Duration of antidepressant treatment

Q 2: How long should treatment with antidepressants continue in adults with depressive episode/disorder?

Background

Short-term therapy with antidepressant medication is considered standard treatment for acute treatment of moderate to severe depressive episode/disorder. However, because of the long-term nature of depressive disorders, with many patients at substantial risk of later recurrence, there is a need to establish how long, in general, such patients should stay on antidepressants if they have responded to the treatment.

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

- **Population:** individuals with depressive episode/disorder
- **Interventions:** antidepressant medications: tricyclic antidepressants (TCA) and related, selective serotonin reuptake inhibitors (SSRI)
- **Comparison:** placebo
- **Outcomes:**
    - treatment effectiveness in terms of reduction symptoms
    - treatment effectiveness in terms of improvement in functioning
    - acceptability profile

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Deshauer D et al (2008). Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. *Canadian Medical Association Journal*, 178:293-1301.

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Geddes JR et al (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*, 361:653-61.

Hansen R et al (2008). Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatric Services*, 59:1121-30.

Kaymaz N et al (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, 69:1423-36.

NICE (2004). Depression: Management of depression in primary and secondary care. National Clinical practice Guideline 23.

WHO (2009). Mental health systems in selected low- and middle-income countries: a WHO-AIMS cross-national analysis. Geneva, World Health Organization.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Barbui C et al (2007). Depression in adults: drug and physical treatments. *British Journal of Medicine Clinical Evidence*, 6:1003.

Zimmerman M, Posternak MA, Ruggero CJ (2007). Impact of study design on the results of continuation studies of antidepressants. *Journal of Clinical Psychopharmacology*, 27:177-81.

Zimmerman M, Thongy T (2007). How often do SSRIs and other new-generation antidepressants lose their effect during continuation treatment? Evidence suggesting the rate of true tachyphylaxis during continuation treatment is low. *Journal of Clinical Psychiatry*, 68:1271-6.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Antidepressants vs placebo	treatment effectiveness in terms of reduction symptoms treatment effectiveness in terms of improvement in functioning acceptability profile	Kaymaz et al (2008) No data Geddes et al (2008)	Kaymaz et al (2008) included TCAs and SSRIs, and is more recent that Geddes et al (2003). Deshauer et al (2008) and Hansen et al (2008) included SSRIs and newer antidepressants only. NICE (2004) mentioned as

				footnote.
2	TCAs and related vs placebo	treatment effectiveness in terms of reduction symptoms treatment effectiveness in terms of improvement in functioning acceptability profile	Kaymaz et al (2008) No data No data	Kaymaz et al (2008) reported the summary estimate for TCAs, Geddes et al (2003) reported a graphical plot with no estimate. NICE (2004) mentioned as footnote.
3	SSRIs vs placebo	treatment effectiveness in terms of reduction symptoms treatment effectiveness in terms of improvement in functioning acceptability profile	Kaymaz et al (2008). Deshauer et al (2008) as footnote No data Hansen et al (2008). Deshauer et al (2008) as footnote	Kaymaz et al (2008) reported the summary estimate for SSRIs, Geddes et al (2003) reported a graphical plot with no estimate. Deshauer et al (2008) included only long-term studies with a "classic" design and is mentioned as foot note. NICE (2004) mentioned as footnote.

Narrative description of the studies that went into the analysis

Kaymaz et al (2008) included 30 studies (4890 patients) performed in both primary and secondary care settings. These studies included 2749 patients who continued with the antidepressant and 2141 patients who were switched to placebo. Fifteen studies were found in which the allocated drug was an SSRIs, with a total of 2984 patients, and 15 studies were found in which the allocated drug was a TCAs, with a total of 1906 patients. A total of 23 studies included data at 3 months, 21 studies at 6 months, 15 studies at 9 months and 7 studies at 12 months.

GRADE Tables

Table 1
Author(s): Barbui C, van Ommeren M.
Date: 2009-05-05
Question: Should Antidepressants vs placebo be used for the long-term treatment of major depression?
Settings:
Bibliography: Geddes JR et al (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*, 361:653-61.

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Kaymaz N et al (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, 69:1423-36.

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		
Loss of response (relapse/recurrence) at three months												
23[1]	randomized trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)[5]	0%	OR 0.25 (0.17 to 0.36)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	CRITICAL
Loss of response (relapse/recurrence) at six months												
21[6]	randomized trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)[5]	0%	OR 0.19 (0.13 to 0.29)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	CRITICAL
Loss of response (relapse/recurrence) at 9 months												
15[7]	randomized trials	serious[2]	serious[8]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)[5]	0%	OR 0.29 (0.21 to 0.4)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	CRITICAL
Loss of response (relapse/recurrence) at 12 months												
7[9]	randomized trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	OR 0.27 (0.12 to 0.6)[10]	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
Loss of response (relapse/recurrence) at endpoint												
30[11]	randomized trials	serious[2]	serious[8]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)	0%	OR 0.30 (0.25 to 0.35)[12,13]	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	IMPORTANT
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
Treatment acceptability (total dropouts)												
32[14]	randomized trials	serious[2]	no serious inconsistency[15]	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	OR 1.30 (1.07 to 1.59)	0 more per 1000 (from 0 more to 0 more)	MODERATE	CRITICAL

