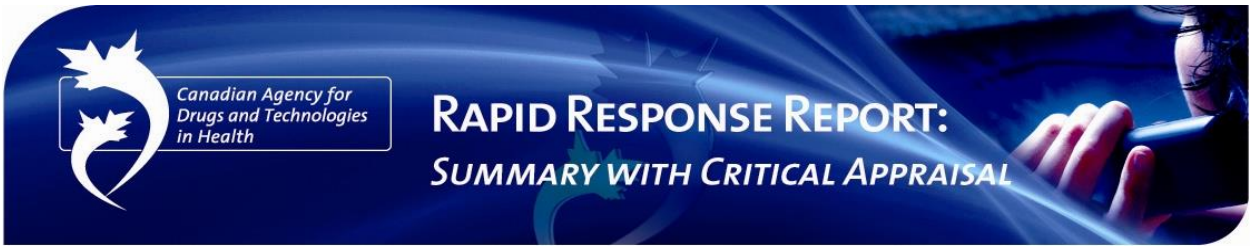

TITLE: Antidepressants in Elderly Patients with Major and Minor Depression: A Review of Clinical Effectiveness and Guidelines

DATE: 17 August 2015

CONTEXT AND POLICY ISSUES

Depression is common in older adults, disproportionately affecting this segment of the population. While the general population prevalence of major depressive disorder (MDD) is approximately 5%,[1] an estimated 14% to 20% of community dwelling older adults experience symptoms of depression, with even higher rates being observed in inpatients (12% to 43%) and in those who reside in long-term care facilities, where the estimated prevalence may reach 40%.[2] Similarly, the median prevalence of minor depression was higher in elderly inpatients in medical settings (14.4%) than in community-based settings (7.7%).[3] Depression in older adults is associated with a significant morbidity burden, impairing the ability to function both physically and cognitively and increasing the risk comorbid medical illnesses, delayed recovery, placement in long-term care facilities and mortality due to suicide and other causes.[2]

Pharmacotherapy is the cornerstone of management for depression, with guidelines recommending their use in mild, moderate and severe depression.[4,5] Antidepressants are categorized into classes based upon their structure or the neurotransmitters that they affect, with therapeutic options including:

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

While clinical trials of antidepressants may include some individuals over the age of 65, it is not clear that evidence of safety and efficacy in such subgroup analyses are reflective of the this age group more broadly. The generalizability of outcome data across populations can potentially

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be uncertain and the comparative efficacy of different antidepressants in older adults could potentially differ than what is seen in younger populations. As well, age-related changes that affect the pharmacokinetics and pharmacodynamics of drugs can affect the safety and potential harms with antidepressants in older adults. Older adults are at increased risk of anticholinergic side effects (common to a number of antidepressant classes), and orthostatic and sedative effects.[6] These effects can exacerbate underlying conditions such as cardiovascular disease, cognitive impairment, delirium and can increase the risk of falls and fractures.[6]

The purpose of this Rapid Review is to summarize the evidence of clinical efficacy and harms associated with antidepressant in older adults, and guidelines regarding their use in the population.

RESEARCH QUESTIONS

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

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

KEY FINDINGS

Four systematic reviews, two pooled analyses, two randomized controlled trials and one cohort study provided evidence of the efficacy and safety of antidepressants in older adults.

A number of antidepressants appear to be effective in those aged 65 and older, relative to placebo, in achieving remission of symptoms and treatment response, but there is limited evidence of comparative efficacy between antidepressants.

Potential concerns regarding safety were identified across multiple classes of antidepressant, but were based upon cohort studies, suggesting more rigorous, long-term studies of safety in this population are needed.

Four evidence-based guidelines included recommendations that antidepressant dosages be adjusted in elderly patients to improve tolerability and to consider the impact of comorbidities.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies containing safety data, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and July 15, 2015.

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

Selection Criteria and Methods

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

Table 1: Selection Criteria

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

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

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2010. As well, review articles that were not based upon a systematic literature search and guidance documents or consensus statements that did not include a description of the methodology used in their development, were not clearly evidence-based, or did not make explicit recommendations were not summarized in the report, but listed in Appendix 5.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR tool,[7] randomized and nonrandomized studies were critically appraised using Downs and Black Checklist,[8] and guidelines were assessed with the AGREE II instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Quantity of Research Available

A total of 760 citations were identified in the literature search. Following screening of titles and abstracts, 724 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 28 publications were excluded for various reasons, while 13 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

> *What is the clinical effectiveness and safety of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

Study Design

Four systematic reviews,[10-13] two reports of pooled analyses of RCTs,[14,15] two individual RCTs,[16,17] and one population-based cohort study[18] met the inclusion criteria for this Rapid Response. Two of the systematic reviews included only RCTs,[12,13] while two included other designs (systematic reviews, non-randomized studies, epidemiologic studies) as well.[10,11] The number of studies that were selected for inclusion into the systematic reviews and were relevant to this Rapid Response ranged from two[12] to 18 studies.[10] Ruxton 2015,[10] which was a systematic review of safety, had the most current search, with a cutoff of June of 2013. Other reported cutoffs were September 2012[11] and September 2010.[12] One systematic review did not describe the timeframe of the search.[13] The pooled analyses of RCTs combined individual patient-level data from multiple studies, rather than using meta-analytic techniques based on group results. One pooled analysis included two RCTs[14] and one included nine RCTs, and did not report search timeframes.[15] (See Table A1, Appendix 2) Two additional RCTs[19,20] met the inclusion criteria for the review, but were included in one or more of the systematic reviews so are not summarized individually.

Country of Origin

The systematic reviews were performed by authors from Australia,[10] Italy,[11] the United States,[12] and Canada.[13] Both pooled analyses were performed by authors from the United States.[14,15] (See Table A1, Appendix 2) One RCT was conducted at a single centre in China,[16] while the

other was a multi-centre study, with sites in North America (Canada and the United States), Australia and Europe.[17] The population-based cohort study was conducted in the United Kingdom.[18] (See Table A2, Appendix 2)

Patient Population

As per the inclusion criteria for this Rapid Response, the patient populations included only adults aged 65 and over with depression. In one SR, the inclusion criteria for age was 55 and over[11] and in another systematic review,[12] there was no restriction on age; however, in both reviews study outcomes were not pooled and described narratively.[11] Thus, for these two systematic reviews,[11,12] it was possible to identify specific studies that included only the population aged 65 and over and report the results in this Rapid Response. One pooled analysis (Kornstein 2010) included individuals aged 18 and older, but reported subgroup results for the population aged 65 and over.[15] The remaining systematic reviews[10,13] and pooled analysis[14] included studies only with patients aged 65 and over. One systematic review[12] and one pooled analysis[14] focused on outpatients. Ruxton 2015[10] specified inclusion across multiple settings (community, aged care facilities, institutions or hospitals), whereas the remaining SRs did not specify the setting.[11,13] (See Table A1, Appendix 2)

In one RCT patients were required to have a DSM-IV diagnosis for MDD and a Geriatric Depression Scale (GDS) scale score of greater than 20 at baseline.[16] It was unclear if this study was conducted in inpatients or outpatients. The other RCT enrolled outpatients, but did not specify the diagnostic criteria for MDD.[17] In both studies, the majority of patients were female.[16,17] The population-based cohort study included primary care patients, the majority of whom were female, with a new episode of MDD, defined according to database coding.[18] (See Table A2, Appendix 2)

Interventions and Comparators

The efficacy of duloxetine was evaluated in one SR[11] and one pooled analysis.[14] For the SR, there was no restriction on comparator (placebo controlled, studies with any active comparator, and single arm studies were eligible for inclusion),[11] whereas in the pooled analysis, all trials were placebo controlled.[14] Kornstein 2010 included only placebo controlled trials of desvenlafaxine,[15] while Seitz 2010 included only studies in which citalopram was compared to other antidepressants.[13] The remaining two SRs assessed multiple antidepressants, in comparison to other antidepressants[12] and to drugs with no anticholinergic activity or placebo.[10] (See Table A1, Appendix 2)

Both included RCTs were placebo controlled trials, one of escitalopram[16] and one of bupropion XR.[17] The population-based cohort study compared patients treated with TCAs, monoamine oxidase inhibitors (MAOIs), SSRIs or other antidepressants to a group of patients who received no treatment.[18] (See Table A2, Appendix 2)

Outcomes

The efficacy of antidepressants was measured using various standardized scales, which were then used to categorize patients as achieving a treatment response or remission of symptoms. The amount of change from baseline in the scale scores was also an outcome that was reported. Ruxton 2015[10] evaluated only safety outcomes, including falls, cognitive impairment, and all-cause mortality. Similarly, the pooled analysis by Oakes 2013[14] focused only on safety outcomes, which included adverse effects and changes in weight, vital signs and laboratory

values. The other pooled analysis assessed only the change in depressive symptoms,[15] while the remaining three SRs assessed both safety and efficacy outcomes.[11-13] (See Table A1, Appendix 2)

Both included RCTs assessed change in depressive symptoms, one with the GDS[16] and one with the Montgomery Asberg Depression Rating Scale (MADRS).[17] Other scales were also used to capture change in symptoms, disability and quality of life.[17] The population-based cohort study assess only safety outcomes.[18] (See Table A2, Appendix 2)

> *What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

Four evidence-based guidelines met the inclusion criteria for this Rapid Response, all of which were based upon systematic literature searches. Guidelines were produced by the British Association for Psychopharmacology,[21] the Institute for Clinical Systems Improvement,[22] the American Psychiatric Association,[4] and by National Institute for Health and Care Excellence.[23] The guidelines differed in their approaches to evidence synthesis, approach to recommendation formulation and grading of the evidence and rating of strength of recommendations.[4,21-23] The included guidelines addressed the management of major depressive disorder in adults, not restricted to geriatrics. Within each guideline, however, there were recommendations or considerations specific to geriatric patients. The guideline from the Institute for Clinical Systems Improvement intended for use in primary care settings.[22] The remaining three guidelines were not setting-specific.[4,21,23]

Summary of Critical Appraisal

> *What is the clinical effectiveness and safety of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

The critical appraisal of the included SRs and pooled analyses is summarized in Appendix 3, Table A4, while the critical appraisal of the included RCTs and cohort study is summarized in Appendix 3, Table A5.

