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

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CONTEXT AND POLICY ISSUES

The global population is aging and the World Health Organization has estimated that within 20 years more than 10% of the world population will be over 65 years old.[1] In Ontario census reports from the years 1981 to 2005 documented that the percentage of the population over 65 grew from 9.9% to 12.8%.[2] This number was projected to increase to over 20%, or an estimated one in five people, by the year 2031.[2] There is a distinct dichotomy in gender in this population because women typically live longer than men, resulting in over 75% of the population above 90 being female.[2]

As aging progresses there is a steady movement towards a reduction in cognitive function which normally results in minor alterations to processes such as memory recall and the speed at which information is processed.[3,4] Under normal circumstances this decrease in functionality is not significant enough to have any detrimental effect on average daily activities.[3] In circumstances where this deterioration is more dramatic there are three conditions that may develop. These conditions are dementia, delirium and depression.[3]

Dementia is a psychological abnormality that is a result of an alteration in cognitive functionality.[3,5] Several neurological domains affected by the progression of this condition are executive function, learning/memory, language and social cognition.[3,5-8] As of 2010 it was estimated that 364,000 Canadians over 65 have some form of dementia.[6] The Canadian Study of Health and Aging Working Group estimates that this number will increase to 750,000 by 2031.[6] Due to the progression of this disease and the fact that quite often early signs are dismissed as normal issues associated with aging, development of dementia often proceeds unchecked.[6] There are many different types of dementia affecting elderly people but Alzheimer's disease (AD) is the most prevalent and accounts for between 60 to 80 percent of cases.[3,9] In the United States of America approximately 5.2 million people over the age of 65 have AD.[3] Conditions such as altered or reduced cognition, judgement and altered insight are all common in AD [7,10] The economic strain that these conditions put on healthcare budgets is high and accounts for approximately 1% of the global gross domestic product ($600 billion USD

worldwide annually).[7] In addition there are detrimental effects to health care workers and care givers who are required to monitor patients suffering from these conditions on a daily basis.[7,8]

Depression occurs at a prevalence of between 10-15% in the elderly population,[4,6,11] and is found in more than 20% of cases of dementia. When depression coexists with dementia it will exacerbate distress and decrease quality of life.[4,5,7] In extreme situations this can also lead to an increase in mortality.[6,7,12] Evidence has suggested that approximately 4% of adults who have depression commit suicide and two-thirds of these cases are a direct result of depression.[13] Disabilities associated with depression, called major depressive disorders, account for the fourth largest health care burden globally and in addition make up the second largest condition leading to long-term disability.[13]

The type and severity of dementia and depression are used to determine the type of aid that is given.[6] There are two types of pharmacotherapy prescribed for people with these disorders: first and second generation antidepressants.[14] The first generation treatments are made up of tricyclic antidepressants and monoamine oxidase inhibitors. These are not used very often as they have significant side effects and there is a high risk of overdose or reaction with other medications.[14] The second generation medications are made up of selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic agents (NaSSAs), and other antidepressants such as bupropion, refazodone and trazodone.[14] Of these the most commonly prescribed are the SSRIs due a lower level of harmful side effects.[6,10,14]

There has been limited evidence demonstrating the efficacy of the use of antidepressants for the treatment of depression and dementia.[7,8,11,15-17] Additionally when these drugs are prescribed, approximately half the patients will have outcomes resulting in recurrence of the original symptoms.[13] Even with these equivocal results antidepressants are a standard option utilized by attending physicians and are prescribed in 43.2% of dementia and depression cases.[7,8,13,15,18]

The purpose of this report is to analyze the clinical effectiveness and safety of antidepressants prescribed for the treatment of patients with dementia and co-morbid depression and in addition to describe any current certified clinical guidelines associated with their use.

RESEARCH QUESTIONS

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

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

KEY FINDINGS

Although there was a limited suggestion that antidepressants had beneficial effect in patients with depression and dementia this evidence was found to be equivocal and examination was conducted on study populations that were underpowered to achieve statistical significance. The majority of publications identified indicate that the use of antidepressants in these patients does

not result in higher remission rates of depression or any associated improvement in cognitive functionality than to the placebo treatments used as controls.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2000 and July 22, 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 (subpopulation: the frail elderly) in any setting (home, long-term care, hospital) with depression and dementia
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, tricyclic antidepressants, 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	• HTA/ Systematic review/Meta-analysis • Randomized controlled trials • Non-randomized studies (for **safety outcomes only)** • Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2005.

Critical Appraisal of Individual Studies

The included health technology assessment and systematic review were critically appraised using the Assessment of Multiple Reviews (AMSTAR) tool.[19] Randomized controlled trials (RCTs) were assessed using the Downs and Black checklist for the adequacy of allocation concealment, blinding of healthcare providers, clinicians, data collectors and outcome assessors, randomization, losses to follow-up, description of intention-to-treat, and early stopping of the trial.[20] 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 135 citations were identified in the literature search. Following screening of titles and abstracts, 115 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 17 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Clinical effectiveness and safety

Study Design

The systematic review[18] included for this question included seven randomized controlled trials. These publications were found after a limited search of Medline and The Cochrane Controlled Trials Register from 1966 to May 2010. For inclusion, studies were required to be acute phase, double-blinded, placebo controlled randomized controlled trials. The goal was to analyze the efficacy of the use of antidepressants to treat people with depression and dementia.

