[2015]

Pharmacological interventions (antidepressants) for people with dementia who have associated depression. [2015]

SCOPING QUESTION: For people with dementia and comorbid depression, do pharmacological interventions (i.e., antidepressants) produce any benefit and/or harm when compared to control or other comparators?

BACKGROUND

Dementia is one of the leading public health concerns. It is estimated that 44 million individuals worldwide currently have dementia, with the total set to increase to 75.62 million in 2030 and 135.46 million in 2050 (Prince et al., 2013). Alzheimer's disease accounts for more than 60% of all dementias (Reitz et al., 2011), while vascular dementia accounts for approximately 30% of dementia prevalence in low- and middle-income countries (LAMICs) (Ferri et al., 2005).

Particularly rapid increases in the numbers and proportion of older people with dementia are forecast for China, India and the Latin American region (Prince et al., 2011). Depression in dementia worsens already considerable handicaps that dementia poses, and usually goes unrecognized by caregivers and healthcare practitioners while being highly correlated with increased healthcare utilization, risk of suicide and greater severity and acceleration of cognitive impairment (Thomas et al., 2009; Starkstein, 2008). The reported prevalence of comorbid depression or depressive symptoms in individuals with dementia has been quite variable, ranging from 3-50% (Apostolova, 2008), which is likely due to differences in methods of assessment, diagnostic criteria, stages of dementia and other factors. Comorbid depression complicates diagnosis, affects treatment approaches and outcomes and decreases the quality of life of affected individuals, as well as their caregivers.

Mainstream treatments for depression include antidepressants and psychosocial interventions. Recent evidence shows that among people with depression, psychosocial interventions are as effective for treating mild to moderate depression as antidepressants (see updated 2015 mhGAP guideline for more information). For older people with depression in dementia, both psychosocial interventions and the use of antidepressants for patients with dementia accompanied by depressive symptoms are widespread, but their clinical efficacy is uncertain. Many of the individual trials of antidepressants have been too small to provide precise estimates of the moderate benefits that might realistically be expected. Most of placebo-controlled antidepressant studies in people with depression in dementia reported the properties of selective serotonin reuptake inhibitors (SSRIs). However, the use of serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricycle antidepressants (TCAs) was investigated in one and two studies in this population, respectively. The clinical efficacy of psychosocial interventions among people with depression in dementia needs to be re-evaluated given additional publications of evidence for their efficacy since the 2009 mhGAP guidelines. Therefore, this evidence profile is serves as an update to the mhGAP guidelines. For more information, please see the 2014 mhGAP evidence profile on psychological interventions for depression among people with dementia. This question aims to identify the

benefits and/or harm in the use of antidepressants, particularly SSRIs, for treating depression in people with dementia in non-specialist health settings in LAMIC when psychosocial interventions prove ineffective or are unavailable.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with dementia with a coexisting depressive illness
- **Interventions:** Antidepressants including TCAs and SSRIs
- **Comparison:** Placebo or one intervention vs. the other
- **Outcomes:**
    - **Critical** – Reduction of symptoms of depression, adverse events (including measured by treatment dropout)
    - **Important** – Cognitive functioning

Search strategy

To identify relevant systematic reviews, the following databases were searched: Medline, Embase, The Cochrane Library, BMJ Clinical Evidence and Psychinfo up to September 2014. A search strategy that was developed by McMaster University was used, and is as follows:

- systematic[sb] AND (("antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR "antidepressant"[All Fields]) AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields]))

The following additional terms were used:
(“second and third generation antidepressants OR citalopram OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR nefazodone OR paroxetine OR sertraline OR venlafaxine OR desvenlafaxine OR agomelatine” AND “cognitive OR cognition OR neuropsychology OR neuropsychological “AND“dementia OR Alzheimer’s OR Alzheimer’s disease OR vascular dementia OR dementia with Lewy bodies)

In order to identify additional primary studies, the following search strategy was used:

- Cochrane Central Database of Controlled Trials (CENTRAL); (2) MEDLINE; (3) EMBASE.

