Antidepressants (Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors) in treatment of adults with depression

Q 1: Are antidepressants (Tricyclic Antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI)) better (more effective than/as safe as) than treatment as usual (placebo) in adults with depressive episode/disorder?

Background

The relative merits of antidepressants versus placebo for depression have been given considerable scientific attention in recent years. This document covers the use of TCAs and SSRIs as acute phase treatment for depressive episode/disorder.

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

- **Population:** adults with depressive episode/disorder
- **Interventions:** antidepressant medicines: TCAs, SSRIs
- **Comparison:** placebo
- **Outcomes:**
    - treatment effectiveness in terms of reduction of symptoms
    - treatment effectiveness in terms of improvement in functioning
    - acceptability profile
    - suicide related outcomes

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Arroll B et al (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Annals of Family Medicine*, 3:449-56.

Barbui C et al. (2007).Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs). *Cochrane Database of Systematic Reviews*, (3):CD002791.

Furukawa TA, McGuire H, Barbui C (2002). Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *British Medical Journal*, 325:991.

Geddes JR et al (2007). Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression. *Cochrane Database of Systematic Reviews*, (3):CD001851.

Kirsch I et al (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *Public Library of Science Medicine*, 5:e45.

Laughren T (2006). Briefing document for December 13 meeting of Psychopharmacologic Drugs Advisory Committee, *Department Of Health And Human Services Public Health Service Food And Drug Administration Center For Drug Evaluation And Research*, (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf, accessed 14 April 2010)

Mottram P, Wilson K, Strobl J (2006). Antidepressants for depressed elderly. *Cochrane Database of Systematic Reviews*, (1):CD003491.

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National Institute for Clinical Excellence (NICE) (2007). Antenatal and postnatal mental health. *NICE guideline on clinical management and service guidance*. The British Psychological Society & The Royal College of Psychiatrists.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

American Psychiatric Association (2000). Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry,* 157:1-145.

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Turner EH et al (2008). Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *New England Journal of Medicine*, 358:252-60.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Tricyclics and related vs placebo	treatment effectiveness in terms of symptom reduction	Arroll et al (2005) – additional information as footnotes from Furukawa et al (2002)	Arroll et al (2005) has a specific focus on primary health care
		treatment effectiveness in terms of improvement in functioning	No data	
		acceptability profile	Arroll et al (2005)	
		suicide related outcomes	No data	Supplementary information was extracted from FDA analysis (Laughren, 2006)

2	SSRIs vs placebo	treatment effectiveness in terms of symptom reduction	Arroll et al (2005); NICE (2004) Additional information from Geddes et al (2007), Barbui et al (2007) and Mottram et al (2006).	Supplementary information was extracted from Kirsch et al.(2008)
		treatment effectiveness in terms of improvement in functioning	No data	
		acceptability profile	Arroll et al (2005); NICE (2004)	
		suicide related outcomes	No data	Supplementary information was extracted from FDA analysis (Laughren 2006)

Narrative description of the studies that went into the analysis

Arroll et al (2005), who included only studies carried out in the primary health care, analysed 15 studies with 890 participants in SSRI studies, 596 in TCA studies, and 1,267 patients on placebo. Of the 5 possible SSRIs available, 2 studied sertraline, 3 studied escitalopram (a precursor of citalopram), and 1 studied citalopram. Of the TCAs available, 2 studied dothiepin, 4 studied amitriptyline, 2 studied mianserin, and 3 studied imipramine. Ten of the 15 studies were identified as having a competing interest.

NICE (2004) included 48 studies comparing one of the SSRIs with placebo (7460 participants). All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.75 weeks), with 16 trials of eight weeks or longer. Three studies were of inpatients, 31 of outpatients, one in primary care and 13 either mixed or unspecified. In no study were more than 80% of study participants aged 65 years and over. It was possible to determine baseline severity in 19 studies, with four being classified as moderate, six as severe and nine as very severe. No studies focused on mild depressive episode/disorder.

GRADE Tables

Table 1

Author(s): Corrado Barbui, Andrea Cipriani
Date: 2009-05-25
Question: Should TCAs vs placebo be used for adults with depressive episode/disorder (in primary health care)?
Settings: nonspecialized health care
Bibliography: Arroll B et al (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Annals of Family Medicine*, 3:449-56.