The rigor of the included SRs was variable. Gartlehner 2011 was the most rigorous of the included SRs, meeting all of the AMSTAR checklist criteria.[12] Seitz 2010[11] was also methodologically rigorous, with its main limitations being a lack of description of the methods for data extraction and failure to provide definitions for some study outcomes (such as response and remission). Ruxton 2015[10] used comprehensive literature searches to identify relevant literature, critically appraised the included studies using standard tools and used appropriate meta-analytic techniques to pool study results. However, the methods for study selection and data extraction were unclear and there was lack of detail in the description or definition of the outcomes. Despite meeting the AMSTAR checklist criteria for clear and detailed reporting of the study characteristics, populations and outcomes, there was limited detail provided regarding the methodology using by Del Casale 2012[11] in the conduct of their SR. As such, most items on the AMSTAR checklist were not met .

The pooled analyses conducted by Oakes 2013[14] and Korstein 2010[15] shared similar limitations. The manner in which the included studies were identified or selected for inclusion was unclear.

As such, it is not possible to determine if all relevant studies would have been captured. No methodological details were reported about data extraction or assessment of study quality.

The included RCTs had some methodological limitations which could potentially compromise the internal and external validity of the studies. For Chen 2011, the method of allocation concealment was unclear and it could not be ascertained whether the investigators were blinded.[16] The statistical methods appeared to have some limitations in that the analysis did not follow the intention-to-treat principle and there was no sample size calculation. In terms of external validity, details of the outcomes were sparse and adverse effects were not reported. The number of participants was limited and it was not clear if the sample would be considered representative of older adults with depression, particularly since it was a single centre study conducted in China.[16] Hewett 2010[17] appeared to be more rigorous, with greater detail of the research methodology reported, however, the relatively high dropout rate (> 20%) could affect the internal validity. The high dropout rate required that a significant, but similar proportion of the data be imputed to create the intention-to-treat dataset. As well, failure to meet the data assumptions of ANCOVA for the pre-planned statistical analysis prompted the investigators to perform a post-hoc statistical analysis for the primary outcome, based upon a nonparametric statistical test. This post-hoc analysis produced contradictory results to the pre-planned analysis. Neither RCT had an active comparator.[16,17] A head-to-head comparison of efficacy relative to another antidepressant would likely be more relevant to decision-making than comparison to a placebo. Further, there was no discussion of the clinical relevance of the outcomes. The population-based cohort study was limited by its design.[18] The lack of randomization to treatments makes it impossible to control for unknown confounders. The investigators did, however, control for some potential confounders in the analysis and had a sufficiently large sample size to capture some uncommon adverse events.

> *What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

Using the AGREE II instrument, the included guidelines were methodologically rigorous in their development, reported to be based upon systematic reviews of the literature, and presented clear recommendations. It was difficult to ascertain the quality of the systematic literature reviews upon which the guidelines were developed, due to lack of detailed reporting. The guideline from the Institute for Clinical Systems Improvement[22] did, however, use its standard methodology. The systematic review performed by the National Institute for Health and Care Excellence[23] also used its standard methodology and was rigorous in its conduct, satisfying all AMSTAR criteria. Common limitations included a lack of description of monitoring and auditing criteria, barriers to implementation and resource implications.[4,21,23] As well, most groups did not consult the target population to identify patient preferences.[4,21,22] (Appendix 3,Table A6).

Summary of Findings

> *What is the clinical effectiveness and safety of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

Systematic Reviews and Pooled Analyses

The efficacy of citalopram was evaluated in one SR with meta-analyses for some outcomes.[13] The odds ratio for remission of symptoms with citalopram was 0.84 (95% confidence interval [CI]: 0.56 to 1.42) relative to other antidepressants combined (based off of two studies of TCAs, one study of mianserin, and one study of venlafaxine). The odds ratio for treatment withdrawal was not significantly different between citalopram and other antidepressants (OR 0.70, 95% CI: 0.48 to 1.52). Changes in symptom severity were similar between citalopram and other antidepressants, but were not pooled using meta-analysis. The authors concluded that there was no overwhelming evidence of the efficacy of one antidepressant over another.(See Appendix 4, Table A7)

The efficacy and safety of duloxetine was assessed in one SR[11] and one pooled analysis.[14] Reporting of numerical efficacy data was limited in the SR, but duloxetine was reported as superior to placebo in improving symptoms of depression, with similar rates of discontinuation due to adverse effects. In single-arm, open-label studies included in the SR, duloxetine reduced Hamilton Depression Rating Scale (HAMD)-17 scores by 13.0 to 17.5 points. The clinical importance of this observation was not reported, and also limited by the lack of comparator and open-label design. Rates of response ranged from 63% to 89% and remission from 41% to 72%, but again there was no placebo or active comparator in these studies. In one study included in the SR, duloxetine was compared to vortioxetine and placebo. Rates of response and remission were similar with the two active treatments, and higher than that of placebo, but no statistical analysis was presented. The authors concluded that duloxetine was safe and effective in elderly populations, with similar efficacy to other antidepressants (despite there being limited head-to-head comparisons in the elderly to support this conclusion). The pooled analysis of safety of duloxetine compared with placebo demonstrated no statistical differences in the discontinuations for any reason, serious adverse effects, and most vital signs.[14] Higher rates of treatment emergent adverse effects, dry mouth, constipation, nausea, dizziness, diarrhea and weight loss were observed with duloxetine. It was concluded that the safety findings for patients aged 65 and over were similar to adults those observed in adults over the age of 18, despite there being no analyses or reporting of outcome data for the general adult population in the pooled analysis. (See Appendix 4, Table A7)

The efficacy and safety of escitalopram was assessed in one SR, which included results of one RCT of escitalopram compared with fluoxetine and placebo.[12] While escitalopram-treated patients had a greater improvement in MADRS score than fluoxetine treated patients (scores not reported), escitalopram did not differ from placebo. As well, no statistical differences were noted for response or remission outcome variables; however, nausea was greater with both active treatments than placebo (data not reported). An RCT with a head-to-head comparison of fluoxetine and paroxetine in patients over the age of 65 was also included in the same SR. Limited details of the study outcomes were presented; however, significant improvement in HAMD scores and cognitive impairment were reported in both groups, with a faster onset for paroxetine. Severe adverse events (AEs) were more common with fluoxetine (n=22) than paroxetine (n=9; $P < 0.002$). The authors concluded that efficacy and tolerability of the antidepressants included in the review were similar in older adults (greater than 60 years of age) and younger adults. (See Appendix 4, Table A7)

The efficacy of desvenlafaxine relative to placebo was assessed in a pooled analysis of nine RCTs.[15] In the subgroup of individuals aged 65 and over, the mean ± standard deviation change from baseline in HAMD-17 scores was larger with desvenlafaxine (-12.5 ± 1.1) than with

placebo (-8.1 ± 1.3; P = 0.004). The odds of response (OR 4.59; 95% CI: 2.13 to 9.89) or remission (OR 3.83; 95% CI: 1.46 to 10.00) also favored desvenlafaxine over placebo. No harms data were presented in this report. The authors concluded that desvenlafaxine was effective across subpopulations.(See Appendix 4, Table A7)

In an SR of harms with antidepressants in individuals aged 65 and older, the risks of falls was increased with TCAs (imipramine, nortriptyline, amitriptyline), trazodone, mirtazapine, and paroxetine).[10] All-cause mortality was also increased with amitriptyline, trazodone, mirtazapine, and paroxetine.(See Appendix 4, Table A7)The authors concluded that based upon limited evidence, their analyses demonstrated an increased risk of falls, cognitive impairment and mortality with drugs with anticholinergic activity. Of note, the conclusions regarding cognitive impairment were based upon anticholinergic drugs other than antidepressants.