The search terms used included the following text words:

- name of medications ("second and third generation antidepressants OR citalopram OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR nefazodone OR paroxetine OR sertraline OR venlafaxine OR desvenlafaxine OR agomelatine"); and
- ("cognitive OR cognition OR neuropsychology OR neuropsychological "AND "dementia OR Alzheimer's OR Alzheimer's disease OR vascular dementia OR dementia with Lewy bodies") in combination with any of the above words.

This search was supplemented by the search strategy developed by the McMaster University, and is as follows:

- (randomized controlled trial [Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]). The following additional terms were used: (second and third generation antidepressants OR citalopram OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR nefazodone OR paroxetine OR sertraline OR venlafaxine OR desvenlafaxine OR agomelatine), AND ("cognitive OR cognition OR neuropsychology OR neuropsychological " AND " dementia OR Alzheimer's OR Alzheimer's disease OR vascular dementia OR dementia with Lewy bodies)

The MEDLINE search identified 36 systematic reviews, including four meta-analyses. The search of the Cochrane database found 113 reports. If meta-analysis of placebo-controlled antidepressant studies in people with depression in dementia before 2009 were excluded (two studies from 2002 and 2007), two meta-analyses (from 2011 and 2012) remained. No recent trial of antidepressants in people with depression in dementia have been published since the publication of the last two meta-analyses.

Included in GRADE tables or footnotes

- Banerjee S, Hellier J, Romeo R, Dewey M, Knapp M, Ballard C, Baldwin R, Bentham P, Fox C, Holmes C, Katona C, Lawton C, Lindesay J, Livingston G, McCrae N, Moniz-Cook E, Murray J, Nurock S, Orrell M, O'Brien J, Poppe M, Thomas A, Walwyn R, Wilson K, Burns A (2013). Study of the use of antidepressants for depression in dementia: the HTA-SADD trial – a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health Technology Assessment.17(7):1-166. doi:10.3310/hta17070.

- Nelson JC and Devanand DP (2011). A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression in dementia. Journal of the American Geriatrics Society.59(4):577-585. doi:10.1111/j.1532-5415.2011.03355.x

- Sepehry AA, Lee PE, Hsiung GY, Beattie BL, Jacova C (2012). Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression – A meta-analysis of depression and cognitive outcomes. Drugs & Aging.29(10):793-806. doi:10.1007/s40266-012-0012-5.

Excluded from GRADE tables and footnotes

Leong C (2014). Antidepressants for depression in patients with dementia: A review of literature. The Consultant Pharmacist.29(4):254-263. doi:10.4140/TCP.n.2014.254.
REASON FOR EXCLUSION: This study was a narrative synthesis of evidence.

Thompson S, Herrmann N, Rapoport MJ, Lanctôt KL (2007). Efficacy and safety of antidepressants for treatment of depression in Alzheimer´s disease: a meta-analysis. Canadian Journal of Psychiatry.52(4):248-55.
REASON FOR EXCLUSION: Nelson and Devanand (2011) included all of the studies analyzed by this study, with the addition of two more RCTs.

PICO Table

Population: People with depression in dementia					
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE**	**Justification for systematic review used**	**Relevant GRADE table**
Antidepressants (TCAs, SSRIs and SNRIs)	Placebo	Depression symptoms	Nelson and Devanand (2011)	This systematic review of antidepressants in people with depression in dementia included two additional studies of TCAs (Reifler et al., 1989; Petracca et al., 1996) and one study of SNRIs (Vasconcelos et al., 2007) that were not included in Sepehry et al. (2012).	Table 1
		Treatment dropout			Table 1
SSRIs	Placebo	Depression symptoms	Sepehry et al. (2012)*	This systematic review on the effect of SSRIs in AD with comorbid depression included only SSRIs studies. Three studies (Weintraub et al., 2010; Rozzini et al., 2010; Banerjee et al., 2011) included in this meta-analysis were not included in Nelson and Devanand (2011).	Table 2
		Cognitive functioning			Table 2

* This study included only patients with Alzheimer's disease

Narrative description of the studies that went into analysis

The review conducted by Nelson and Devanand (2011) aimed to determine the efficacy of antidepressants in people with depression in dementia. Seven trials published between 1989 and 2010, with a total of 330 participants, met selection criteria. Most of the trials required participants to have a Mini-Mental State Examination (MMSE) score of **10 or greater, and less than 27,** with baseline depression symptom scores said **to vary**. Measures used across the pooled studies include retention of participants randomized, baseline and end point depression scale scores, response and/or remission and discontinuation rates. Random-effects meta-analysis was performed for response and remission rates change scores using standardized mean differences and discontinuation rates.