The study by Banerjee et al.[7] was published in 2013 and had a total of 326 participants with an average age of 79 years old. As a result of equivocal evidence on the efficacy of antidepressant use in the elderly, their goal was to examine the clinical effectiveness of sertraline and mirtazapine to decrease depression in people with depression and dementia and the impact on their care givers. This was conducted using a multi-center, parallel group, double-blinded, randomized controlled trial with follow-up conducted at 13 and 39 weeks. Patients were included if they met the criteria for Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders

Association (NINCDS/ADRDA) and had coexisting depression for a minimum of four weeks. They were excluded if they had too high of a clinical risk for participation in randomization (i.e. suicide likely), were contraindicated to the medications under investigation, were already on antidepressant therapy, they were already participating in another trial, or had no care giver.

The study conducted by Munro et al.[21] in 2012 included 131 participants with an average age of 79 years old. The goal was to determine if drug treatment had any efficacy on cognitive performance for patients with depression and Alzheimer's disease after a 24 week period. This was completed using a double-blinded, placebo controlled randomized controlled trial. Their patients were recruited from five outpatient memory disorder clinics. In order to be eligible for inclusion, patients must have had a Mini Mental State Examination (MMSE) score of 10-26 and must not have been already taking an antidepressant or a benzodiazepine. This study was conducted in the same population as Weintraub et al.[9]

The final study was conducted by Weintraub et al.[9] in 2010 in order to examine the delayed effects of sertraline on cognition in patients with depression and Alzheimer's disease. A total of 131 patients were recruited from five memory disorder clinics. For inclusion these patients must have been diagnosed with Alzheimer's disease using the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV).and have an MMSE score of 10-26. Follow-up was conducted at 24 weeks post randomization. This study was conducted in the same population as Munro et al.[21]

Country of Origin

All of the studies found for this question were produced in the United States of America. These included one systematic review and three randomized controlled trials.

Intervention

The selection criteria for antidepressants used in the systematic review[18] was that they were required to be marketed in the United States of America. As a result, there were three papers included that used sertraline at average doses of 91, 100 and 150 mg/day. Another study utilized clomipramine at an average dose of 100 mg/day. Imipramine was used in another study at 83 mg/day. In the final two studies, one utilized fluoxetine at 40 mg/day and the other used venlafaxine at 131.25 mg/day.

All of the randomized controlled trials that were included used the SSRI sertraline as one of their interventions. In the study by Banerjee et al.[7] patients were randomized to receive 150 mg sertraline daily, 45mg of the NaSSA mirtazapine daily, or placebo. Munro et al.[21] used sertraline at a rate of 100 mg/day. The investigation by Weintraub et al. began their study with patients taking a sertraline dose of 50 mg daily for the first week. After this time the clinician increased the dose up to a maximum of 100 mg/day based on patient response and their observations.

Comparator

The publications included in the systematic review and all of the randomized controlled trials analyzed in this report used a placebo as the control in their investigations. These were presented in tablet form and mimicked the appearance of the pharmacologic intervention that was under study.

Outcomes

The systematic review[18] did not limit their investigation for any specific type of outcome. As a result of this, the included papers utilized a variety of examinations including the Hamilton Depression Rating Scale (HDRS), the Montgomery-Asberg Depression Rating Scale (MADRS), Cornell Scale for Depression in Dementia (CSDD) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC). In addition the change in scoring for depressive symptoms was examined based on standardized mean difference. For situations where means and standard deviations were not reported the result was imputed using the mean baseline and the mean endpoint scores. The standard deviation of end point scores was used to estimate the standard deviation of the change score. The authors defined the criteria for remission as achieving an HDRS score of 7 or less, a CSDD score of ≤6, an MADRS score ≤10, or an mADCS-CGIC rating of "very much improved".

In the investigation by Banerjee et al.[7] both primary and secondary outcomes were examined. The primary outcome was used to analyze the severity of depression in dementia and was the CSDD score. Secondary outcomes were focused on the overall quality of life and utilized the disease specific Dementia Quality of Life (DEMQL and DEMQL-Proxy), the generic European Quality of Life-5 Dimensions (EQ-5D), cognitive impairment using MMSE, medication adherence, adverse events, carer mental health using the General Health Questionnaire, carer quality of life using SF-12v2, carer burden using Zarit Scale, behavioral disorder using Neuropsychiatric Inventory (NPI) and baseline dementia vascularity index using a modified Hachinski Scale.

Munro et al.[21] examined depression at week 12 of their study using mADCS-CGIC. In addition they also analyzed cognitive functionality at baseline and at week 8, 16 and 24 using MMSE, the Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the digit Span Subtest (Wechester Memory Scale-III), Letter Fluency, Digit Symbol Modalities, and the Finger Tapping Test. Since the authors hypothesized that changes in cognition would occur later in time than any changes in mood the primary analysis of cognition for all study groups was focused on data at week 24. For calculations, they used linear regression on the scores from all of the secondary outcomes.