Randomized Controlled Trials

One additional RCT provided evidence of the safety and efficacy of escitalopram relative to placebo in patients aged 65 and over.[16] After eight weeks of treatment, the GDS score was lower in the escitalopram treated group (10.7 ± 3.7) than in the placebo group (21.1 ± 3.5; P < 0.05). As well, the percentage reduction in GDS score was greater with escitalopram (54.4% versus 12.1%). The clinical cure rate was greater with escitalopram (40.7%) than with placebo (0%, P < 0.01). Similar results were observed for the Clinical Global Impressions Severity of Illness (CGI-SI). The adverse event rate was higher in patients treated with escitalopram (22.2%) than with placebo (4.2%). There was limited detail on the specific events, which were described as mild, with nausea, dry mouth and dizziness provided as examples. No severe adverse reactions were reported. The authors concluded that escitalopram was efficacious for the treatment of geriatric depression, with no serious adverse effects. (See Appendix 4, Table A8)

An RCT compared bupropion XR with placebo in patients over the age of 65 using a number of different scales.[17] The primary outcome was the change from baseline in MADRS score, which failed to show a statistically significant result based up the pre-planned statistical analysis. However, a post-hoc analysis that was performed due to failure to meet the statistical test assumptions for the pre-planned analysis showed a greater median change from baseline with bupropion XR (-15.0) than with placebo (-11.0; P = 0.033). Rates of response for the MADRS (53% versus 43%, P = 0.014) and Clinical Global Impression – Improvement (CGI-I) responders (69% versus 46%, P < 0.001) were greater with bupropion XR than with placebo. Improvements in disability measured with the Sheehan Disability Scale (SDS) and in quality of life measured with the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) were also noted, however, the clinical importance of the improvements was unclear. Discontinuations due to adverse effects, increases in blood pressure and heart rate, and changes in weight were similar with placebo and bupropion XR. The authors concluded that buproprion XR was effective in improving symptoms of depression, quality of life and function in elderly patients with depression and that bupropion XR was an appropriate treatment option given its tolerability profile. (See Appendix 4, Table A8)

Non-Randomized Studies

Adverse effects of different antidepressant classes (TCAs, SSRIs and 'other') were assessed in individuals aged 65 and older in a population-based cohort study.[18] Relative to those individuals who did not receive treatment, each antidepressant class evaluated was associated with an

increased risk of all-cause mortality, attempted suicide or self-harm, falls, fracture, and upper gastrointestinal (GI) bleeding. Relative to TCAs, the SSRIs were associated with an increased risk of all-cause mortality (hazard ratio [HR]: 1.32; 95% CI: 1.26 to 1.39), stroke or transient ischemic attack (HR: 1.15; 95% CI: 1.05 to 1.26), falls (HR: 1.27; 95% CI: 1.20 to 1.35), fracture (HR: 1.26; 95% CI:1.15 to 1.37), epilepsy or seizures (HR: 1.80; 95% CI: 1.32 to 2.43), and hyponatremia (HR: 1.44; 95% CI:1.19 to 1.75). The authors concluded that SSRIs and 'other' antidepressants had an increased risk of a number of adverse events, but that there was potential for confounding and, as such, additional studies were needed to confirm the results. (See Appendix 4, Table A8)

> *What are the evidence-based guidelines associated with the use of antidepressants in elderly patients with major and minor depression in any setting (home, long-term care, or hospital)?*

The key guideline recommendations specific to elderly patients with depression are summarized in Appendix 4, Table A9. The four guidelines[4,21-23] contained recommendations to consider the effects that age-related changes may have on antidepressant therapy. The guidelines all recognize the need for awareness of the potential for reduced tolerability of antidepressant therapy in older adults and changes in drug metabolism. Recommendations include initiating treatment at lower dosages to improve tolerability or adjusting dosages to ensure safety.[4,21-23] The need to consider comorbidities is also emphasized in the guidelines, as comorbidities may increase the risk of relapse,[21] may mimic depression,[4] or affect the choice of medication or dose.[4] In terms of efficacy of antidepressants in elderly patients, guidelines from the British Association for Psychopharmacology note smaller treatment effects relative to placebo in patients over the age of 65.[21] Guidelines from the American Psychiatric Association state that treatment for depression in older adults should parallel that of younger populations.[4] Close monitoring of elderly patients while on antidepressant therapy was also recommended.[23] No recommendations were made with regards to the use of specific drug classes. (See Appendix 4, Table A9)

Limitations

This Rapid Response included four SRs,[10-13] two reports of pooled analyses of RCTs,[14,15] two RCTs,[16,17] and one cohort study[18] that reported efficacy and safety outcomes of antidepressants in adults aged 65 and over. Definitions of 'elderly', 'advanced age', and 'older adults' used in clinical trials was variable, with different cut-offs being observed when screening the literature for inclusion in this review. Of note, cut-offs of 55 years and 60 years were used in some studies, which resulted in their exclusion from this Rapid Response. However, it is not clear if the results from younger populations (e.g., those between the ages of 55 and 64 years) would be reflective of the age-related changes that affect antidepressant safety and efficacy.

There were some limitations noted with some of the SRs, particularly with clarity of reporting of the methodology used in the conduct of the SRs. Further, it was unclear from the pooled analyses how the included studies were identified and if all eligible studies would have been considered.[14,15] In addition, the amount of evidence for each antidepressant was limited in some SRs,[10,12] with findings often based upon a single study for some drugs and outcomes. In addition, the duration of studies was variable, with the included RCTs following patients for 8 weeks[16] and 13 weeks.[17] Studies included in the SRs and pooled analyses were frequently eight to 16 weeks in duration as well.[12-15] It is unclear if this duration would be sufficient to capture long-term safety and risk. While the population-based cohort study was of longer duration and

demonstrated an increased risk of many serious adverse effects, the ability to make conclusions based upon it is limited by the lack of control for confounders.[18] Further, actual numerical data were not reported for individual drugs. Similarly, the included SR[10] that assessed harms was based mainly on cohort studies, which cannot control for confounding factors in the same manner as an RCT.

There was limited evidence of comparative efficacy of antidepressants in older adults. Efficacy evidence was in comparison with placebo in some reports[11,14,15] or included evidence from open-label single arm studies,[11] which is likely to be less informative to clinical decision-making than a head-to-head active comparison. Where evidence from active comparator studies was available in systematic reviews,[11,12] the comparison was made to fluoxetine, which is often avoided in the elderly in current practice due to safety concerns.[6]

The clinical importance of differences in efficacy outcomes was generally not considered. However, the definitions used for remission and response, where reported, were consistent with those reported in the literature for the HAMD-17 and the MADRS (for example, a 50% decrease in symptom severity as a definition of response).[24,25] Frequently, the difference in change in depression scores was not reported, so comparisons could not be made to minimally clinically important differences (MCIDs) from the literature. For example, an MCID of approximately two points has been reported for the MADRS,[25] but none of the included reports presented data for this outcome. No MCIDs for the HAMD-17, SDS, Q-LES-Q-SF, and CGI scales were discussed in the included studies.

No literature was identified that reflected subgroups of interest, such as the frail elderly or those with minor depressive symptoms. As well, setting-specific literature (e.g. inpatients, long-term care patients) was lacking. Further, the generalizability of the included RCTs to Canadian practice was unclear, given that one RCT[16] included only a limited number of patients enrolled at a single centre in China, and the other enrolled approximately 50% of the patients screened,[17] creating uncertainty about whether the included patients were reflective of those that would be seen in practice.

No guidelines were identified from the past five years that were developed specifically to make recommendations about the management of depressive symptoms in older adults. In the included guidelines,[4,21-23] consideration was given to older adults as a subgroup, with the focus being mainly on safety in this population and presenting no specific recommendations with regard to the use of specific classes or individual agents.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Four SRs,[11-13,15] and two RCTs[16,17] provide evidenced of the efficacy of antidepressants in patients aged 65 and older. Duloxetine[11] and desvenlafaxine[15] improved symptoms of depression relative to placebo and had higher rates of response and remission in patients who received active treatment. Based upon the presented data or availability of MCIDs, the clinical importance of the change in depressive symptoms could not be assessed, but definitions used for response and remission appeared to be consistent with the literature. In one RCT included in one SR,[12] patients treated with escitalopram had greater improvements in MADRS scores than patients aged 65 and over treated with fluoxetine but given no data were reported, the clinical importance of the difference could not be ascertained. In a comparison to placebo in the same age group, escitalopram was more effective, but limitations to this study make its internal validity and generalizability uncertain.[16] Paroxetine was more effective than fluoxetine in the

aged 65 and over age group as well, based on one RCT included in one SR, but again, the clinical relevance of the difference could not be determined due to lack of data reporting.[12] An SR found citalopram to have similar efficacy to other antidepressants (with TCAs, mianserin, and venlafaxine combined in as single group), but no conclusions about comparative efficacy to single agents could be made from this analysis. In one RCT, bupropion XR was more effective than placebo across a number of outcomes,[17] but uncertainties with the statistical analysis for the primary outcome in this study and lack of MCIDs for a number of secondary outcomes compromise the ability to make conclusions based upon it.

