Q4: For people with dementia with associated depression, do antidepressants when compared to placebo/comparator produce benefits/harm in the specified outcomes?

Background

Worldwide, there are estimated to be 25 million people with dementia, majority of them in developed countries have Alzheimer's disease. However, Alzheimer's disease accounts for 60% whereas vascular dementia accounts for approximately 30% of the prevalence in low and middle income countries (LAMIC). People with dementia are commonly afflicted with depression and it has been correlated with increased disability, impaired quality of life, and higher mortality. Dementia with depression is an important clinical problem that clinicians manage without the benefit of treatment guidelines. The use of antidepressants for patients with dementia accompanied by depressive symptoms is widespread, but their clinical efficacy is uncertain. This uncertainty is due to the difficulties of interpreting the results of clinical trials. Many of the individual trials of antidepressants have been too small to provide precise estimates of the moderate benefits that might realistically be expected.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	people with dementia with a coexisting depressive illness
Interventions:	antidepressants
Comparison:	placebo
Outcomes:	depression improvement
	cognition improvement
	activities of daily living
	clinical global impression

number of dropouts

adverse events

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Bains J, Birks J, Dening T (2002). Antidepressants for treating depression in dementia. *Cochrane Database Systematic Reviews,* 4: CD003944 (last assessed as up to date April 2005).

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Thompson S et al (2007). Efficacy and Safety of antidepressants for treatment of depression in Alzheimer's disease: A meta-analysis. *Canadian Journal of Psychiatry,* 52:248-255.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	**Antidepressants vs. placebo**	Depression Improvement Cognition improvement Activities of daily living Clinical Global Impression Number of dropouts Adverse events	Bains J, Birks J, Dening T (2002). Antidepressants for treating depression in dementia. *Cochrane Database Systematic Reviews,* (4):CD003944 (last assessed as up to date April 2005)	This meta-analysis included more studies (7) than Thompson et al (5). Also, it included more patients 1140 subjects vs.165.

Narrative description of the studies that went into the analysis

The review carried out by Bains et al, 2002 included seven studies with a total of 1140 subjects out of which 769 met inclusion criteria. Four included studies 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 last one adverse event, showed a significant difference in favour of placebo. There were no other significant results.

GRADE tables

Table 1

Author(s): Castro-Costa E, Dua T, Huynh N
Date: 2009-08-29
Question: Should antidepressants vs. placebo be used for dementia?
Settings:
Bibliography: Bains J, Birks J, Dening T (2002). Antidepressants for treating depression in dementia. *Cochrane Database Systematic Reviews,* (4):CD003944.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressants	placebo	Relative (95% CI)	Absolute		
Depression(Hamilton) (Better indicated by lower values)												
4	randomized trials	no serious limitations	no serious inconsistency	Serious[2]	Serious[3]	none	63	65		MD, 0.93 lower (3.27 lower to 1.41 high)	LOW	CRITICAL
Cognition(Lyketsos et al, 2003) (Better indicated by lower values)												

1	randomized trials	no serious limitations	no serious inconsistency	Serious[4]	very serious[5]	none	24	20	-	MD 1.90 lower (7.93 lower to 4.13 higher)	VERY LOW	IMPORTANT
Cognition(Petracca et al, 1996) (Better indicated by lower values)												
1	randomized trials	no serious limitations	no serious inconsistency	Serious[4]	very serious[5]	none	11	10	-	MD 1.16 higher (6.63 lower to 8.95 higher)	VERY LOW	IMPORTANT
Cognition(Petracca et al, 2001) (Better indicated by lower values)												
1	randomized trials	no serious limitations	no serious inconsistency	Serious[4]	very serious[5]	none	15	20	-	MD 1.20 lower (6.87 lower to 4.47 higher)	VERY LOW	IMPORTANT
Cognition(Reifler et al, 1989) (Better indicated by lower values)												
1	randomized trials	no serious limitations	no serious inconsistency	Serious[4]	very serious[5]	none	13	15	-	MD 0.50 higher (5.28 lower to 6.28 higher)	VERY LOW	CRITICAL
Activities of daily living (Better indicated by lower values)												
4	randomized trials	no serious limitations	no serious inconsistency	Serious[2]	very serious[5]	none	63	65	-	MD 0.05 higher (0.30 lower to 0.40 higher)	VERY LOW	IMPORTANT
Clinical Global Impression												
1	randomized trials	no serious limitations	no serious inconsistency	Serious[4]	very serious[5]	none	20/24 (83.3%)	7/20 (35%)	OR 7.33 (2.20 to 24.46)	448 more per 1000 (from 192 more to 579 more)	VERY LOW	IMPORTANT
Number of Dropouts												
5	randomized trials	no serious limitations	no serious inconsistency	Serious[6]	no serious imprecision	none	28/130 (21.5%)	27/134 (20.1%)	OR 1.07 (0.59 to 1.94)	11 more per 1000 (from 72 fewer to 127 more)	MODERATE	IMPORTANT
Adverse events												
3	randomized trials	no serious limitations	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	196/397 (49.4%)	159/394 (40.4%)	OR 1.42 (1.07 to 1.89)	86 more per 1000 (from 16 more to 158 more)	HIGH	

[1] I Sq<50%.