Weintraub et al.[9] also examined primary and secondary outcomes in their study. The primary outcomes were mADCS-CGIC and CSDD. Remission was characterized as a CSDD score ≤6 and a mADCS-CGIC score of ≤2. A first remission incident occurred on the first occasion that a patient achieved these scores and a sustained remission was when every subsequent evaluation also met these goals. Secondary outcomes focused on both quality of life and cognitive functioning and utilized MMSE for global cognition, NPI for non-mood neuropsychiatric symptoms, function using Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADLS), and quality of life using Alzheimer's Disease Related Quality of Life Scale (ADRQL). Adverse events were also examined using a checklist obtained from the Food and Drug Administration.

Evidence-based guidelines

No evidence-based guidelines were found for the use of antidepressants in elderly patients with depression and dementia.

Summary of Critical Appraisal

The included systematic review[18] contained well defined study inclusion and exclusion criteria as well as a flow chart describing the selection process. Two authors were involved in study selection and data extraction. A small number of trials were found that met the inclusion criteria. As a result of this the total number of patients included in this review for all seven papers was 330. Several of the included papers were conducted on fewer than 50 participants. This small number made it difficult for the authors to make any defined conclusion which therefore means that caution must be used when interpreting these results. In addition no evidence is provided indicating that grey literature sources had been searched, however publication bias was explored with a funnel plot and none was detected. Finally, no information was provided analyzing conflict of interest for the papers included in the review.

The randomized controlled trials by Banerjee et al.[7] and Weintraub et al.[9] both suffered from high patient dropout rates. The dropout rates in the Banerjee et al study were 26.1%, 36.4% and 29.6% for the placebo, sertraline, and mirtazapine groups respectively. In addition adjustments also had to be made to the study design during experimental phases as recruitment rates were slow and funding sources were at risk of depletion. The initial target for patient recruitment was 507 which was calculated to give 90% power for the comparison of each treatment group to placebo at 13 weeks and 86% power at 39 weeks. This was adjusted to 339 after slow enrollment and only 326 were achieved. Dropout rates were higher in the study by Weintraub et al.[9] where 43.3% and 43.7% of participants were lost in the sertraline and placebo groups respectively. Overall, 56.5% of the initial participants recruited completed all 24 weeks of the trial. Circumstances of above average dropout rates such as these have the potential to bias results if the lost patients represent unique populations that react differently to treatments and this data is not included and analyzed in the results.

The studies by Munro et al.[21] and Weintraub et al.[9] included a patient population representative of the typical population of patients with Alzheimer's disease and depression. While this population does represent a well-balanced grouping and is not prone to gender or ethnic selection bias it is specific to patients who have depression in Alzheimer's disease. This condition differs from other types in that patients are more prone to irritability and social anxiety.[21] As a result of this, conclusions may be limited for use to these patients and not generalizable in abroad spectrum analyses. Additionally in the publication by Munro et al.[21] the authors have indicated that the cognitive examinations utilized may not have been sensitive enough to analyze all of the potential changes occurring in the depressed and demented participants. One key area identified is for critical flicker fusion tasks which are potentially more sensitive to the effects of the treatment and may respond differently.

The participant population in the study by Banerjee et al.[7] represents a broad spectrum of patients recruited from several different areas in the United Kingdom. The treatment groups were randomized on a 1:1:1 ratio so that analysis would not be skewed for any individual population. Overall the patients recruited into the study were 93% Caucasian. While this may represent the typical population found living in these areas, it could potentially impart an ethnic bias in the results indicating that caution should be used when applying these results to other populations.

Finally, the procedures for randomization were not described sufficiently in the study by Weintraub et al.[9] The protocol used for blinding of patients and clinical staff are alluded to but

not described in an appropriate level of detail. There is also no discussion of blinding of staff conducting statistical analysis.

Summary of Findings

Clinical effectiveness and safety

The systematic review by Nelson and Daranand[18] examined a total of seven randomized controlled trials on patients having depression and dementia. Of these seven studies, two demonstrated a beneficial effect from the use of an antidepressant. The included paper by Lyketsos et al. found that sertraline resulted in statistically significant improvements on global ratings, HDRS, and the CSDD. The second publication by Petracca et al. and demonstrated that participants taking clomipramine had significantly lower HDRS scores and higher remission rates than those on placebo. The remaining five studies showed no statistically significant difference between the treatment and placebo groups in depression scores. Overall, this review concluded that there was no significant difference for aspects such as dropout or remission rates. Authors concluded that the beneficial effects found in two of their included studies were likely a result of drug effects that are difficult to analyze in the small patient populations that were included in the studies. Their evidence suggested that any efficacy found with the use of an antidepressant is a result of the management process itself not genuine success from the trial drugs themselves.