In terms of safety, one SR found increased risk of mortality and falls with TCAs, paroxetine, mirtazapine, and trazodone, but this SR included mainly cohort studies, not RCTs.[10] A pooled analysis of two RCTs found that duloxetine appeared to be relatively safe in individuals aged 65 and older, but rates of discontinuation due to adverse effects were over 25% in both the placebo and active treatment groups. The RCTs[16,17] demonstrated that escitalopram and bupropion XR appeared to be safe in patients over the age of 65; however, these studies involved select populations and were of limited duration. The population-based cohort study found increased risks of serious adverse effects with TCAs, SSRIs and other antidepressants (mortality, suicide, stroke, falls, fractures, upper GI bleeding, etc), but is inherently limited by its nonrandomized design and inability to control for all confounding factors, making it mainly hypothesis generating.

Guidelines recognize the need for caution when prescribing antidepressants in the elderly, emphasizing consideration of age-related changes that can increase the risk of adverse events and comorbidities that may be affected by antidepressants or affect antidepressant risk. One guideline specifically recommended against the use of TCAs in older adults when possible,[22] which is consistent with the literature on inappropriate prescribing in older adults.[6]

In summary, based upon the literature included in this Rapid Response, a number of antidepressants appear to be effective in those aged 65 and older, relative to placebo, but there is limited evidence on comparative efficacy between antidepressants and quality issues with the available evidence. Potential concerns regarding safety were identified across multiple classes of antidepressant, but were based upon cohort studies, suggesting more rigorous, long-term studies of safety in this population are needed.

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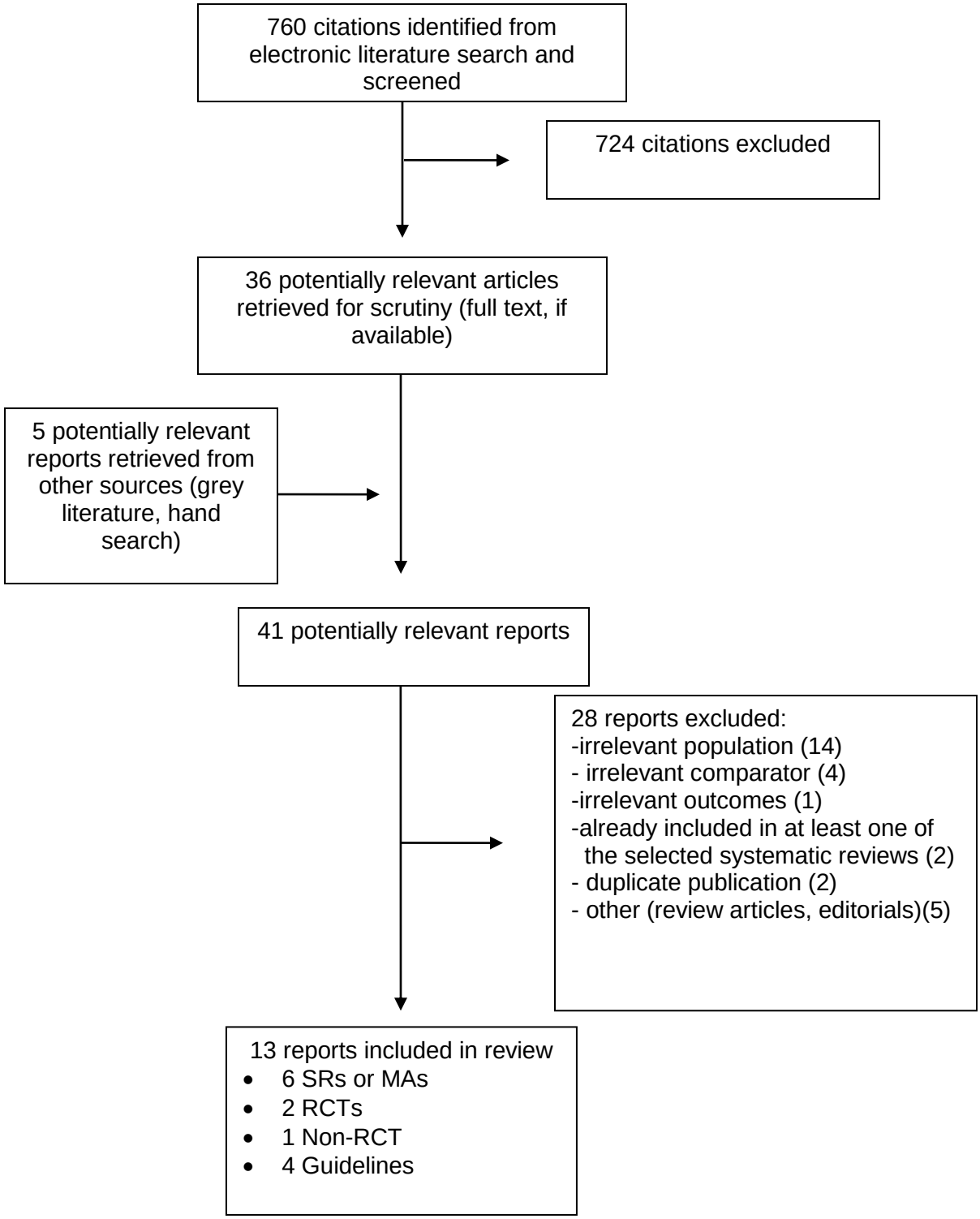
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included, Search Timeframe	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Ruxton, 2015[10] Australia	RCTs (2), prospective cohort (10) and retrospective cohort(4) and case-control(2) studies Up to June 2013	Adults aged 65 and over with MDD residing in the community, an aged-care facility, institution or hospital	Drugs with anticholinergic adverse effects, of which included all antidepressants	Drugs with no anticholinergic activity or placebo	Falls, cognitive impairment†, all-cause mortality Length of follow-up not specified
Oakes 2013,[14] United States	RCTs (2) Details of literature search not reported	Adult outpatients aged 65 and over with MDD	Duloxetine 60mg per day (n=456)	Placebo (n=225)	Adverse effects Weight Vital signs Laboratory values 8 to 12 weeks of treatment
Del Casale, 2012[11] Italy	Clinical Trials (8) SR or MA (3) Up to September 2012	Elderly patients* treated with duloxetine	Duloxetine (dose 60mg to 120mg per day, but unspecified for some studies)	Not specified	Symptoms of depression, adverse effects 6 weeks to 52 weeks
Gartlehner, 2011[12] United States	RCTs (2 in patients aged 65 and over) 1980 to September 2010	Adult outpatients with depressive disorders (older adults were analyzed as a subgroup)	Second generation antidepressants (SSRIs, SNRIs, bupropion, nefazodone and mirtazapine)	Other second generation antidepressants	Symptoms of depression, adverse effects 8 weeks
Kornstein, 2010[15] United States	RCTs (9) Details of literature search not reported	Adults aged 18 or over with a diagnosis of MDD. Subgroup analysis presented for patients	Desvenlafaxine 50 mg to 400 mg per day according to fixed dose or flexible regimen	Placebo	Change in depressive symptoms from baseline Up to 8 weeks

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included, Search Timeframe**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
		aged 65 and over.			
Seitz, 2010[13] Canada	RCTs (7) Search timeframe not reported.	Adult patients aged 65 and over with a diagnosis of MDD (referred to as LLD)	Citalopram (n=647)	Other antidepressants (n=641) TCAs – 4 studies Mianserin – 1 study Venlafaxine – 1 study Reboxetine – 1 study	Remission†, response†, change in severity of depressive symptoms, adverse effects 30 days to 16 weeks

LLD=Late life depression; MA= Meta-analysis; MDD=Major depressive disorder; RCT = randomized controlled trial; SSRI= Selective serotonin reuptake inhibitors; SNRI= Serotonin and norepinephrine reuptake inhibitors; TCA=Tricyclic antidepressant; SR=Systematic review

* Elderly was not defined according to age. Two included studies enrolled patients aged 55 and older. Only outcome data from the studies that included patients aged 65 and over were summarized in this Rapid Review.