[2] 3 studies included all dementia patients and 1 study included only patients with Alzheimer's Disease.

[3] Less than 200 participants.
[4] Only one study reported.
[5] Less than 100 participants.
[6] 4 studies included all dementia patients and 1 study included only patients with Alzheimer's Disease.

Additional information that was not GRADEd

The Lyketsos et al, 2003 study included in the systematic review produced two significant differences in favour of treatment in the Cornell Scale for Depression in Dementia (CSDD) at 12 weeks (WMD -6.70, 95% CI -11.50, - 1.90) and in the psychiatrist's global rating (Peto odds ratio (OR) (95% Fixed) 7.33 (2.20, 24.46)). However, the CSDD was not used in any of the other included studies, and no statistical differences were found with the other measures used in the meta-analysis.

Reference List

Bains J, Birks J, Dening T (2002). The efficacy of antidepressants in the treatment of depression in dementia. *Cochrane Database Systematic Reviews,* (4): CD003944 (last assessed as up to date April 2005).

Lyketsos CG et al (2003). Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Archives of General Psychiatry,* 60:737–46.

Petracca GM, Chemerinski E, Starkstein SE (2001). A double-blind, placebo-controlled study of fluoxetine in depressed patients with Alzheimer's disease. *International Psychogeriatrics,* 13:233–240.

Petracca G et al (1996). A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences,* 8:270–5.

Reifler BV et al (1989). Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *American Journal of Psychiatry,* 146:45–9.

Thompson S et al (2007). Efficacy and Safety of antidepressants for treatment of depression in Alzheimer's disease: a meta-analysis. *Canadian Journal of Psychiatry,* 52:248-55.

From evidence to recommendations

Factor	Explanation	
Narrative summary of the evidence base	Depression	4 studies, MD -0.93 (-3.27 to 1.41, no difference)
	Cognition (Lyketsos et al, 2003)	1 study MD -1.90 (-7.93 to 4.13, no difference)
	Cognition (Petracca et al, 1996)	1 study MD 1.16 (-6.63 to 8.95, no difference)
	Cognition (Petracca et al, 2001)	1 study MD -1.20 (-6.87 to 4.47, no difference)
	Cognition (Reifler et al, 1989)	1 study MD 0.50 (-5.28 to 6.28, no difference)
	Activities daily living	1 study MD 0.05 (-0.30 to 0.40, no difference)
	Clinical global impression	1 study OR 7.33 (2.20 to 24.46, favouring active treatment)
	Number of dropouts	5 studies OR 1.07 (0.59 to 1.94, no difference)
	Adverse events	1 studies OR 1.42 (1.07 to 1.89, favouring active treatment)
Summary of the quality of evidence	Depression	LOW
	Cognition (Lyketsos et al, 2003)	VERY LOW

	Cognition (Petracca et al, 1996)	VERY LOW
	Cognition (Petracca et al, 2001)	VERY LOW
	Cognition (Reifler et al, 1989)	VERY LOW
	Activities daily living	VERY LOW
	Clinical Global Impression	VERY LOW
	Number of dropouts	MODERATE
	Adverse events	HIGH
Balance of benefits versus harms	Although depression is common in people with dementia and many patients are prescribed antidepressants, the evidence to support this practice is weak. Only four studies are included in the meta-analysis relating to efficacy and sample sizes are small. Only two included studies investigated the properties of the more commonly used SSRIs. The meta-analysis produced only two statistically significant results. There was a significant difference in favour of treatment compared with placebo in the CSDD at 12 weeks and in the psychiatrists' global rating. However, both of these results originate from a single study (Lyketsos et al, 2003) with a small sample size (n = 44). Moreover, clinicians must be vigilant regarding the potential side effects of antidepressants in this population. Tricyclic antidepressants (TCAs) are associated with side-effects that are potentially more problematic for elderly patients. In particular their anti-cholinergic properties are associated with a negative impact on cognition, involving postural hypotension and risk of falls.	
Values and preferences including any	People with dementia are commonly afflicted with depression and it has been correlated with increased disability, impaired quality of life, and higher mortality. Given the complex nature of both depression and dementia, understanding the relationship between the two is difficult. Depressive	

variability and human rights issues	illness in older people can present as a 'pseudo-dementia' and be difficult to 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, in 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.
Costs and resource use and any other relevant feasibility issues	Amitriptyline as a class of drug and fluoxetine (a SSRI) are the antidepressants on WHO Essential Medicine List. Requires clinical monitoring in people with dementia.
Final recommendation(s) 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. Strength of recommendation: STANDARD	

Limitations

Only short-term data are available, and it is not easy to ascertain whether the statistically significant advantage of antidepressants over placebo translates into a clinically significant benefit under real-world circumstances.

Update of the literature search – June 2012

Role of antidepressants in people with dementia and associated depression

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Bains J, Birks J, Dening T. Antidepressants for treating depression in dementia. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD003944. DOI: 10.1002/14651858.CD003944.

Nelson JC, Devanand DP. A Systematic Review and Meta-Analysis of Placebo-Controlled Antidepressant Studies in People with Depression and Dementia. JAGS 2011, 59:577–585, DOI: 10.1111/j.1532-5415.2011.03355.x