Laughren T (2006). Briefing document for December 13 meeting of Psychopharmacologic Drugs Advisory Committee, *Department Of Health And Human Services Public Health Service Food And Drug Administration Center For Drug Evaluation And Research*, (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf, accessed 14 April 2010).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tricyclic antidepressants	placebo	Relative (95% CI)	Absolute		
Response on severity of depressive symptoms												
8[1]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	323/535 (60.4%)	216/460 (47%)	RR 1.26 (1.12 to 1.42)[3]	122 more per 1000 (from 56 more to 197 more)	LOW	CRITICAL
Functioning												
0	no evidence available					None	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Suicide ralated outcomes												
1[4]	randomized trials	very serious[5]	serious[6]	serious[7]	serious[8]	None	0/0 (0%)[9]	0%	OR 0.71 (0.45 to 1.12)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Adverse effects leading to withdrawal												

11[10]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	81/692 (11.7%)	30/578 (5.2%)	RR 2.35 (1.69 to 3.46)	70 more per 1000 (from 36 more to 128 more)	⨁⨁⨁◯ LOW	CRITICAL

[1] From Figure 2 of Arroll et al (2005).
[2] Dropout rate exceed 30% in the majority of studies.
[3] Another systematic review included randomized trials comparing low dosage tricyclics (<100 mg/day) with placebo or with standard dosage tricyclics in adults with depression (any settings) (Furukawa et al (2002)). It found that low dosage tricyclics, mostly between 75 and 100 mg/day, were 1.65 (95% confidence interval 1.36 to 2.0) and 1.47 (1.12 to 1.94) times more likely than placebo to bring about response at 4 weeks and 68 weeks, respectively.
[4] From Table 15 of FDA analysis. The total number of included studies is not reported.
[5] Studies were not primarily designed to assess the risk of suicide-related outcomes.
[6] This is a rare outcome that has been inconsistently reported in the included studies.
[7] Adults with any psychiatric disorders recruited in any settings are included.
[8] The 95% confidence interval includes both no effect and appreciable benefit.
[9] Absolute numbers not reported in the FDA analysis.
[10] From Figure 4 of Arroll et al (2005).

Table 2

Author(s): Corrado Barbui, Andrea Cipriani
Date: 2009-05-27
Question: Should SSRIs vs placebo be used for adults with depression (any settings)?
Settings:
Bibliography: Laughren T (2006). Briefing document for December 13 meeting of Psychopharmacologic Drugs Advisory Committee, *Department Of Health And Human Services Public Health Service Food And Drug Administration Center For Drug Evaluation And Research*, (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf, accessed 14 April 2010).

National Institute for Clinical Excellence (NICE) (2004). Depression: Management of depression in primary and secondary care. *National Clinical Practice Guideline Number 23*. The British Psychological Society & The Royal College of Psychiatrists.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**selective serotonin reuptake inhibitors**	**placebo**	**Relative (95% CI)**	**Absolute**		
Depressive symptoms (Better indicated by lower values)												
16[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	1177	1046	-	SMD 0.34 lower (0.47 to 0.22 lower)[4]	VERY LOW	CRITICAL
Lack of response on severity of symptoms												

17[5]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	992/1883 (52.7%)[6]	836/1260 (66.3%)	RR 0.73 (0.69 to 0.78)[7]	179 fewer per 1000 (from 146 fewer to 206 fewer)	LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Treatment acceptability (total dropouts)												
40[8]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1597/4190 (38.1%)	1349/3196 (42.2%)	RR 0.92 (0.67 to 0.97)	34 fewer per 1000 (from 13 fewer to 139 fewer)	HIGH	CRITICAL
Suicide related outcomes												
1[9]	randomized trials	very serious[2,10]	serious[11]	serious[12]	no serious imprecision	none	0/0 (0%)[13]	0%	OR 0.86 (0.69 to 1.06)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Adverse effects leading to withdrawal												
39[14]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	594/4234 (14%)	179/3226 (5.5%)	RR 2.45 (2.08 to 2.89)	80 more per 1000 (from 60 more to 105 more)	HIGH	CRITICAL

[1] From page 374 of Appendix 19 of NICE (2004).

[2] In the majority of included trials more than 30% of patients failed to complete the study, plus dropouts were not equally distributed in some studies.

[3] Heterogeneity exceeds 50% (I-squared=50.5%).

[4] The group of SSRIs has additionally been compared with that of tricyclic and related antidepressants. See details in the Additional evidence that was not graded section.