† No definition was provided

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design, Duration of Follow-up**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Randomized Controlled Trials					
Chen, 2011[16] China	Randomized, double-blind, placebo controlled trial 8 weeks of treatment	Adults aged 65 years and older, meeting the DSM-IV criteria for major depression, with a GDS score ≥ 20. Mean (SD) Age: 68.9 (6.1) % Female: 62%	Escitalopram 10 mg daily (n=29)	Placebo (n=26)	GDS - % reduction CGI-SI
Hewett, 2010[17] North America, Europe, Australia	Randomized, double-blind, placebo controlled trial 10 weeks of treatment with an additional 3 weeks of follow-up	Outpatients over the age of 65 years with MDD. Placebo: **Age** 65 to 74 – 74%; ≥ 75 – 26%; Female – 70%; White – 86% Bupropion XR: **Age** 65 to 74 – 78%; ≥ 75 – 21%; Female – 74%; White – 84%	Bupropion XR 150mg – 300mg daily (n=211)	Placebo (n=207)	MADRS, CGI-I, CGI-S SDS, MEI Q-LES-Q-SF Adverse effects

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design, Duration of Follow-up	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Non-Randomized Studies					
Coupland, 2011[18] United Kingdom	Population based cohort study (n=60746) 12 years of follow-up	Primary care patients aged 65 to 100 diagnosed with a new episode of MDD over the follow-up period. Mean (SD) Age – 75.0 (7.6) Female – 67%	TCAs and related antidepressants MAOIs SSRIs Other antidepressants	No treatment	All-cause mortality Attempted suicide/self-harm MI Stroke/TIA Falls Fracture Upper GI bleeding Epilepsy/seizure Traffic accidents Adverse drug reactions Hyponatremia

CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions Scale; CGI-SI – Clinical Global Impressions Severity of Illness; DSM = Diagnostic and Statistical Manual; GI= Gastrointestinal; MADRS = Montgomery-Asberg Depression Rating Scale; MAOI = Monoamine oxidase inhibitor; MDD= Major depressive disorder; MEI = Motivation and Energy Inventory; MI = Myocardial infarction; Q-LES-Q-SF = Short Form Quality of Life Enjoyment and Satisfaction; RCT = randomized controlled trial; SD = Standard deviation; SDS = Sheehan Disability Scale; SSRI= Selective serotonin reuptake inhibitor; TIA = Transient ischemic attack; XR = Extended release

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Cleare, 2015[21] – British Association for Psychopharmacology						
All doctors seeing and treating patients with depressive disorders, specifically targeting non-specialists in psychiatry, such as general practitioners and other primary care physicians.	Antidepressant drugs to treat unipolar depressive disorders in adults	Response, remission, relapse, tolerability, safety	Update from previous guidelines, based upon systematic literature search.	**"*Categories of Evidence*** *I: evidence from meta-analysis of randomized controlled trials*, at least one large, good quality, randomized controlled trial* or replicated, smaller, randomized controlled trials** *II: evidence from small, non-replicated, randomized controlled trials*, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study* *III: evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies* *IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities*	Key areas presented by each co-author of the guidelines to development group with an emphasis on SRs and RCTs Discussion within the whole group about the quality of evidence and its implications. Revisions as necessary	Circulated to all participants, user groups and other interested parties for feedback which was incorporated into the final version of the guidelines. Identification

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				Strength of recommendation *A: directly based on category I evidence* *B: directly based on category II evidence or extrapolated# recommendation from category I evidence* *C: directly based on category III evidence or extrapolated# recommendation from category I or II evidence* *D: directly based on category IV evidence or extrapolated# recommendation from category I, II or III evidence* *S: standard of good practice*" p.461		
Mitchell, 2013[22] – Institute for Clinical Systems Improvement						
Health professionals and other expert audiences	Assessment, diagnosis and ongoing management of MDD in adults age 18 and over	Relapse, symptoms, function, adverse effects	Systematic literature search to identify SRs, RCTs, MAs, guidelines, regulatory statements and other relevant literature	Evidence evaluated according to GRADE: **High Quality Evidence** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate Quality Evidence** Further research is likely to have an important impact on	A working group used graded evidence to update clinical practice algorithms, write recommendations, and identify gaps in the literature. A consensus approach was taken.	Guideline reviewed by ICSI's group members and sponsors during the revision process. Final version reviewed by a committee of practicing clinicians and nurses.

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				our confidence in the estimate of effect and may change the estimate. **Low Quality Evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.		
American Psychiatric Association, 2010[4]						
Psychiatrists	Treatment (pharmacological and non-pharmacological) of adults with MDD	Psychiatric management, symptoms, relapse, adverse effects, special populations	Comprehensive literature review Development of evidence tables Initial drafting of the guideline by a working group	**Strength of Recommendation** I - Recommended with substantial clinical confidence II - Recommended with moderate clinical confidence III - May be recommended on the basis of individual circumstances	Multiple review cycles with commentary	Final draft reviewed by an Independent Review Panel of experts and approved by the APA
National Institute for Health and Care Excellence, 2010[23]						
Primary, community, secondary, tertiary and other healthcare professionals who have direct contact with, and make	Adults with a primary diagnosis of depression	Relapse, symptoms, function, adverse effects	Followed NICE's standard methodology for conducting SRs. Consultation with	**Strength of Recommendation** High: further research is very unlikely to change our confidence in the estimate	Grading of evidence and development of clinical evidence summaries by guidelines development group,	Drafted recommendations reviewed by experts outside the guidelines

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
decisions concerning the care of adults with depression			stakeholders. Comprehensive literatures search and selection of evidence relevant to each research question. Standardized data extraction, synthesis of data using MA where appropriate.	of the effect Moderate: further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate Low: further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate Very low: any estimate of effect is very uncertain.	which then drafted recommendations.	development group for peer review and comment.

APA = American Psychiatric Association; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICSI = Institute for Clinical Systems Improvement ; MA = Meta-analysis; MDD = Major depressive disorder; NICE = National Institute for Health and Care Excellence; RCT= Randomized controlled trial; SR = Systematic review; *Randomized controlled trials must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition.
# extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[7]

Strengths	Limitations
Ruxton 2015[10]	
• An a priori design was provided. • A comprehensive literature search of multiple electronic databases was conducted. • The scientific quality of the included studies was assessed and documented using the Cochrane Risk of Bias instrument and New Castle Ottawa Scale where appropriate. • Data were extracted by one individual and verified by another individual. • Fixed and random-effects meta-analyses were used where appropriate. • The quality of the included studies was considered in formulating conclusions. • Conflict of interest was declared, with no competing interests noted.	• Unclear if duplicate study selection. Did not appear to have searched the grey literature. • A list of excluded studies was not provided. • Characteristics of included studies and their populations were not provided. • Publication bias was not assessed, but a valid explanation as to why it was not (too few studies) was provided. • No definition of cognitive impairment was provided.
Oakes, 2013[14]	
• An a priori design was provided. • Conflict of interest was declared, with no competing interests noted. • Detailed characteristics of the included studies and their populations were provided.	• Unclear how the included RCTs were identified (no database or grey literature search). • Did not assess the scientific quality of the included studies. • Data were pooled for the two studies, but it was unclear if meta-analytic statistical methods were used. • Publication bias was not assessed, but there were too few studies to do so. • Methods for study selection and data extraction were not reported. • A list of excluded studies was not provided. • The quality of the included studies was not considered in formulating conclusions.
Del Casale, 2012[11]	
• Conflict of interest was declared, with no competing interests noted. • Detailed characteristics of the included studies and their populations were provided. • Detailed narrative summary of study results were presented.	• An a priori design was provided, but many methodological details were omitted. • Database search used to identify included studies, but detailed selection criteria were not provided. • Did not appear to have searched the grey literature. • Did not assess the scientific quality of the included studies. • Publication bias was not assessed. • Methods for study selection and data extraction were not reported. • A list of excluded studies was not provided. • The quality of the included studies was not

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[7]

Strengths	Limitations
	considered in formulating conclusions.
Gartlehner, 2011[12]	
• An a priori design was provided. • Database search used to identify included studies, with a detailed search strategy provided. • Contacted manufacturers to submit dossiers. • Study selection and data extraction was performed by two individuals. • Assessed study quality using criteria from the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination • Fixed and random-effects meta-analyses were used where appropriate, with heterogeneity being assessed. • Detailed characteristics of the included studies and their populations were provided. • The quality of the included studies was considered in formulating conclusions. • Publication bias was assessed where feasible. • Conflict of interest was declared, with no competing interests noted. • A list of excluded studies was provided.	• All checklist criteria were met.
Kornstein, 2010[15]	
• An a priori design was provided. • Detailed characteristics of the included studies and their populations were provided, but were presented as pooled data across all studies. • Limitations of the data analysis and included studies were considered in the discussion. • Conflict of interest was declared.	• Unclear how included studies were identified. • Unclear if grey literature was searched. • Publication bias was not assessed. • Did not assess the scientific quality of the included studies. • Data were pooled for the two studies, but it was unclear if meta-analytic statistical methods were used. • Methods for study selection and data extraction were not reported. • A list of excluded studies was not provided.
Seitz, 2010[11]	
• An a priori design was provided. • Database search used to identify included studies, with key words reported • Searched the grey literature, contacted manufacturer and clinical experts to identify unpublished studies. • Study selection was performed by two individuals. • Assessed study quality using the Cochrane Risk of Bias Tool.	• Publication bias was not assessed. • Methods for data extraction were not reported. • A list of excluded studies was not provided.

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[7]

Strengths	Limitations
• Fixed and random-effects meta-analyses were used where appropriate, with heterogeneity being assessed. • Detailed characteristics of the included studies and their populations were provided. • The quality of the included studies was considered in formulating conclusions. • Conflict of interest was declared, with no competing interests noted.	