Regarding depression severity, the effect of the diagnosis of major depression, depression severity and duration in trials reporting response was examined. Two trials reporting response rates restricted enrollment to major depression. One of these trials showed a clear advantage of antidepressants, while the other showed no effect. Alternatively, the ORs for response in five trials with less-severe depression (mean HDRS[i]<20 or MADRS[ii] equivalent) and the four trials that did not limit inclusion to major depression were modest (1.33, 95% CI50.80–2.21, Z=1.08, p=.28; and 1.39, 95% CI=0.81–2.38, Z=1.19, p=.23); neither was significant and in each case there was minimal heterogeneity (I^2 = 0%).

All of the trials were significantly underpowered to detect differences, which resulted in inconclusive findings. Variable trial methods, comorbid conditions and differences in antidepressants further confounded findings. Findings did not confirm evidence of efficacy of antidepressants in participants with depression in dementia.

Sepehry et al. (2012) carried out a meta-analysis of the effect of SSRIs on depression and cognitive impairment among patients with Alzheimer's disease with comorbid major or minor depression. The study did not give a mean baseline score for cognitive impairment (using the MMSE) but it did exclude patients with mild cognitive impairment. There was no sub-group analysis based on depression severity.

From 598 examined studies, 12 SSRI studies met the inclusion criteria, with only six that met all criteria. Among these, there were five studies that reported sufficient and consistent data to be included in the meta-analysis. Outcomes reported were depression score and cognition (i.e., cognitive function). Within a random effect model, effect size estimates of the first and second nested global analyses were non-significant, non-heterogeneous and small to null at the endpoint for depression, favoring SSRIs. The effect size for global cognition, as measured by the MMSE, was negligible. Current evidence does not support the efficacy of SSRI treatment for symptoms of comorbid depression in AD. Studies differed in terms of criteria for diagnosis of depression, the compound tested and outcome measures for depression.

Banerjee et al. (2013) was not included in the systematic reviews above, despite it being an RCT. However, the study has been included in the analysis due to its size, methodological quality and its influence in the field. Banerjee et al. (2013) produced a high quality parallel-group, double-blind placebo-

controlled RCT of the clinical effectiveness of sertraline and mirtazapine with 13- and 39-week follow-up that took place across nine 'old-age' psychiatry services in the United Kingdom (UK).

Patients with probable or possible Alzheimer's disease and depression (**50% were assigned a score of +8-+11 and 50% a score of 12+ on the Cornell Scale for Depression in Dementia** and lasting for more than 4 weeks and not clinically high risk, e.g., suicidal) were randomized to receive sertraline, mirtazapine or placebo. The absolute change from baseline at 13 weeks was greatest for placebo, –5.6 (SD 4.7), compared with –3.9 (SD 5.1) for sertraline and –5.0 (SD 4.9) for mirtazapine. This difference was maintained through to 39 weeks, with change scores of –4.8 (SD 5.5) for placebo, –4.0 (SD 5.2) for sertraline and –5.0 (SD 6.1) for mirtazapine. The results from the linear-mixed modeling, after adjusting for baseline depression and centre, made clear that there was no evidence of a difference between sertraline and placebo or mirtazapine and placebo on the CSDD score at 13 or 39 weeks. Findings **did not differ in subgroup analyses examining outcomes by baseline depression severity (CSDD score 8–11 vs. ≥ 12)**. This analysis provides robust evidence of an absence of clinical effectiveness of the antidepressants tested here compared with placebo.