[5] From page 372 of Appendix 19 of NICE (2004).

[6] Another systematic review was carried out by Kirsch et al(2008). It included data on all clinical trials submitted to the US Food and Drug Administration (FDA) for the licensing of 4 new-generation antidepressants. This analysis found that drug–placebo differences increased as a function of initial severity. See details in the Additional evidence that was not graded section.

[7] Arroll et al (2005) and colleagues, who carried out a systematic review of studies comparing SSRIs with placebo conducted in the primary health care, included 4 trials that showed a statistically significant advantage of SSRIs over placebo (RR 1.37, 95% CI 1.21 to 1.55).

[8] From page 375 of Appendix 19 of NICE (2004)

[9] From Table 15 of FDA analysis Laughren (2006). The total number of included studies is not reported.

[10] Studies were not primarily designed to assess the risk of suicide-related outcomes.

[11] This is a rare outcome that has been inconsistently reported in the included studies.

[12] Adults with any psychiatric disorders were included.

[13] Absolute numbers not reported in the FDA analysis Laughren(2006).

[14] From page 376 of Appendix 19 of NICE (2004).

Additional information that was not GRADEd

SEVERITY OF DEPRESSION

Kirsch et al (2008) obtained data on all clinical trials submitted to the US Food and Drug Administration (FDA) for the licensing of the four new-generation antidepressants. It included data on all clinical trials submitted to the US Food and Drug Administration (FDA) for the licensing of 4 new-generation antidepressants. Meta-analytic techniques were applied to assess linear and quadratic effects of initial severity of depression on improvement scores for drug and placebo groups and on drug–placebo difference. It found that drug–placebo differences increased as a function of initial severity, rising from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category.

The results of this analysis, together with the information that the vast majority of randomized trials assessing the efficacy of TCA and SSRIs have been carried out in populations of patients with moderate to severe depression, have led most treatment guidelines to recommend drug treatment in patients with depression of at least moderate severity.

DIFFERENCE BETWEEN TCA AND SSRI

The group of SSRIs has been compared with that of TCAs in several randomized trials. Geddes et al (2007), who conducted a Cochrane review to examine the relative efficacy of SSRIs compared to any other antidepressants included 98 trials (5044 patients treated with an SSRI or related drug, and 4510 treated with an alternative antidepressant). It found a standardized effect size for SSRIs and related drugs together versus alternative antidepressants of 0.035 (95% CI -0.006 to 0.076). The authors concluded that there are no clinically significant differences in effectiveness between SSRIs and TCAs. In terms of treatment acceptability, Barbui et al (2007), who assessed the comparative tolerability of SSRIs and tricyclic/heterocyclic antidepressant drugs, included 136 studies. The analysis showed that, compared with the tricyclic/heterocyclic group, the SSRIs showed a relatively modest advantage in terms of participants dropping out (odds ratio 1.21, 95% confidence interval 1.12 to 1.30). In the elderly, Mottram et al (2006) analysed 29 studies that assessed the comparative beneficial and harmful effects of antidepressant classes. It found that TCAs compared less favourably with SSRIs in terms of numbers of patients withdrawn irrespective of reason (RR 1.24, CI 1.04, 1.47) and number withdrawn due to side effects (RR: 1.30, CI 1.02, 1.64).

USE DURING PREGNANCY AND LACTATION

NICE (2007) has recently provided guidance on the use of antidepressants during pregnancy and lactation.

According to NICE:
(a) The risks of taking TCAs during pregnancy and when breastfeeding are better established than those of newer drugs, although the issues of tolerability and risk in overdose remain.
(b) TCAs, such as amitriptyline, imipramine and nortriptyline, have lower known risks during pregnancy than other antidepressants.

(c) Fluoxetine is the SSRI with the lowest known risk during pregnancy.
(d) Most TCAs have a higher fatal toxicity index than SSRIs.
(e) SSRIs taken after 20 weeks' gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate.
(f) Paroxetine taken in the first trimester may be associated with fetal heart defects.
(g) All antidepressants carry the risk of withdrawal or toxicity in neonates; in most cases the effects are mild and self-limiting.
(h) Most antidepressants appear in some concentration in breast milk although the effects on the infant are not well understood.

Reference List

American Psychiatric Association (2000). Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry,* 157:1-145.

Arroll B et al (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Annals of Family Medicine*, 3:449-56.

Anderson IM et al (2008). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, 22:343–96.