The randomized controlled trial by Banerjee et al.[7] found a reduction in depression severity in all of the included treatment groups. The most significant reduction occurred at the 13 week time point in the placebo group and was followed by the sertraline group and finally the mirtazapine group. This trend continued at the 39 week time point; though, when the results were analyzed using linear-mixed regression, no significant difference was detected between any of the study populations. When secondary outcomes were analyzed, no differences for any of the treatment groups were found. The one exception to this was for health-related quality of life (HRQL and DEMQOL-Proxy). Fewer neuropsychiatric symptoms and higher care provider rated participant scores were found in the mirtazapine group versus the sertraline group at 13 weeks but this difference disappeared by the 39 week time point. The experimentation using the NPI separated the results into four separate subsections and analyzed them via a negative binomial distribution and a cross sectional method. These subsections were:

1) Agitation, disinhibition and irritability
2) Delusions, depression and anxiety
3) Hallucinations, aberrant motor behavior and sleep
4) Elation, apathy and appetite

The only statistically significant difference for this examination was found at 13 weeks where sertraline was found to be more beneficial than mirtazapine for subsection 2 and 3 (Odds Ratio 1.39, *P*=0.009). This did not continue through to 39 weeks as there were no significant differences between groups at that time point. When safety was examined, 119 subjects reported a total of 240 adverse effects. When separated into each trial group 26% occurred in the placebo group, 43% in the sertraline group and 41% in the mirtazapine group. Overall this showed a significant difference between the drug treatments and placebo group (*P*=0.017). The most common issues were nausea in the sertraline group and drowsiness or sedation in the mirtazapine group. There was no significant difference found between any group for the number

of adverse events at 13 weeks. The percentage of these events that were classified as severe adverse events (SAEs) was higher in the sertraline and mirtazapine groups (SAE 20% in placebo, 67% in sertraline and 71% in mirtazapine). Five deaths occurred in each group by the end of the trial therefore no difference was found. These results suggested that the two most commonly prescribed antidepressants have no more clinical benefit than placebo. The authors recommend that clinicians modify their strategies for the treatment of individuals with depression and dementia.

In the study by Munro et al.[21] the baseline characteristics of the patients randomized to either sertraline or placebo groups differed only in the level of education. Those in the sertraline group had a higher level of education. Initial examination found that the only difference in cognitive testing scores occurred during the Letter Fluency examination. This test demonstrated that the sertraline group performed better at baseline. For all of the testing conducted in this trial, four models were calculated. Firstly, an overall effect of the treatment group which resulted in no significant differences between sertraline and placebo for cognitive performance at week 24 (*P* values range from 0.24 to 0.77). The second model examined whether the treatment effects were different in females or males and resulted in no significant difference. The third model included the term for remission status at week 12 in order to analyze whether effects of treatment differ in patients whose depression receded at this time point. No statistically significant results were found. The final model examined whether any improvement in memory proficiency had occurred. The authors used the number of words remembered from the verbal memory test in the ADAS-Cog. There were ten people able to recall one word or greater in the sertraline group and 11 in the placebo group and this difference was not statistically significant. As a result of these trials no cognitive advantage was found for the use of antidepressants over placebo.

Weintraub et al.[9] found that the baseline MMSE and CSDD scores for all of their participants indicated mild to moderate dementia and moderate depression and that 40% had major depression. After the 24 week trial period no difference was found between treatment or placebo group for mADCS-CGIC score. The odds ratio (OR) for sertraline was 1.23 (95% confidence interval [CI] 0.64 to 2.35, *P*=0.54). There was also no difference found for CSDD scores between the groups. There was no effect found for treatment outcome on the change in CSDD score as time increased indicating that a model for treatment group and time shows no benefit over a model without these terms (*P*=0.97). At the end of the trial 37.8% of the sertraline group and 21.8% of the placebo group achieved remission. This difference was not statistically significant (OR 1.61, 95% CI 0.70 to3.68, *P*=0.26). When the time to first remission was examined no between group difference was found (hazard ratio $[HR]_{sertraline}$ 1.13, 95% CI 0.58 to 2.18, *P*=0.71). Similar findings were also found for the time to sustained remission ($HR_{sertraline}$ 1.90, 95% CI 0.93 to 3.88, *P*=0.08). Non-mood outcomes such as ADRQL, ADCS-ADL and MMSE did not show any significant changes for either improvement or decline. The exception to this trend occurred for NPI which resulted in an improvement after the 24 week period. This improvement was found for both the groups under study with no statistically significant difference between them. The examination of safety demonstrated that adverse events occurred more frequently in the sertraline group that in placebo. The most commonly occurring effects were dizziness, diarrhea and dry mouth with *P*-values of 0.005, 0.03 and 0.03 respectively. Severe adverse events occurred in 27.3% of patients treated with sertraline versus 12.7% for those in placebo (*P*=0.05). 12.1% of the severe adverse events were a result of pulmonary events and 6.1% of these occurred in the extended phase from 12 to 24 weeks compared to none in the placebo group (*P*=0.006). These events were caused by infections and

pneumothorax, and pulmonary embolism. These results indicate that the use of sertraline did not correlate with an improvement in long-term health outcomes for any of the treatment groups. As a result of this the authors stated that they could not recommend its use for patients suffering from depression and dementia. In addition the results demonstrate that there is a significant increase in the risk of adverse events, especially pulmonary severe events, when sertraline is used.

Evidence-based guidelines

No evidence-based guidelines were found for the use of antidepressants in elderly patients with depression and dementia.