Harms: A total of 119 participants reported 240 adverse reactions, with 29/111 (26%) in the placebo group experiencing adverse reactions compared with 46/107 (43%) in the sertraline group (p = 0.010) and 44/108 (41%) in the mirtazapine group (p = 0.031; overall p-value for placebo vs either medication = 0.017). Overall, the number of serious adverse events reported did not differ between groups; however, more of these events were categorized as severe in those on antidepressants compared with placebo (p = 0.003). Mortality did not differ between groups (five deaths in each group by 39 weeks).
Banerjee et al. (2013) concluded that this is a trial with negative findings but important clinical implications. The data suggest that, given normal care, the antidepressants tested are not clinically effective (when compared with placebo) for clinically significant depression in AD. This implies a need to change the current practice of administering antidepressants as a first-line treatment of depression in AD.

GRADE Tables

Table 1. Antidepressants vs. placebo for treatment of depression in dementia

Authors: E Castro-Costa and M Harper
Question: Should antidepressants vs. placebo be used for treatment of depression in dementia?
Bibliography: Nelson JC and Devanand DP (2011). A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression in dementia. Journal of the American Geriatrics Society.59(4):577-585. doi:10.1111/j.1532-5415.2011.03355.x

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant	Placebo	Relative (95% CI)	Absolute		
Depression improvement (assessed with response rated ≥ 50% improvement on HDRS or MADRS or an equivalent rating on a global assessment)												
6[1]	Randomized trials	Serious[2]	Serious[3]	No serious indirectness	Very serious[4,5,6]	None	80/150 (53.3%)	58/149 (38.9%)	OR 2.12 (0.95 to 4.7)[8]	185 more per 1000 (from 12 fewer to 360 more)	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Depression improvement (assessed with remission rates reported using a HDRS score ≤ 7 or CCSD in dementia score ≤ 6)												
6[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,5,6]	None	53/133 (39.8%)	36/135 (26.7%)	OR 1.97 (0.85 to 4.55)	151 more per 1000 (from 31 fewer to 357 more)	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Discontinuation for any reason												
7[7]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,5,6]	None	29/166 (17.5%)	27/167 (16.2%)	OR 1.12 (0.62 to 2.02)	16 more per 1000 (from 55 fewer to 119 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Discontinuation for adverse events												
7[7]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,5,6]	None	15/166 (9%)	10/167 (6%)	RR 1.52 (0.67 to 3.46)	31 more per 1000 (from 20 fewer to 147 more)	⨁◯◯◯ VERY	IMPORTANT

								0%			LOW	

[1] From Fig. 2 of Nelson and Devanand.(2011).
[2] One or more of the following criteria is not met in 10-30% of the pooled studies: trials not fully randomized, outcome assessment is not blind or dropout rate is more than 30%.
[3] Heterogeneity between 50-75% (I squared = 56.0%).
[4] Wide confidence interval (WHO defines wide as a confidence interval of more than 0.5 for continuous outcomes and more than 2 for dichotomous outcomes).
[5] Confidence interval crosses the line of no effect.
[6] Number of individuals between 100-200.
[7] From Fig. 3 of Nelson and Devanand.(2011).
[8] One additional RCT (Banerjee et al., 2013) was published after the publication of this systematic review (see above). It found that the absolute change from baseline at 13 weeks was greatest for placebo, –5.6 (SD 4.7), compared with –3.9 (SD 5.1) for sertraline and –5.0 (SD 4.9) for mirtazapine. This difference was maintained through to 39 weeks, with change scores of –4.8 (SD 5.5) for placebo, –4.0 (SD 5.2) for sertraline and –5.0 (SD 6.1) for mirtazapine. Based on these findings, the authors concluded that, given with normal care, antidepressants are not clinically effective (compared with placebo) for clinically significant depression in AD.