RCT= Randomized controlled trial

Table A5: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[8]

Strengths	Limitations
Chen, 2011[16]	
Internal Validity • The main outcomes were clearly described • Characteristics of patients included in study were clearly described (inclusion and exclusion criteria given). • Interventions of interest clearly stated • Main study findings clearly described • Number of patients lost to follow-up provided and was small (2 participants) and equal between groups. • The outcomes were measured with standard scales. • Participants were randomized to intervention groups	Internal Validity • The objective of the study was not clearly described. • There was a lack of detail in the description of the main study findings, in particular the adverse effects. • Allocation concealment was not described. • The number of participants in each group was limited and there was no report of a sample size calculation. • Exact p-values were not reported. • There was no titration of dose, which may not reflect real-world practice. • While matching placebos were used, it was unclear if the study was double-blinded. • The statistical analysis only looked at the scores at follow-up, but did not consider the change from baseline or adjust for baseline values in the analysis. • An ITT analysis was not used. • Compliance with the treatment regimen was not reported. External Validity • Given the small number of patients and setting (in China) it is unclear if the study results would be generalizable to Canada • The duration of the study was 8 weeks, so the long-term efficacy and safety of escitalopram could not be determined. • There was no active comparator. Head to head comparison with another antidepressant would be more informative. • The number of patients screened was not stated and it was unclear if the enrolled participants were

Table A5: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[8]

Strengths	Limitations
	inpatients or outpatients.
Hewett, 2010[17]	
Internal Validity • Objective of the study was clearly stated • Characteristics of patients included in study clearly described (inclusion and exclusion criteria given) • Interventions of interest clearly stated and dose titration was permitted, which may better reflect real word practice. • Patients, investigators and outcome assessors were blinded. • Standardized scales were used to assess study outcomes, but no rationale was provided for the cut-points selected for categorization of remission and response on the MADRS • Main study findings were clearly described and important adverse events reported • Actual probability values reported External Validity • Patients at risk increased risk of seizures with bupropion were appropriately excluded.	Internal Validity • Methods of randomization and allocation concealment were not reported. • More than 20% (22% in the bupropion XR group and 23% in the placebo group) withdrew from the study. This required a significant amount of data to be imputed using a LOCF approach. • Clinical importance of the study results was not discussed. • The assumptions on ANCOVA for the primary outcome were not met, requiring a post-hoc nonparametric statistical approach. The findings of the two analyses were contradictory. • No power calculation was provided • Refill records were used to assess compliance, which might not be an accurate representation as to whether medication was actually consumed. External Validity • Extensive inclusion and exclusion criteria, which resulted in less than one-half of the patients screened being enrolled in the study. This could compromise the generalizability of the study. • Most patients were under the age of 75 and were female, which may limit the generalizability of the findings. • Key exclusion criteria were MMSE < 24, patients who failed to respond to two prior antidepressants from different classes for MDD. Generalizability to these groups is, therefore, uncertain. • There was no comparison to an active treatment, which would be more informative.
Non-Randomized Studies	
Coupland, 2011[18]	
• Objective of study was clearly stated. • Main outcomes of the study were clearly described. • Clear description of the study cohort with definition of MDD and other eligibility criteria • Interventions of interest clearly stated and grouped antidepressants according to the British National Formulary. The exposure was clearly described. • Analyses were adjusted for a number of confounders, including age, sex, year of diagnosis, severity of depression, deprivation, smoking status, comorbidities, other drugs, and previous falls. • Main study findings were clearly described.	• Performed a large number of statistical tests. Unclear if they were all specified a prior. • Medication adherence was not captured. • Study power was not reported. • As this was not a randomized study, it is not possible to control for unknown confounders. • The definitions of the outcomes were not clearly described or reported.

Table A5: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[8]	
Strengths	**Limitations**
• 95% CI's reported for Hazard Ratios • Compliance with intervention reliable • Main outcome measures used accurate • Sample size was sufficiently large to capture relatively rare adverse events. • All eligible patients were included, thereby reducing the risk of selection bias.	

ANCOVA = Analysis of covariance; CI = Confidence interval; ITT = Intention to treat; MADRS = Montgomery Asberg Depression Rating Scale; MDD = Major depressive disorder; MMSE = Mini-mental state examination; XR = Extended release; LOCF = Last observation carried forward

Table A6: Strengths and Limitations of Guidelines using AGREE II[9]	
Strengths	**Limitations**
Cleare, 2015[21]	
• Overall objective was clearly described • Health questions covered by guideline specifically described • Population to whom the guideline is meant to apply is specifically described (adults with unipolar depressive disorders) • Relevant professional groups included in guideline development (experts in the field of depression and antidepressant treatment, user representatives and medical and scientific staff from pharmaceutical companies) • Target users of the guideline clearly defined (non-specialist primary care providers) • Systematic methods used for literature search, but it did not appear that grey literature was searched. • Strengths and limitations of the body of evidence were clearly described. • Method for formulating recommendations clearly described. • Health benefits, side effects, risks considered in formulating recommendations • Explicit link between recommendations and supporting literature. • Specific and unambiguous recommendations • Options for management (both pharmacological and nonpharmacological) were clearly described • Recommendations easily identifiable • Competing interests of develop group members stated	• Did not seek views and preferences of the target population • Selection criteria for the evidence was not described • The guideline was reviewed, but it did not appeared to be by individuals external to the development process. • There was no procedure described for future updates to the guidelines. • There was no description of monitoring and auditing criteria, facilitators and barriers to application, advice for implementation, resource implications.
Mitchell, 2013[22]	
• Overall objective was clearly described • Health questions covered by guideline specifically described • Population to whom the guideline is meant to apply is specifically described (adults with major depressive disorder) • Relevant professional groups included in guideline development (representation from ICSI member	• Did not seek views and preferences of the target population • Selection criteria for the evidence was not described

Table A6: Strengths and Limitations of Guidelines using AGREE II[9]	
Strengths	**Limitations**
groups) • Target users of the guideline clearly defined • Systematic methods used for literature search • Strengths and limitations of the body of evidence were clearly described. • Method for formulating recommendations clearly described. • Health benefits, side effects, risks considered in formulating recommendations • Explicit link between recommendations and supporting literature. • Specific and unambiguous recommendations • Options for management (both pharmacological and nonpharmacological) were clearly described • Recommendations easily identifiable • Competing interests of develop group members stated • The guideline was reviewed by individuals external to the development process but who were members of ICSI • Procedure described for future updates to the guidelines described. • Described monitoring and auditing criteria, facilitators and barriers to application, advice for implementation, resource implications.	
American Psychiatric Association, 2010[4]	
• Overall objective was clearly described • Population to whom the guideline is meant to apply is specifically described (adults with major depressive disorder) • Systematic methods used for literature search • Strengths and limitations of the body of evidence were clearly described. • Health benefits, side effects, risks considered in formulating recommendations • Explicit link between recommendations and supporting literature. • Specific and unambiguous recommendations • Options for management (both pharmacological and nonpharmacological) were clearly described • Recommendations easily identifiable • Competing interests of develop group members stated • The guideline was reviewed by individuals external to the development process and without industry • Procedure described for future updates to the guidelines described.	• Did not seek views and preferences of the target population • Unclear if all relevant professional groups included in guideline development • Target audience not explicitly stated, but appears to be intended for mainly psychiatrists • Selection criteria for the evidence was not described • Method for formulating recommendations not explicitly described. • Did not describe monitoring and auditing criteria, facilitators and barriers to application, advice for implementation, resource implications.
National Institute for Health and Care Excellence, 2010[23]	
• Overall objective and health questioned covered by the guidance were clearly described • Population to whom the guideline is meant to apply	• Unclear if all relevant professional groups included in guideline development. • Did not describe monitoring and auditing criteria,

Table A6: Strengths and Limitations of Guidelines using AGREE II[9]	
Strengths	**Limitations**
and the target audience were specifically described • Individuals from the target population were involved in the development process • Systematic methods used for literature search and to select the relevant literature for inclusion. • Strengths and limitations of the body of evidence were clearly described • Methods for formulating recommendations were described • Health benefits, side effects, risks considered in formulating recommendations • Explicit link between recommendations and supporting literature. • Recommendations were specific, unambiguous and easily identifiable. • Options for management (both pharmacological and nonpharmacological) were clearly described • Competing interests of develop group members stated • The guideline was reviewed by individuals external to the development process • Procedures are in place for future updates to the guidelines.	facilitators and barriers to application, advice for implementation, resource implications.