Limitations

This report is limited in the analysis of the evidence-based guidelines for the use of antidepressants in patients with depression and dementia as no publications could be identified. The systematic review included for the analysis of clinical effectiveness and safety of antidepressants suffered from an overall lack of robust patient examination with a total of 330 patients across the seven studies. Several of the included studies were conducted on initial populations of 50 patients, suggesting that generalization of their results must be conducted with caution. The randomized controlled trials that were found were all well-conducted and utilized appropriate placebo controls during the study procedures. Patients and staff were also blinded to treatment usage, though in the study by Weintraub et al.[9] an insufficient amount of detail was included. For example, the method used to blind patients and clinical staff to the interventions that were used was not discussed. All of these investigations suffered from a high rate of patient dropout. In the most extreme case this dropout resulted in only 56.5% of the initial population completing all of the trial period.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence found regarding the question on the clinical effectiveness and safety of antidepressant use in the elderly indicated that their use may not be appropriate. The majority of the publications that were included found no statistically significant benefit from their use and in most situations any benefit that was found was mimicked in the placebo trial group. It has been suggested that any efficacy that occurred was more likely a result of undefined benefits of the overall trial process itself rather than genuine effect by antidepressant drugs. In the included systematic review two of the seven publications did demonstrate significant success from pharmacotherapy over placebo. After analysis was completed the authors stated that this benefit was attributed to drug effects that are too difficult to analyze in the small study populations that were included.

The question regarding evidence-based guidelines for the use of antidepressants in the elderly remains unanswered as no publications could be identified on this topic.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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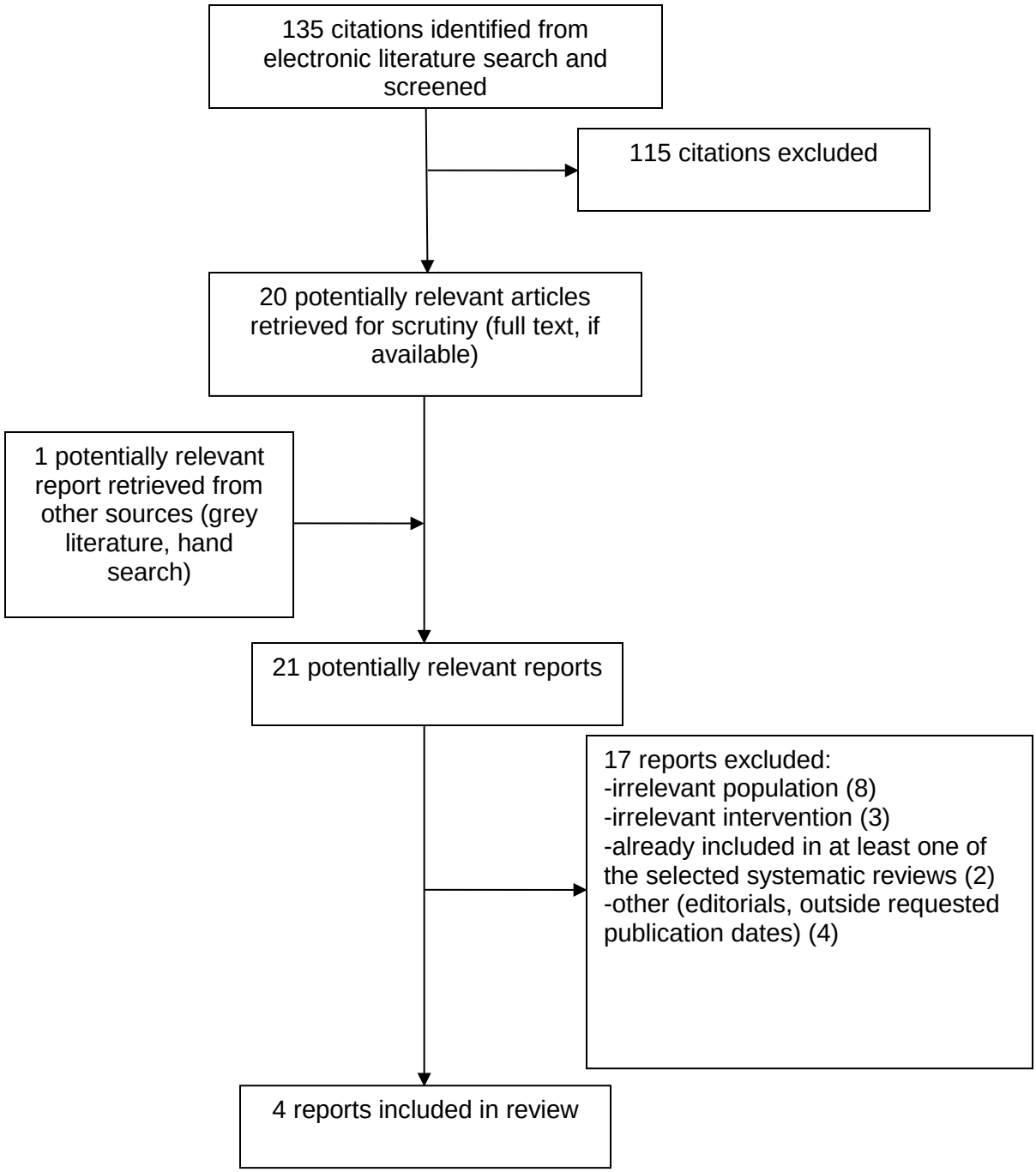
APPENDIX 1: Selection of Included Studies