Table 2. Antidepressants vs. placebo for treatment of comorbid depression with Alzheimer's disease

Authors: E Castro-Costa and M Harper
Question: Should antidepressants vs. placebo be used for treatment of comorbid depression with Alzheimer's disease?
Bibliography: Sepehry AA, Lee PE, Hsiung GY, Beattie BL, Jacova C (2012). Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression – A meta-analysis of depression and cognitive outcomes. Drugs & Aging.29(10):793-806. doi:10.1007/s40266-012-0012-5.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antidepressant**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Depression Improvement (measured with HAM-D and CSSD; better indicated by lower values)												
5[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3,4]	None	187	191	-	Hedges 0.06 lower (0.26 lower to 0.14 higher)	⨁⨁⨁◯ LOW	CRITICAL
Cognitive improvement – Baseline (measured with MMSE; better indicated by lower values)												
4[5]	Randomized trials	Serious[2]	No serious inconsistency	no serious indirectness	Serious[3,4]	None	187	191	-	Hedges 0.09 lower (0.08 lower to 0.26 higher)	⨁⨁⨁◯ LOW	IMPORTANT

Cognitive improvement – endpoint (measured with MMSE; better indicated by lower values)												
4[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3,4,6]	None	187	191	-	Hedges 0.001 higher (0.19 lower to 0.19 higher)	⨁⨁⨁◯ VERY LOW	IMPORTANT

[1] From Fig. 2 of Sepehry et al. (2012). This result is in keeping with the results from the large RCT from Banerjee et al. (2013).
[2] One or more of the following criteria is not met in 10-30% of the pooled studies: trials not fully randomized, outcome assessment is not blind or dropout rate is more than 30%.
[3] Confidence interval crosses the line of no effect.
[4] Number of individuals is between 100-200.
[5] From Fig. 6 of Sepehry et al. (2012).
[6] Wide confidence interval (WHO defines wide as a confidence interval of more than 0.5 for continuous outcomes and more than 2 for dichotomous outcomes).

Additional evidence not mentioned in GRADE tables

Bains J, Birks J, Dening T (2002). Antidepressants for treating depression in dementia. Cochrane Database Systematic Reviews.4:CD003944. doi:10.1002/14651858.CD003944.

This Cochrane review was the basis for the mhGAP evidence profile for the same scoping question in 2009. The 'Summary of the evidence to recommendation' section from 2009 is provided below:

> "The review carried out by Bains et al. (2002) and updated in 2009 included seven studies with a total of 1140 subjects out of which 769 met inclusion criteria. Four included studies for the outcome of depression symptoms reported sufficiently detailed results to enter into meta-analyses, with a total of 137 subjects. Two of these studies investigated the properties of drugs not commonly used in this population with only two studies using the more common selective serotonin reuptake inhibitors (SSRIs). Lyketsos et al. (2003) produced two significant differences in favour of treatment in the Cornell Scale for Depression in Dementia (CSDD) at 12 weeks and in the psychiatrists' global rating. However, the CSDD was not used in any of the other studies and no statistical differences were found with the other measures used in the meta-analysis. The meta-analysis of the number of patients suffering at least one adverse event showed a significant difference in favour of placebo. There were no other significant results."

In the 'Summary of the Evidence' and the final recommendation from the 2012 update to the mhGAP evidence profile, there were four studies reporting the effect of antidepressants on mood, which were deemed of low quality and showed no difference when compared to placebo (MD -0.93 (-3.27 to 1.41). There were four studies of very low quality that reported the effect of antidepressants on cognition (measured using different metrics), all showing no difference between antidepressant and placebo (MD -1.90 95% CI -7.93 to 4.13, MD 1.16 95% CI -6.63 to 8.95, MD -1.20 95% CI -6.87 to 4.47 and MD 0.50 95% CI -5.28 to 6.28). Finally, adverse events showed mixed results. Five moderate-quality studies measuring adverse events through the proxy "number of dropouts" found no difference between placebo and antidepressant arms (OR 1.07, 95% CI 0.59 to 1.94). One high quality study investigating direct comparison of adverse events among participants taking antidepressants and placebo found more adverse events among the antidepressants group (OR 1.42, 95% CI 1.07 to 1.89).