ICSI = Institute for Clinical Systems Improvement

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews and Meta-analyses

Main Study Findings	Author's Conclusions
Ruxton, 2015[10]	

Increased risk of falls* with
• Imipramine
  ○ RR: 2.2 (95% CI: 1.80 to 2.60)
• Mirtazapine
  ○ HR: 1.19 (95% CI: 1.05 to 1.36)
• Nortriptyline
  ○ RR: 2.0 (95% CI: 1.80 to 2.30)
• Amitriptyline
  ○ HR: 1.32 (95% CI: 1.22 to 1.42)
  ○ RR 1.9 (95% CI: 1.70 to 2.10)
• Paroxetine
  ○ HR: 1.45 (95% CI: 1.31 to 1.59)
  ○ RR: 1.7 (95% CI: 1.50 to 1.90)
• Trazodone
  ○ HR: 1.55 (95% CI: 1.29 to 1.87)
  ○ RR: 1.2 (95% CI: 1.00 to 1.40)
 	
Increased risk of all-cause mortality* with
• Amitriptyline
  ○ HR 1.10 (95% CI: 1.03 to 1.18)
• Mirtazapine
  ○ HR 1.76 (95% CI: 1.62 to1.91)
• Paroxetine
  ○ HR 1.24 (95% CI: 1.14 to 1.35)
• Trazodone
  ○ HR 1.82 (95% CI: 1.59 to 2.08)
	"In summary, although our analysis was confined to a relatively limited number of studies, it provides preliminary evidence for negative effects of DACEs on cognitive impairment, falls and mortality." p. 217

Oakes, 2013[14]	
Discontinuation for any reason • Duloxetine – 25.2% • Placebo – 29.8%; P = 0.198 Serious adverse events • Duloxetine – 2% • Placebo – 2.7%; P = NR ≥ 1 TEAEs • Duloxetine – 73.7% • Placebo – 62.7%; P = 0.003 Dry Mouth • Duloxetine – 13.4% • Placebo – 3.6%; P <0.001 Constipation • Duloxetine – 11.2% • Placebo – 4.4%; P = 0.004 Nausea • Duloxetine – 8.1% • Placebo – 1.3%; P = 0.040 Dizziness • Duloxetine – 8.6% • Placebo – 3.6%; P = 0.016	*"The results presented here are generally consistent with safety findings in adults 18 years of age and older. Although the rates of some TEAEs were different in the elderly, these rates were generally lower than those observed in younger patients. These safety results may better inform clinicians providing individualized care to elderly patients with MDD." p.10*

Table A7: Summary of Findings of Included Systematic Reviews and Meta-analyses	
Main Study Findings	**Author's Conclusions**
Fatigue • Duloxetine – 5.5% • Placebo – 2.7%; P = 0.097 Diarrhea • Duloxetine – 9.6% • Placebo – 3.1%; P = 0.002 Vital Signs • No difference in supine systolic, standing systolic, or standing diastolic BP; greater increase in supine diastolic BP with duloxetine. Weight Loss • Duloxetine – 0.76 kg weight loss • Placebo – 0.02 kg weight loss; P < 0.001	
Del Casale, 2012[11]	
• Duloxetine versus placebo ○ Improved cognitive score, GDS, HAMD-17, CGI-Severity, HAMD-17 response and remission rates (data and statistical significance not reported). ○ Discontinuations due to AEs similar to placebo in one study (9.7% versus 8.7%) ○ Discontinuations due to AEs higher than to placebo in a second study (15.3% versus 5.8%) ○ Dry mouth, nausea, and diarrhea more frequent with duloxetine. ○ Most measures of blood pressure did not differ from placebo except for mean change in orthostatic systolic BP (-2.45 vs 0.93 mmHg; p=.017) ○ ECG changes were not significantly different between duloxetine and placebo ○ Greater weight loss with duloxetine than placebo (-0.73 kg vs -0.13 kg; P = 0.009). • Compared to vortioxetine and placebo (no statistical comparison reported) ○ 8 week response ▪ Duloxetine – 63% ▪ Vortioxetine – 53% ▪ Placebo – 35% ○ Remission ▪ Duloxetine – 35% ▪ Vortioxetine – 29% ▪ Placebo – 19% • Open-label, uncontrolled studies ○ Statistically significant improvements in	"*Duloxetine is effective, safe and well-tolerated in elderly populations with depressive disorders in a similar manner to adults. Its' efficacy is similar to that of other antidepressants, like the SSRIs or other SNRIs, like venlafaxine and milnacipran, although regretfully, comparisons in elderly populations are lacking." p.486*

Table A7: Summary of Findings of Included Systematic Reviews and Meta-analyses	
Main Study Findings	**Author's Conclusions**
HAMD-17 scores over 6 to 52 weeks, ranging from 13 to 17.5 points. ○ Improvements also seen in CGI and patient global impression ○ Rates of response ranging from 63% to 89% ○ Rates of remission ranging from 41% to 72% ○ Adverse events affecting > 10% of patients included dizziness, nausea, constipation, somnolence, insomnia, dry mouth and diarrhea	
Gartlehner, 2011[12]	
RCT with comparison of escitalopram, fluoxetine and placebo • MADRS Score ○ Escitalopram treated patients experienced greater improvement than those on fluoxetine (data not reported; P < 0.01) ○ Escitalopram and placebo did not differ significantly. • MADRS Response (P > 0.05 for all comparisons) ○ Escitalopram – 46% ○ Fluoxetine – 37% ○ Placebo – 47% • MADRS Remission ○ Escitalopram – 40% ○ Fluoxetine – 30% ○ Placebo – 42% (P = 0.05 vs fluoxetine) • Nausea ○ Patients treated with escitalopram and fluoxetine had more nausea than those treated with placebo (data not reported; P < 0.01). RCT with comparison of fluoxetine and paroxetine • Significant improvement in HAM-D scores and cognitive impairment in both groups (data not reported) • Faster onset with paroxetine during the first six weeks (data nor reported, P < 0.002). • % responders over time showed a significant difference in favor of paroxetine (P<0.002). • No difference in CGI scores. • Greater frequency of severe AEs with fluoxetine (n=22) than paroxetine (n=9; P < 0.002).	No conclusions specific to adults aged 65 and over. *"Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ."p.103*

Table A7: Summary of Findings of Included Systematic Reviews and Meta-analyses	
Main Study Findings	**Author's Conclusions**
Kornstein, 2010[15]	

• Mean ± SD change from baseline in HAMD-17
  ○ Desvenlafaxine: -12.50 ± 1.12
  ○ Placebo: -8.12 ± 1.32; p = 0.004
• Response (desvenlafaxine versus placebo)
  ○ OR: 4.59; 95% CI: 2.13 to 9.89; P < 0.001
• Remission (desvenlafaxine versus placebo)
  ○ OR: 3.83; 95% CI: 1.46 to 10.00; P < 0.01
	"Desvenlafaxine treatment was generally effective in improving symptoms of depression across the age and sex groups studied. No significant sex-treatment, age-treatment, or sex-age treatment interactions were noted for primary or secondary outcome measures. These findings add to the clinical evidence that a wide range of patient subpopulations respond positively to antidepressant therapy with SNRIs." p.298

Seitz, 2010[13]	

• Remission (citalopram versus other antidepressants)
  ○ OR: 0.84 (95% CI: 0.56 to1.28); P = 0.42
• Depressive symptom severity
  ○ Data were summarized narratively
  ○ Improvement in depressive symptom severity was similar for citalopram and other medications in most studies.
• Trial withdrawal (citalopram versus other antidepressants)
  ○ OR: 0.70 (95% CI: 0.48 to 1.02); P = 0.06
	"Citalopram can be considered one option for LLD as it has been studied in older adults, however, clinicians should feel free to select from other suitable alternatives in the absence of overwhelming evidence favouring this antidepressant over others. Further research is required to provide improved outcomes for all people suffering from LLD." p. 1304

* Each estimate of treatment effect is from a single study

AE = Adverse effect; BP = Blood pressure; CGI = Clinical Global Improvement; CI = Confidence interval; DACE=Drugs with anticholinergic effects; ECG = Electrocardiogram; GDS = Geriatric depression scale; HAMD = Hamilton Depression Rating Scale; HR = Hazard ratio; kg = Kilogram; LLD = Late life depression; MADRS = Montgomery Asberg Depression Rating Scale; MDD = Major depressive disorder; OR = Odds ratio; RCT = Randomized control trial; RR = Relative risk; SSRI= Selective serotonin reuptake inhibitors; SNRI= Serotonin and norepinephrine reuptake inhibitors; TEAE = Treatment emergent adverse effect

Table A8: Summary of Findings of Included Randomized Controlled Trials	
Main Study Findings	**Author's Conclusions**
Chen, 2011[16]	
GDS – Mean ± SD Score at Week 8 • Escitalopram: 10.7 ± 3.6 • Placebo: 21.1 ± 3.5; P < 0.05 GDS – % Reduction from Baseline • Escitalopram: 54.4% • Placebo: 12.1% GDS – % with a Clinical Cure** • Escitalopram: 40.7% • Placebo: 0%; (P<0.01) CGI-SI – Mean (SD) Score at Week 8 • Escitalopram: 2.6 (1.1) (3.6) • Placebo: 4.6 (1.0); P < 0.05 CGI-SI – % Reduction from Baseline • Escitalopram: 52.9% • Placebo: 14.5% Adverse Effects (nausea, dry mouth and Dizziness) • Escitalopram: 22.2% • Placebo:4.2%	*"Escitalopram was efficacious in the treatment of geriatric depression without serious adverse reactions, supporting the use of escitalopram in the elderly population with major depression." p.1952*
Hewett, 2010[17]	
MADRS (LS mean change (SE) from baseline) • Bupropion XR: −13.9 (0.7) • Placebo: −12.4 (0.7) (p=0.085) Post-hoc MADRS Analysis (Median change from baseline) • Bupropion XR: −15 • Placebo: −11 (p=0.033) MADRS Responders* • Bupropion XR: 53% • Placebo: 43% (p=0.014) CGI-I Responders† • Bupropion XR: 69% • Placebo: 46% (p<0.001) MADRS Remission‡ • Bupropion XR: 38% • Placebo: 33% (p=0.167) CGI-S Mean change from baseline • Bupropion XR: -1.5 • Placebo: -1.3 (P=0.077) SDS Mean change from baseline • Bupropion XR: -7.8 • Placebo: -5.7 (P=0.003) Q-LES-Q-SF Life Satisfaction and Contentment Mean change from baseline	*"bupropion XR is effective in improving depressive symptoms in elderly patients, increasing energy and motivation, reducing functional impairments, and improving QoL. Taking into consideration the efficacy and tolerability profile demonstrated for bupropion XR and the advantageous health outcomes obtained in this study, once daily bupropion XR appears to be an appropriate treatment option for the management of elderly patients with MDD."p.528*