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	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Goal
Systematic Reviews					
Nelson and Devanand[18], 2011, United States of America	- Included 7 studies - Searched Medline and The Cochrane Controlled Trials Register for RCT's from 1966 to May 2010 - Search terms – antidepressants, depression, dementia - Must be acute phase, parallel group, double-blinded and random assignment - Studies must include response and remission rates	- Patients must be diagnosed with depression and dementia using established criteria	- Antidepressants marketed in the USA	- Placebo controlled	- HDRS, MADRS, CSDD, mADCS-CGIC - Change in depressive symptoms examined using standard deviations - The goal was to analyze the efficacy of the use of antidepressants to treat people with depression and dementia

CSDD – Cornell Scale for Depression in Dementia, HDRS – Hamilton Depression Rating Scale, mADCS-CGIC - Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, MADRS – Montgomery-Asberg Depression Rating Scale

Table A2: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country	**Study Design, Length of Follow-up, Goal**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparator**	**Clinical Outcomes**
Banerjee et al.[7], 2013, United Kingdom	- Multi-center, parallel group, double-blinded RCT - Follow-up is 13 and 39 weeks post randomization - Goal: to fill gaps in the evidence base definitively and enable formulation of good quality guidance on care for people with dementia and their care givers	- n = 326, 111 placebo 107 sertraline and 108 mirtazapine - Mean patient age is 79 years old (227 females and 97 males) - patients must meet criteria for probable Alzheimer's disease according to NINCDS/ADRDA criteria and coexisting depression lasting at least 4 weeks - CSDD score must be ≥8 - recruited from 9 English old age psychiatry services (Biringham, Cambridge, Leicaster, Liverpool, Manchester, Newcastle, North	- SSRI, sertraline 150 mg daily - NaSSA, mirtazapine 45 mg daily	- Placebo, tablets appearing exactly as intervention treatments	- CSDD score is primary outcome - Secondary outcomes are : DEMQL or DEMQL-Proxy, generic quality of life (European Quality of Life-5 Dimensions), cognitive impairment (MMSE), medication adherence, carer mental health (General Health Questionnaire), carer quality of life (SF-12v2) and carer burden (Zarit Scale), behavioral disorder (Neuropsychiatric Inventory), baseline dementia vascularity index (modified Hachinski scale)

Table A2: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country	**Study Design, Length of Follow-up, Goal**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparator**	**Clinical Outcomes**
		London, Southampton, South London and Kent) between Dec 2006 to Jan 2010			
Munro et al.[21], 2012, United States of America	- Double-blinded, placebo controlled RCT - Follow-up completed up to 24 weeks post randomization - The goal was to examine the effect of sertraline on the cognitive performance in elderly patients with depression and Alzheimer's Disease after a 24 week trial versus placebo	- n = 131, mean age is 79 - Patients recruited from 5 outpatient memory disorder clinics - Must have MMSE score of 10-26 - Exclude if already on antidepressants or benzodiazepines	- SSRI, sertraline 100 mg daily	- Placebo, tablets appearing exactly as drug treatment	- Depression analyzed at week 12 using mADCS-CGIC - Cognitive testing completed at week 8, 16 and 24 for; MMSE, ADAS-Cog, Digit Span Subtest (Wechester Memory Scale-III), Letter Fluency, Digit Symbol Modalities Test, Finger Tapping Test
Weintraub et al.[9], 2010, United States of America	- Double-blinded, placebo controlled RCT - Follow-up completed up to 24 weeks post randomization	- n = 131, mean age 79 (67 in sertraline group, 64 in placebo) - recruited from 5 memory disorder clinics in the	- SSRI, sertraline (50 mg for initial week then increase to maximum of 100 mg based on clinician recommendation)	- Placebo, tablet appearing exactly as drug treatment	- Primary: mADCS-CGIC, CSDD - Secondary; MMSE, NPI, ADCS-ADLS, ADRQL - Adverse events examined using checklist obtained from

Table A2: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country	**Study Design, Length of Follow-up, Goal**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparator**	**Clinical Outcomes**
	- The goal was to examine if there was any delayed benefit from sertraline in patients with depression and Alzheimer's disease	United States - patients must meet criteria for dementia due to Alzheimer's Disease according to DSM-IV, Have MMSE score of 10-26, meet criteria for depression of Alzheimer's Disease - exclude if already on antidepressants, antipsychotics or benzodiazepines			FDA

ADAS-Cog - Cognitive Subscale of the Alzheimer's Disease Assessment Scale, ADCS-ADLS – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale, ADRQL – Alzheimer's Disease Related Quality of Life Scale , CSDD – Cornell Scale for Depression in Dementia, DSM-IV - Diagnostic and Statistical Manual of Mental Disorders 4th Edition, FDA – Food and Drug Administration, mADCS-CGIC – Alzheimer's Disease Cooperative Study-Clinical global Impression of Change scale, MMSE – Mini Mental State Examination, NaSSA – Noradrenergic/Specific Serotonergic Agent, NINCDS/ADRDA - National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, NPI – Neuropsychiatric Inventory, SSRI – Selective Serotonin Reuptake Inhibitor