The final mhGAP recommendation in 2010 (and updated in 2012) was as follows:

> "**In people with dementia with symptoms and/or signs suggestive of moderate or severe depression, use of selective serotonin reuptake inhibitors may be considered by non-specialist health care providers. In case of non-response after at least 3 weeks, they should preferably be referred to mental health specialist for further assessment and management."**
>
> **The strength of the recommendation was standard.**

Thompson S, Herrmann N, Rapoport MJ, Lanctôt KL (2007). Efficacy and safety of antidepressants for treatment of depression in Alzheimer´s disease: a meta-analysis. Canadian Journal of Psychiatry.52(4):248-55.

Thompson et al. (2007) conducted a meta-analysis aiming to quantitatively summarize the data on the efficacy and safety of antidepressant treatment for depression that complicates Alzheimer's disease (DSM III or IV diagnosis of major depressive episode, dysthymic disorder and minor depression). It included five studies, which involved 82 subjects treated with antidepressants and 83 subjects who received placebo treatment. Antidepressants were superior to placebo for both treatment response (OR 2.32; 95% CI 1.04 to 5.16) and remission of depression (OR 2.75; 95% CI, 1.13 to 6.65). There were no significant differences between the 2 groups for change in cognition (WMD -0.71, 95% CI, -3.20 to 1.79), overall dropouts (OR 0.70; 95% CI, 0.29 to 1.66) or dropout due to adverse events (OR 1.41; 95% CI 0.36 to 5.54). There was no subgroup analysis according to depression severity. The numbers needed to treat for one additional AD patient to respond to antidepressant treatment were 5 (95% CI, 3 to 59) and 5 (95% CI, 2 to 24) for remission of depression. Note: All of the studies in this paper are included in the Nelson and Devandand (2011) study, with the study quality determined using GRADE.

Leong C (2014). Antidepressants for depression in patients with dementia: A review of literature. The Consultant Pharmacist.29(4):254-263. doi:10.4140/TCP.n.2014.254.

This report includes a narrative systematic review of antidepressants for depression in patients with dementia. A literature search was conducted using MEDLINE, PUBMED, EMBASE, and Cochrane databases (from inception to May 2013) for studies in English that evaluated the treatment of depression in patients with dementia. All relevant RCTs and meta-analysis were identified using the search terms “dementia” or “Alzheimer’s diseases”, and “depression” or “major depressive disorder”. Ten RCTs (n=1,646) and three meta-analyses were included in this review. The majority of the RCTs consisted of a small sample size and the antidepressants studied were not routinely used in practice. There was no synthesis of information according to depression severity. The evidence for antidepressants in the treatment of depression in patients with dementia is **inconclusive**. The study suggests that treatment for depression in people with dementia should take a stepped-care approach, with psychosocial interventions being implemented first, followed by pharmacological interventions if need be. However, this conclusion is an expert opinion and is not directly related to the evidence cited.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Outcome	**Intervention**	
	TCAs, SSRIs and SNRIs vs. placebo *(Number of studies, OR or Hedges [95% CI], quality)*	SSRIs only (among people with Alzheimer’s disease) vs. placebo *(Number of studies, OR [95% CI], quality)*
Depression response	6 studies, OR: 2.12 (0.95- 4.70) No difference, VERY LOW quality	
Depression remission	6 studies, OR: 1.97 (0.85- 4.53) No difference, VERY LOW quality	
Depression improvement		5 studies, Hedges g 0.062 lower (0.264 lower to 0.139 higher)

		No difference, LOW quality
Cognition (MMSE baseline/endpoint)		4 studies, Baseline Hedges g 0.09 lower (0.08 lower to 0.26 higher) Endpoint Hedges g 0.001 higher (0.19 lower to 0.19 higher) No difference, VERY LOW quality
Treatment dropout for any reason	7 studies, OR: 1.12 (0.62 -2.02) No difference, VERY LOW quality	
Treatment dropout for adverse events	7 studies, OR: 1.52 (0.07 – 3.46) No difference, VERY LOW quality	

