outcome measure, the NBRS-A, although statistically significant, is of questionable clinical relevance (< 1 point difference on an 18 point scale).
- Interpreting the results of the other co-primary outcome, the mADCS-CGIC, is difficult. In general, the odds of being in a better CGIC category were higher with citalopram; however, the trial did not report or evaluate statistical differences between the individual categories of the mADCS-CGIC.
- It is important to note that 60% of participants did not demonstrate a notable improvement in their NPS when using citalopram compared to placebo.
- Results of secondary outcomes in the CitAD trial were mixed.
  - The NPI caregiver distress evaluation showed a statistically significant benefit; however, the clinical relevance of a small change on a 60 point scale is unclear.
  - There were no differences in the rates of lorazepam use between treatment arms; however, the use of lorazepam was higher at endpoint compared to baseline in both treatment groups. The increase in lorazepam use may be an indication of escalating NPS during the trial.
  - The NPI agitation subscale was used as the measure of agitation/aggression for inclusion in the trial; however, there were no significant differences between treatment arms for this outcome after 9 weeks of treatment.
- It is important to note that an intensive psychosocial intervention was provided to all patients in the CitAD trial. It is reasonable to expect that this increased the overall response rate in both treatment groups. (106)
- While one of the largest studies evaluating antidepressants in the frail elderly population to date, it included only 186 patients. In light of the high prevalence of dementia, it is surprising that larger and longer studies have not been performed.
- The maximum daily dose of citalopram in patients greater than 65 years of age is 20 mg/day, as established by Health Canada. The CitAD trial studied a dose of 30 mg/day. The effect of citalopram 20 mg/day for the treatment of agitation/aggression in dementia is unknown.
CitAD was the only study which evaluated the time to effect. The time to reach effect with citalopram was later than 3 weeks for over 50% of patients who responded, while approximately 15% of patients who responded at 3 weeks did not maintain a response by study endpoint at 9 weeks. Therefore, treatment with citalopram is not a good treatment option where acute management of symptoms is required, and a therapeutic trial of at least 9 weeks is required to adequately assess response.

Withdrawals due to any cause or due to adverse events did not differ for any of the comparisons in the Seitz Cochrane Review. The interpretation is hindered by the small number of patients in the clinical trials. Diarrhea was an adverse event which occurred more frequently in patients treated with SSRIs compared with placebo.

In the CitAD trial, adverse effects were generally more common in patients who were treated with citalopram. Participants treated with citalopram had greater increases in QTc interval and worsening cognition compared to placebo.