Barbui C et al (2007). Depression in adults. *Clinical Evidence*, 6:1-28.

Bauer M et al (2002). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. *The World Journal of Biological Psychiatry*, 3:69-86.

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Cipriani A et al (2007). Meta-review on short-term effectiveness and safety of antidepressants for depression: an evidence-based approach to inform clinical practice. *Canadian Journal of Psychiatry*, 52:553-62.

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Turner EH et al (2008). Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *New England Journal of Medicine*, 358:252-60.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base for	In terms of proportion of individuals showing an improvement in depressive symptoms, there is evidence that both TCAs (response analysis: RR 1.26, 1.12 to 1.42, absolute risk difference 12.2%) and SSRIs (lack of response analysis: RR 0.73, 0.69 to

the scoping question	0.78 absolute risk difference 17.9%) were significantly more effective than placebo. In terms of functioning, no meta-analysed evidence was available. In terms of acceptability profile, there is consistent evidence that both TCAs (RR 2.35, 1.69 to 3.46) and SSRIs (RR 2.45, 2.08 to 2.89) significantly increased the risk of withdrawal due to adverse effects.
Summary of the quality of evidence	The quality of evidence was LOW for studies of both TCAs and SSRIs.
Additional evidence (eg related evidence that was not scoped)	Available evidence suggests that the drug–placebo difference increases as a function of initial severity, rising from virtually no difference in mild depression to a relatively small difference for adults with moderate depression and a medium difference in severe depression (see additional evidence that was not graded). In terms of efficacy, there is unlikely a clinically important difference between TCAs and the SSRIs (see additional evidence that was not graded). In terms of tolerability, there is consistent evidence of a very small advantage in favour of the SSRIs (see additional evidence that was not graded).
Balance of benefits versus harms	In studies carried out in individuals with moderate to severe depressive episode, both TCAs and SSRIs are associated with a beneficial effect. In comparison with placebo, both TCAs and SSRIs are associated with an increase in the risk of adverse events leading to treatment discontinuation. Differences between the 2 types of drugs in terms of adherence are so small that they are unlikely clinically important.
Define the values and preferences including any variability and human rights	Clinicians should assess psychosocial stressors (e.g. domestic abuse, unemployment) associated with depression and include appropriate psychosocial interventions in their treatment plan .

issues	
Define the costs and resource use and any other relevant feasibility issues	Diagnosis of depression and its different levels of severity is a challenge. In many low and middle income countries, continuous availability of psychotropics in non-specialized health care is a challenge. Both generic TCAs and many generic SSRIs are associated with low acquisition costs. Amitriptyline (as a representative of the TCAs) and fluoxetine (*not* as a representative of SSRIs) are included in the WHO list of essential medicines for the treatment of depressive disorders.

Final recommendation

Antidepressants should not be considered for the initial treatment of adults with mild depressive episode.
Strength of recommendation: STANDARD

Tricyclic antidepressants (TCA) or fluoxetine should be considered in adults with moderate to severe depressive episode/disorder.
Strength of recommendation: STANDARD

If drug treatment is required in older people, tricyclic antidepressants (TCA) should be avoided if possible.
Strength of recommendation: STANDARD

If drug treatment is required in women with depressive episode who are planning a pregnancy or pregnant or breastfeeding, tricyclic antidepressants (TCA) or fluoxetine should be considered
Strength of recommendation: STANDARD

Limitations

The relative efficacy and tolerability of tricyclic antidepressants in comparison with the selective serotonin reuptake inhibitors, and the relationship between severity of depression and antidepressant effect, were analysed only descriptively, but were not assessed with GRADE.

Update of the literature search – June 2012

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:

NICE Clinical Guidelines. CG90. Depression in adults: The treatment and management of depression in adults. Appendix 19: Clinical evidence forest plots. National Institute for Health and Clinical Excellence, 2010.

Cipriani A, Barbui C, Butler R, Hatcher S, Geddes. Depression in adults: drug and physical treatments. Clinical Evidence 2011;05:1003

Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux LJ, Van Noord M, Mager U, Gaynes BN, Thieda P, Strobelberger M, Lloyd S, Reichenpfader U, Lohr KN. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center, Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC012-EF.

Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Ban Noord M, Mager U, Thieda P, Gaynes BN, Wilkins T, Stroberger M, Lloyd S, Relchenpfader U, Lohr KN. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder. Ann Intern Med. 2011;155:772-785.