Evidence to recommendation table

Benefits	Although depression is common in people with dementia and many patients are prescribed antidepressants, the evidence to support this practice is weak. In people with Alzheimer's disease and depression and in people with depression in dementia, meta-analyses showed no difference of effect between antidepressants vs. placebo. The large RCT by Banerjee et al. (2013) did not show clinical effectiveness either.
Harms	The large RCT by Banerjee et al. (2013) reported that the number of serious adverse events reported did not differ between the antidepressant vs. the placebo groups; however, more of these events were categorized as severe in those on antidepressants compared with placebo. Mortality did not differ between groups. The Nelson and Devanand (2011) systematic review showed no difference between the antidepressant and placebo groups in discontinuation rates due to any reason or due to adverse events (which is the proxy

	measure of acceptability). Therefore, the evidence is inconclusive. At this time, it is not possible to establish if there is a clinically relevant difference in harms between antidepressants and placebo in people with dementia. However, clinicians must be vigilant regarding the potential side-effects of antidepressants in this population. TCAs are associated with side-effects that are potentially more problematic for elderly patients. In particular, the anti-cholinergic properties of TCAs are associated with a negative impact on cognition, involving postural hypotension and risk of falls.
Summary of the quality of evidence	The quality of the available evidence is very low.

Value and preferences	
In favour	Control of depressive symptoms is of critical importance. Comorbid depression complicates diagnosis, adds to suffering, disability, suicide risk and mortality rates. It also leads to greater functional impairment in people with dementia and decreases the quality of life of caregivers. Clinicians in non-specialized care may prefer to offer antidepressant medication, as they often do not have the skills or time to provide psychosocial interventions. WHO recommends TCAs or fluoxetine in adults with moderate to severe depressive episodes.
Against	In older people with depressive episodes, WHO recommends to avoid TCAs if possible because TCAs are known to be associated with more adverse effects among elderly people.
Uncertainty or variability?	There is some uncertainty with regards to treatment preferences.

Feasibility (including resource	Given the complex nature of both depression in dementia, understanding the relationship between the two is difficult. Depressive illness in older people can present as a 'pseudo-dementia' and be difficult to

use considerations)	distinguish from a dementing illness. On the other hand, depression is often associated with deterioration in cognitive functioning, which is sometimes not completely reversible with treatment. Moreover, for older people, a history of depression in later life may be associated with an increased risk of subsequently developing a dementing illness. Both disorders are common in older people and may therefore be expected to occur together solely by chance. In many LAMICs, there is no continuous availability of psychotropic medications in non-specialized health care settings. In many LAMICs, there is limited supportive supervision of mental health care in non-specialized health care settings. Both generic TCAs and many generic SSRIs are associated with low acquisition costs.
Uncertainty or variability?	There is some variability in the capacity of country's to deliver interventions for depression in dementia due to resource constraints.

Recommendation and remarks

Recommendation

In people with dementia and severe depression, or when psychosocial interventions prove ineffective, the use of selective serotonin reuptake inhibitors (SSRIs) (but not tricyclic antidepressants [TCAs]) may be considered.
In people with dementia and mild to moderate depression, antidepressants should not be offered as a first-line treatment.

Rationale: The evidence to support the use of antidepressants for the treatment of comorbid depression in dementia is inconclusive. Clinicians must be vigilant regarding the potential side-effects of antidepressants in this population, especially tricyclic antidepressants, as they are associated with side-effects that are potentially more problematic for elderly patients.

Remarks

This evidence implies a need to change current practice of antidepressants being the first-line treatment of depression in individuals with dementia.

Tricyclic antidepressants (TCAs) are associated with more adverse effects than are selective serotonin reuptake inhibitors (SSRIs) in older adults.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate **X Low** □Very low
Balance of benefits versus harms	□ Benefits clearly outweigh harms □ Benefits and harms are balanced **X Potential harms clearly outweigh potential benefits**
Values and preferences	**X No major variability** □ Major variability
Resource use	**X Less resource-intensive** □ More resource-intensive

Strength	**CONDITIONAL**

OTHER REFERENCES

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[i] Hamilton Depression Rating Scale (HDRS)
[ii] Montgomery-Asperg Depression Rating Scale (MADRS)