Conclusions

- Our review has shown there is considerable uncertainty about the efficacy of antidepressants for those with behavioural symptoms of dementia.
- Families and patients need to be aware of the limited potential for benefit based on the numbers that will not likely benefit, and balance this with the potential for adverse effects from antidepressants.
- When treatment is initiated, provide careful and ongoing follow up to assess treatment response, with the aim of stopping medications if benefit is not achieved. A trial of at least 9 weeks is required to adequately assess response.
<table>
<thead>
<tr>
<th>Scale</th>
<th>Subscales</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog</td>
<td>Alzheimer’s Disease (AD) Assessment Scale cognitive subscale</td>
<td>Evaluates cognitive impairment in AD assessment. Usually administered by a neuropsychologist or psychologist with appropriate training.</td>
<td>0 to 70 higher scores indicate greater cognitive impairment</td>
</tr>
<tr>
<td>ADCS-CGIC</td>
<td>Alzheimer Disease Cooperative Study - Clinical Global Impression of Change in Agitation</td>
<td>Interview with patient and caregiver, conducted by the clinician. Measures overall current functioning including symptoms of depression.</td>
<td>7 point scale: 1=markedly improved 2=moderately improved 3=minimally improved 4 = no change 5=minimally worse 6 = moderately worse 7=markedly worse</td>
</tr>
<tr>
<td>BEHAVE-AD</td>
<td>Behavioural Pathology in AD Agitation subscale, aggressiveness category</td>
<td>Assessment of BDAD in the community, outpatients, and residential care and clinical trials. 25 items grouped into seven major categories: Paranoid and delusional ideation, hallucinations, activity disturbance, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties and phobias. No formal training, but should be used by a person with some health training.</td>
<td>25 items 0-3 score for each item 75 maximum score</td>
</tr>
<tr>
<td>BRSD-ERAD)</td>
<td>Behavioural Rating Scale for Dementia Irritability/agitation category</td>
<td>Assesses/evaluates behavioral disturbance in people with dementia or cognitive impairment and effectiveness of drug treatment or other non-pharmacological interventions.</td>
<td>46 items 0-4 score for each item 148 maximum score</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression Scale</td>
<td>Measures symptom severity, treatment response and the efficacy of treatments Considered somewhat subjective as the user must subjects to typical patients in the clinician experience.</td>
<td>Scores range 1-7 1= normal, not at all ill 2= borderline mentally ill 3=mildly ill 4= moderately ill 5= markedly ill 6= severely ill 7= extremely ill</td>
</tr>
<tr>
<td>CDR</td>
<td>Clinical Dementia Rating sum of the boxes (CDR)</td>
<td>The Clinical Dementia Rating is a five point scale.</td>
<td>CDR- 0 = no cognitive impairment,</td>
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<tr>
<td>Scale</td>
<td>Subscales</td>
<td>Description</td>
<td>Score</td>
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| CMAI                      | Cohen Mansfield            | An empirical scale that measures only observable behaviours and does not consider mood or thought content. Developed for nursing home use. Behaviours characterized in four clusters: verbally aggressive (e.g. directed at a person or object), verbally nonaggressive (not directed at a person or object), physically aggressive (directed), and physically nonaggressive (undirected), but total score is most commonly used to quantify behavioural disturbance. Used by professional caregivers and training required. | CDR-0.5 = very mild dementia  
CDR-1 = mild  
CDR-2 = moderate  
CDR-3 = severe  
Long form  
29 items  
1-7 score for each item  
203 maximum score  
Considered reliable and valid.  
Additional versions developed including one for community (CMAI-C), a 38 item questionnaire for interviews with caregivers or relatives, and a short form (14 items). |
| GBS                       | Gottfried, Brane and Steen | Includes a number of items on which scores range from zero to six, where six implies maximal impairment.                                                                                                   |                                                                                           |
| NBRS                      | Neurobehavioral Rating     | The NBRS is a 28 item observer-rated instrument derived from the Brief Psychiatric Rating Scale (BPRS). The NBRS was originally designed to assess drug treatment effects in a general adult psychiatric population                                                                 | Total score  
16 item scale with a score of 1-7 for each item and a maximum score of 112  
Agitation subscale:  
0-18 |
|                           | Rating Scale               | Agitation subscale  
Psychosis subscale                                                                                                                                  |                                                                                            |
|                           |                            | **Agitation subscale**: assesses agitation, hostility/uncooperativeness, and disinhibition                                                                                                                     |                                                                                            |
|                           | NPI                        | Neuropsychiatric Inventory  
Agitation subscale                                                                                                                                    | 0-144  
12 items  
0-12 score for each item  
Frequency (0-4) and severity (0-3) multiplied to give domain scores                                                                 |
<p>|                           |                            | Assesses psychopathology in dementia to distinguish between different causes (e.g., AD, fronto-temporal) and caregiver distress associated with behavioral symptoms. One item on carer stress. Specific training is not required. Rates frequency and severity. |                                                                                            |</p>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
<td>MMSE is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language.</td>
<td>Maximum score is 30. A score of 23 or lower is indicative of cognitive impairment</td>
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<tr>
<td>SIB</td>
<td>Severe Impairment Battery (SIB)</td>
<td>Evaluates cognitive abilities at the lower end of the range and is appropriate for individuals who are too impaired to complete standard neuropsychological tests.</td>
<td>Total 133 points</td>
</tr>
</tbody>
</table>
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Appendix 1. Guidelines on the use of antidepressants in seniors for depression, dementia and NPS