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews based on AMSTAR[19]

Strengths	Limitations
Nelson and Devanand 2011 [18]	
• All criteria for study inclusion and exclusion are clearly defined and a flow chart for interpretation is included • The results are well discussed and other related, but not included, studies with similar comparisons are described and interpreted • Review utilized two independent reviewers • The included study characteristics are well described and included detailed analysis of patients and interventions • The methods for combining and analyzing the data of the included papers are well developed and appropriate for the conclusions that were drawn • Publication bias was explored and none was detected	• Only a small number of trials were found meeting the inclusion criteria • The total participant population of the included studies is very small therefore making the ability to draw defined conclusions very difficult and as a result caution must be used when generalizing these results • No examination of a search preformed of grey literature is provided • No discussion of the conflict of interest of the included studies was included

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[20]

Strengths	Limitations
Banerjee et al 2013 [7]	
• The inclusion criteria reflect the full spectrum of depressed and demented patients as no restrictions were implemented therefore the results will be easily generalized for many patients • The antidepressants utilized represent the two most commonly prescribed in clinical practice • Well described method of randomization and double blinding is included and made an effective use of placebo control	• Study contained a high rate of patient dropout which may influence the results if these patients had differing responses to interventions or placebo • Patient population is made up of 86% Caucasians which may impart an ethnic bias in results • The study designers had to revise their target sample size during the middle of the trial due to extremely slow recruitment (initial required 507 to achieve 90% power to detect two-point difference in CSDD score at 13 weeks and 86% power at 39 weeks, revised to 339) • Total population fell short of revised target population by 13 patients (goal was 339 achieved 326)
Munro et al 2012 [21]	
• Double-blinded, randomized and contained appropriate placebo control • >90% of the included patients completed all follow-up visits • All of the methods used for analysis of depression and dementia followed standardized psychosocial intervention techniques and were not modified to accommodate sample variation • Contained a detailed description of potential conflict of interest	• Study only examined a specific population of depressed Alzheimer's disease patients therefore not allowing for generalizability of results to a wide degree of the population • Testing techniques utilized for cognitive function may not have been sensitive enough to detect all of the potential changes and should have included protocol such as the Critical Flicker Fusion test
Weintraub et al 2010 [9]	
• Utilized placebo controls effectively and appropriately • The statistical methods used for result interpretation are appropriate for the data being analyzed • The testing procedure used for analysis of depression and dementia are well described and follow those used in previously published studies	• The method of randomization is not clearly described • The blinding of patients and clinical staff is alluded to but not described in full detail • A high patient dropout rate was encountered which may detrimentally effect the results

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Nelson and Devanand, 2011[18]	
• Only two studies found a significant result for their primary outcome. One examined global response ratings and the other demonstrated greater remission than that found in placebo group • The odds ratio for response rates of the papers was 2.12 (95% CI 0.95-4.70, Z=1.84 P=0.07) • Heterogeneity between papers was χ^2=11.26 df=5 P=0.05 I^2=56% • Response rates were 53.3% in drug treatment groups and 38.9% in placebo groups • The standardized mean difference for the change in scores was 0.29 (95% CI.02–0.60, Z=51.86, P=.06) • Odds ratio for remission was 1.97 (95% CI 0.85-4.55, Z=1.59, P=0.11) • Total patient dropout rate was 17.5% for drug groups and 16.2% for placebo • Pooled remission rates found drug treatment groups at 39.8% and placebo at 26.7% • Dropout due to adverse events was 9% and 6% for drug and placebo groups respectively with no significant difference found (OR=1.52 with 95% CI 0.67-3.47, Z=1.00, P=0.32 and no heterogeneity I^2=0%)	• Evidence from this review does not confirm an efficacy for the use of antidepressants on patients with depression and dementia • Two studies found effective results in treatment groups but the five remaining ones did not • Remission rates failed to show any significant differences (P=0.11) • The beneficial effect found in the two studies is likely a result of drug effects that are difficult to analyze in small populations that were utilized in these studies • Overall the evidence suggests that any beneficial remission rates found are likely due to an unidentified benefit of the clinical management process itself not any contribution from the antidepressants themselves
Banerjee et al., 2013[7]	
• Dropout rates were 26.1% in placebo group, 36.4% in sertraline group and 29.6% in mirtazapine group • Baseline severity of depression (CSDD) Score: 8-11 / ≥12 Placebo: 43 (39%) / 68 (61%) Sertraline: 45 (42%) / 64 (58%) Mirtazapine: 54 (50%) / 54 (50%) • Average CSDD scores at baseline Placebo: 13.6 Sertraline: 12.8 Mirtazapine: 12.5 • Quality of Life DEMQOL-Proxy / EQ-5D Placebo: 88.4 / 60.3 Sertraline: 86.5 / 66.6 Mirtazapine: 86.9 / 66.9 • Neuropsychiatric Symptoms NPI Placebo: 30.2 Sertraline: 26.9 Mirtazapine: 29.9 • Found decreased depression severity (CSDD	• The two most commonly prescribed antidepressants have no more beneficial effect than placebo • These findings do not appear to be dependent on the severity of dementia or on the type of dementia • There does appear to be a strong and consistent benefit for patients from referral to old age psychiatric services at three and nine month follow-up but that this result is independent of antidepressant use • Safety concerns are more prevalent in patients in the drug treatment groups • Clinicians should modify the way that they approach treatment for people with depression and dementia