Table A8: Summary of Findings of Included Randomized Controlled Trials	
Main Study Findings	**Author's Conclusions**
• Bupropion XR: 1.2 • Placebo: 0.9 (P=0.01) Q-LES-Q-SF General Activities - Mean change from baseline • No difference; data not reported Discontinuations due to adverse effects • Bupropion XR: 8% • Placebo: 10% SBP Increases • Bupropion XR: 11% • Placebo: 17% DBP Increases • Bupropion XR: 9% • Placebo: 7% Heart Rate Increases • Bupropion XR: <1% • Placebo: <1% Weight • Increase or decrease in weight was similar across groups (data not reported)	
Non-Randomized Studies	
Coupland, 2011[18]	
Comparisons to No Antidepressants All-cause mortality- HR (95% CI) • TCAs: 1.16 (1.10 to 1.22) • SSRIs: 1.54 (1.48 to 1.59) • Other: 1.66 (1.56 to 1.77) Attempted suicide/self-harm - HR (95% CI) • TCAs: 1.70 (1.28 to 2.25) • SSRIs: 2.16 (1.71 to 2.71) • Other: 5.16 (3.90 to 6.83) Myocardial infarction - HR (95% CI) • TCAs: 1.09 (0.96 to 1.23) • SSRIs: 1.15 (1.04 to 1.27) • Other: 1.04 (0.85 to 1.27) Stroke/transient ischaemic attack - HR (95% CI) • TCAs: 1.02 (0.93 to 1.11) • SSRIs: 1.17 (1.10 to 1.26) • Other: 1.37 (1.22 to 1.55) Falls- HR (95% CI) • TCAs: 1.30 (1.23 to 1.38) • SSRIs: 1.66 (1.58 to 1.73) • Other: 1.39 (1.28 to 1.52) Fracture- HR (95% CI)	*"This study has found that selective serotonin reuptake inhibitors and drugs in the group of other antidepressants were associated with an increased risk of several adverse outcomes compared with tricyclic antidepressants. Other differences in characteristics may exist between patients prescribed different antidepressant drugs, which we have not adjusted for and which may account for some of the associations between the drugs and the adverse outcomes. Further research is needed to confirm these findings." P.7*

Table A8: Summary of Findings of Included Randomized Controlled Trials	
Main Study Findings	**Author's Conclusions**
• TCAs: 1.26 (1.16 to 1.37) • SSRIs: 1.58 (1.48 to 1.68) • Other: 1.64 (1.46 to 1.84) Upper gastrointestinal bleeding - HR (95% CI) • TCAs: 1.29 (1.10 to 1.51) • SSRIs: 1.22 (1.07 to 1.40) • Other: 1.37 (1.08 to 1.74) Epilepsy/seizures - HR (95% CI) • TCAs: 1.02 (0.76 to 1.38) • SSRIs: 1.83 (1.49 to 2.26) • Other: 2.24 (1.60 to 3.15) Road traffic accidents - HR (95% CI) • TCAs: 0.86 (0.64 to 1.15) • SSRIs: 0.89 (0.70 to 1.13) • Other: 0.67 (0.39 to 1.14) Adverse drug reactions - HR (95% CI) • TCAs: 1.06 (0.86 to 1.29) • SSRIs: 1.16 (0.98 to 1.37) • Other: 0.95 (0.68 to 1.34) Hyponatraemia - HR (95% CI) • TCAs: 1.05 (0.87 to 1.27) • SSRIs: 1.52 (1.33 to 1.75) • Other: 1.28 (0.98 to 1.67) **SSRI versus TCA – HR (95% CI)** All- cause mortality: 1.32 (95% CI: 1.26 to 1.39) Stroke/transient ischemic attack: 1.15 (95% CI: 1.05 to 1.26) Falls: 1.27 (95% CI: 1.20 to 1.35) Fracture: 1.26 (95% CI:1.15 to 1.37) Epilepsy/seizures: 1.80 (95% CI: 1.32 to 2.43) Hyponatremia: 1.44 (95% CI:1.19 to 1.75) Attempted suicide/self-harm: 1.27 (95% CI: 0.97 to 1.66) **Other versus TCA – HR (95% CI)** All-cause mortality: 1.43 (95% CI:1.33 to 1.54) Attempted suicide/self-harm: 3.04 (95% CI: 2.21 to 4.17) Stroke/transient ischemic attack:	

Table A8: Summary of Findings of Included Randomized Controlled Trials	
Main Study Findings	**Author's Conclusions**
1.35 (95% CI:1.18 to 1.54) Fracture: 1.31 (95% CI:1.15 to 1.50) Epilepsy/seizures: 2.20 (95% CI:1.46 to 3.30) Falls 1.07 (95% CI: 0.97 to 1.17) Hyponatraemia 1.21 (95% CI: 0.90 to 1.64)	

* Defined as a >50% reduction in score; † Defined as a CGI-I score of 1 or 2; ‡ Defined as MADRS total score ≤ 11; ** Defined as a > 75% reduction in symptoms

CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions Scale; CGI-SI – Clinical Global Impressions Severity of Illness; CI = Confidence interval; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; GDS = Geriatric depression scale; HR = Hazard ratio; MADRS = Montgomery Asberg Depression Rating Scale; MDD= Major depressive disorder; Q-LES-Q-SF = Short Form Quality of Life Enjoyment and Satisfaction; QoL = Quality of life; SSRI= Selective serotonin reuptake inhibitors; TCA – Tricyclic antidepressant; SD = Standard deviation; SDS = Sheehan Disability Scale; SSRI= Selective serotonin reuptake inhibitor; XR = Extended release

Table A9: Summary of Recommendations from Included Guidelines	
Guideline, Publication Year	**Recommendations**
Cleare, 2015[21]	*"Be aware of age-related factors that may influence treatment with antidepressants (S) including:* *- decreased tolerability of the elderly to antidepressants* *- high risk of depressive relapse in the elderly with comorbid medical illness." p.467* *"Systematic reviews of placebo-controlled antidepressant trials in the elderly suggest somewhat smaller effect sizes, particularly in trials restricted to participants aged 65 and over (I).p.472* *"Side effects from antidepressant medication are related to dose (I). Lower initial doses of antidepressants appear appropriate in the elderly because of pharmacodynamics and tolerability considerations (III)."p.492* *"The chance of responding to a subsequent treatment declines with each failed treatment trial (II). The likelihood of eventual response decreases if there has been no improvement by 4 weeks treatment (II), with only around 20% chance of remission at 12 weeks if there has been no improvement by 6–8 weeks (II). Lack of a continuing trajectory of improvement beyond 3–4 weeks is associated with lack of response by 12 weeks (II). There is no clinically significant difference between younger adults and elderly patients in the rate of improvement (II)." p.495* *" Relapse rates are high in the months after remission and decline with time (I). Other important factors associated with increased risk of relapse include residual symptoms, number of previous episodes, chronicity and severity of last depressive episode, degree of treatment resistance and psychosis (II). In the elderly a greater degree of comorbid medical illness is associated with higher relapse rates (II).p.502*
Mitchell, 2013[22]	*"When using pharmacotherapy in elderly patients, the clinician should carefully consider how the metabolism of the drug may be affected by physiologic changes, their comorbid illnesses and the medications used for them (Low Quality Evidence, Strong Recommendation)."p.27* *"Because of the potential for decreased renal and hepatic function, and also for concomitant diseases and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant medications. For elderly patients with moderate to severe depression, TCAs such as nortriptyline continue to be regarded as the most effective treatment ([Low Quality Evidence]; Gastó, 2003 [High Quality Evidence]).Consider starting at the lowest possible dose and increasing slowly to effective dose or until side effects appear. Tertiary amine tricyclics should generally be avoided in elderly patients because of the high incidence of orthostatic hypotension, sedation, cognitive problems and cardiac effects with these agents."p.49 -50*
American Psychiatric Association, 2010[4]	*"In individuals with late-life depression, identification of co-occurring general medical conditions is essential, as these disorders may mimic depression or affect choice or dosing of medications [I]."* *Older individuals may also be particularly sensitive to medication side effects (e.g., hypotension, anticholinergic effects) and require adjustment of medication doses for hepatic or renal dysfunction [I].* *In other respects, treatment for depression should parallel that used in younger age groups [I]."p.21*
National Institute for Health and Care Excellence, 2010[23]	*"When prescribing antidepressants for older people:* *- prescribe at an age-appropriate dose taking into account the effect of general physical health and concomitant medication on pharmacokinetics and pharmacodynamics* *- carefully monitor for side effects."p.424*

APPENDIX 5: Additional References of Potential Interest

Additional Guidelines (Not clearly evidence-based)

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