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<tr>
<th>Organization</th>
<th>Relevant summary points</th>
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| **Canada**                                                                   | **Canadian Coalition for Seniors’ Mental Health 2014**  
  The assessment and treatment of mental health issues in long term care homes, 2014 Guideline Update  
  Tools:  
  Update of 2006 guidelines—more recent literature” is consistent with or enhances” the recommendations made in 2006.  
  **Two modified recommendations:**  
  1. Residents with less severe depression should receive psychosocial interventions as a first step before an antidepressant.  
  2. Escitalopram and duloxetine added to first-line antidepressants (citalopram, sertraline, venlafaxine, mirtazapine, bupropion).  
  **New recommendation:**  
  1. LTC staff should develop quality improvement initiatives focused on how to optimize prescribing of psychotropic medication |
| **Centre for Effective Practice 2015**                                      | **http://effectivepractice.org/assets/pdf/bpsd_discussion_guide.pdf**  
  This tool is designed to help providers understand, assess, and manage residents in LTC homes with behavioural and psychological symptoms of dementia (responsive behaviours), with a focus on antipsychotic medications. Antidepressants are included for targeted symptoms, when a non-drug approach has failed.  
  For severe depression:  
  - Antidepressants such as SSRIs (e.g. citalopram, sertraline), SNRIs, (e.g. venlafaxine, duloxetine), other antidepressants (bupropion, mirtazapine, moclobemide)  
  - Secondary TCAs (nortriptyline or desipramine) may be suitable if coexisting indication such as neuropathic pain, etc., but caution regarding anticholinergic load |
| **Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4) 2014** | **www.ncbi.nlm.nih.gov/pmc/articles/PMC3516356/pdf/cgi-15-120.pdf**  
  **Relevant statements**  
  There is no good evidence to recommend for or against the use of cholinesterase inhibitors and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication (Grade 2B).  
  We recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality (Grade 2A).  
  There is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression and psychosis associated with dementia (Grade 2B).  
  There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients (Grade 2B)  
  **Alberta**  
  **Antidepressants as a substitute for antipsychotics:** Summarizes literature similar to what was found in our review of Q3. |
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<td><strong>Best practices in the management of behavioural and psychological symptoms of dementia in residents of long-term care facilities in Alberta 2014</strong></td>
<td>A high-quality recent systematic review of 6 RCTs (Seitz 2011) reported no statistically significant differences in BPSD or drug tolerability between antidepressants (SSRIs) and antipsychotics (typical and atypical). One additional RCT (Barak 2011) also reported no significant differences in outcomes measures between SSRIs and antipsychotics. All studies included small sample sizes and were of low to moderate quality. None of the studies reported adverse outcomes.</td>
</tr>
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</table>
| **BC Best Practice Guideline for Accommodating and Managing Behavioural and Psychological Symptoms of Dementia in Residential Care 2012** | - SSRi’s trazodone and benzodiazepines are included in a flow chart as therapies to consider for anxiety.  
- SSRi’s, SNRI’s and NaSSa are considered for depression. |
<p>| <strong>UK</strong>                                                                      | Under review – new report due in 2017. Reports overarching principles for managing aggression and “behavior that challenges”                                                                                           |
| <strong>NICE 2006</strong>                                                               |                                                                                                                                                                                                                        |
| Dementia: supporting people with dementia and their carers in health and social care |                                                                                                                                                                                                                        |
| <strong>US</strong>                                                                      | BPSD                                                                                                                                                                                                                   |
| Practice Guidelines for the treatment of patients with Alzheimer disease and other dementias 2014 | New evidence indicates that antipsychotics provide weak benefits for the treatment of psychosis and agitation in patients with dementia. Adverse effects of antipsychotics reported in new studies include sedation, metabolic effects, and cognitive impairment. |
| Updates from a 2007 guideline                                                | New evidence indicates that for many patients with Alzheimer’s disease, antipsychotics can be tapered and discontinued without significant signs of withdrawal or return of behavioral symptoms. |
|                                                                             | New studies indicate that cholinesterase inhibitors and memantine have no clinically significant effects on disruptive behaviors.                                                                                      |
|                                                                             | <strong>Depression</strong>                                                                                                                                                                                                          |
|                                                                             | There continues to be mixed evidence for the efficacy of antidepressants to treat depression in patients with dementia.                                                                                                 |
| <strong>AUSTRALIA</strong>                                                               | Pharmacological intervention studies for the management of depression in dementia are limited in number and quality. While expert consensus guidelines recommend the use of antidepressants as the treatment of choice for non-psychotic depression in dementia the evidence for their efficacy is limited. |
| Managing Behavioural and Psychological Symptoms of Dementia (BPSD) 2012     | Two smaller studies provided moderate to strong evidence for the efficacy of sertraline although three other larger studies of strong quality did not. Two of these studies, which included greater                                                                 |</p>
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<td>numbers of participants, examined the efficacy of sertraline and/or mirtazapine found no difference in outcome compared to placebo. Sertraline was associated with more adverse events than placebo.</td>
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<td>Strong evidence indicates no significant difference between placebo and fluoxetine or between placebo and venlafaxine in the reduction in depressive symptoms. Adding a ChEI to antidepressant treatment is recommended as a second-line option although no studies for combined therapy were evident in the recent literature.</td>
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<td><em>Where medication is indicated, expert consensus guidelines recommend the use of antidepressants as a first-line approach for non-psychotic depression in dementia and combination therapy with cholinesterase inhibitors as a second-line approach.</em></td>
</tr>
</tbody>
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