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
score) in all groups with greatest decrease found at 13 weeks in the placebo group with -5.6 (SD 4.7) versus sertraline -3.9 (SD 5.1) and mirtazapine -5.0 (SD 4.9). At 39 weeks results similar, -4.8 (SD 5.5), -4.0 (SD 5.2) and -5.0 (SD 6.1) for placebo sertraline and mirtazapine respectively • Analysis using linear-mixed regression with adjustment for baseline depression and stratification factor center showed no significant difference between sertraline versus placebo or mirtazapine versus placebo at either 13 or 39 weeks • The most significant trend difference was found at 39 weeks for mirtazapine, 55% of patients had no depression, though when analyzed using linear-mixed regression with adjustment for baseline depression and stratification factor center no difference was found in the patient classified using CSDD score at 13 or 39 weeks • Secondary Outcomes - Few differences in any outcome for any group - One exception is fewer neuropsychiatric symptoms and higher care provider rated participant scores for health-related quality of life in the mirtazapine versus the sertraline group at 13 weeks, this trend disappeared by 39 weeks - Only significant finding for NPI occurred at 13 weeks where sertraline showed slight benefit over mirtazapine (odds ratio 1.390 95% CI 1.084-1.782, p=0.009 for symptoms of delusion, depression, anxiety, hallucinations, aberrant motor behavior and sleep) • Safety - Total of 119 subjects reported 240 adverse events (26% of placebo group, 43% of sertraline group and 41% of mirtazapine group) p=0.017 - Nausea and gastrointestinal issues most common for sertraline and psychological issues (drowsiness and sedation) most common in mirtazapine	
Munro et al., 2012[21]	
• Only difference in the cognitive testing scores was found for letter fluency where sertraline group performed better at baseline (median number is 18 for sertraline group with 95% CI of 15.0-21.0 versus 14.0 for placebo group 95% CI is 11.5-16.5 at baseline • Examination of four models: - Overall treatment group – no difference found (p values range from 0.24 to 0.77) - Treatment effects for male vs female – no	• No cognitive advantage was found for the use of antidepressant over placebo • Sertraline is safe with regard to cognitive function

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
differences found - Remission at week 12 – no differences found - Improved memory proficiency – no difference found (ADAS-Cog p=0.91)	
Weintraub et al., 2010[9]	
• Baseline MMSE and CSDD scores indicate all patients had mild to moderate dementia and depression (40% had major depression) and were divided into treatment groups on a 1:1 ratio • No difference found between groups for mADCS-CGIC at week 24 (odds ratio =1.23 95% CI 0.64-2.35, Wald χ^2=0.37 df=1, p=0.54) • No difference in CSDD at 24 weeks (difference in medians for placebo versus sertraline is 0.60 (95% CI -2.26 to 3.46) • No treatment effect on change of CSDD score over time was found (likelihood ratio is χ^2=0.26 df=3 and p=0.97 • No significant difference was found for patients achieving remittance was found (odds ratio=1.61 95% CI 0.07-3.68, Wald χ^2=1.28 df=1 and p=0.26) • No difference in between group time to first remission (odds ratio=1.13 95% CI 0.58-2.18, Wald χ^2=0.14 df=1, p=0.71) • No difference in time to sustained remission (odds ratio=1.90 95% CI 0.93-3.88, Wald χ^2=3.13 df=1, p=0.08) • Neuropsychiatric symptoms improved for all groups but no difference found for drug treatment • Adverse events occurred more frequently in the sertraline group and included dizziness, diarrhea and dry mouth - Diarrhea odds ratio 2.22 95% CI 1.04-4.76 p=0.03 - Dizziness odds ratio 2.86 95% CI 1.31-6.25 p=0.005 - Dry mouth odds ratio 2.22 95% CI 1.03-4.76 p=0.03 • Severe adverse events occurred in 27.3% of sertraline patients versus only 12.1% in placebo • Dropout rate in sertraline group was 43.3% and in placebo group was 43.7%. Overall only 56.5% of the original population completed all 24 weeks of the study	• The use of sertraline did not correlate with an improvement in long-term treatment for improved mood, non-mood neuropsychiatric symptoms, function, quality of life or global cognition • While no drug benefit was found 41% of patients did show benefit as indicated by CSDD scoring by 24 weeks • Sertraline cannot be recommended for treatment of depression in depressed Alzheimer's Disease patients • The odds ratios for adverse events were 2-3 times higher in patients treated with sertraline (specifically pulmonary severe adverse events)

CI – Confidence Interval, CSDD – Cornell Scale for Depression in Dementia, df – Degrees of Freedom, DEMQOL-Proxy – Dementia Quality of Life-Proxy, EQ-5D – European Quality of Life-5 Dimensions, MMSE – Mini Mental State Examination, NPI – Neuropsychiatric Inventory, OR – Odds Ratio, SD – Standard Deviation, mADCS-CGIC - Alzheimer's Disease Cooperative Study-Clinical global Impression of Change scale