[1] From Figure 3 of Kaymaz et al (2008).
[2] Discontinuation studies and classic continuation studies were pooled together.
[3] Although no formal test of heterogeneity was performed, a qualitative analysis of the forest plot revealed some degree of heterogeneity (confidence intervals do not overlap).
[4] The overall treatment estimate and the 95% confidence interval is below 0.5.
[5] Absolute numbers not reported.
[6] From Figure 4 of Kaymaz et al (2008).
[7] From Figure 5 of Kaymaz et al (2008).
[8] The chi-squared test for heterogeneity revealed no inconsistency, although graphical inspection of the forest plot showed that some confidence intervals do not overlap.
[9] From Figure 6 of Kaymaz et al (2008).
[10] A previous systematic review and meta-analysis (Geddes et al 2003) similarly showed that continuing antidepressant therapy reduced the risk o relapse (OR 0.30, 95% CI 0.22 to 0.38; proportion of patients treated with antidepressants who relapsed: 465/2527 [18%]; proportion of patients treated with placebo who relapsed: 1031/2505 [41%]).
[11] From Figure 2 of Kaymaz et al (2008).
[12] NICE 2004, who included 24 studies (1831 patients randomized to antidepressant and 1525 to placebo), found an overall treatment estimate (RR 0.43, 95% CI 0.39 to 0.48) that is consistent with the Kaymaz et al (2008) estimate.
[13] Kaymaz et al(2008) carried out an additional analysis comparing patients with recurrent episodes versus those with a single episode. It found that the pooled OR for relapse was 0.12 (95% CI 0.06 to 0.26) in single episode patients and 0.37 (95% CI 0.31 to 0.44) in recurrent episode patients.
[14] From page 659 of Geddes et al (2003).
[15] Inconsistency not assessed because data from individual studies were not reported.

Table 2

Author(s): Barbui C, van Ommeren M.
Date: 2009-05-05
Question: Should Tricyclic and related antidepressants vs placebo be used for the long-term treatment of major depression?
Settings:
Bibliography: Kaymaz N et al (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, 69:1423-36.

Quality assessment	Summary of findings			Importance
	No of patients	Effect	Quality	

Duration of antidepressant treatment

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Tricyclic and related antidepressants	placebo	Relative (95% CI)	Absolute		
Loss of response (relapse/recurrence)												
15[1]	randomized trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)[5]	0%	OR 0.29 (0.23 to 0.38)[6]	0 fewer per 1000 (from 0 fewer to 0 fewer)	HIGH	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
Treatment acceptability (total dropouts)												
0	no evidence available					none	0/0 (0%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL

[1] From Table 1 of Kaymaz et al (2008).

[2] Discontinuation studies and classic continuation studies were pooled together.

[3] Inconsistency not assessed because data from individual studies were not reported.

[4] The overall treatment estimate and the 95% confidence interval is below 0.5.

[5] Absolute numbers not reported.

[6] NICE 2004, who included 7 studies (189 patients randomized to antidepressant and 174 to placebo), found an overall treatment estimate (RR 0.44, 95% CI 0.35 to 0.57) that is consistent with the Kaymaz et al (2008) estimate.

Table 3

Author(s): Barbui C, van Ommeren M.

Date: 2009-05-05

Question: Should SSRIs vs placebo be used for the long-term treatment of major depression?

Settings:

Bibliography: Hansen R et al (2008). Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatric Services*, 59:1121-30.

Kaymaz N et al (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, 69:1423-36.

Duration of antidepressant treatment

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		
Loss of response (relapse/recurrence)												
15[1]	randomized trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	strong association[4]	0/0 (0%)[5]	0%	OR 0.24 (0.2 to 0.29)[6]	0 fewer per 1000 (from 0 fewer to 0 fewer)	HIGH	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
Treatment acceptability (total dropouts)												
17[7]	randomized trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	RR 0.75 (0.69 to 0.83)[8]	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	CRITICAL

[1] Table 1 from Kaymaz et al (2008).

[2] Discontinuation studies and classic continuation studies were pooled together.

[3] Inconsistency was not assessed because data from individual studies were not reported.

[4] The overall treatment estimate and the 95% confidence interval is below 0.5.

[5] Absolute numbers not reported.

[6] NICE 2004, who included 12 studies (1312 patients randomized to antidepressant and 1030 to placebo), found an overall treatment estimate (RR 0.45, 95% CI 0.39 to 0.51) that is consistent with the Kaymaz et al (2008) estimate. Another systematic review and meta-analysis, which included only "classic" long-term randomized controlled trials comparing SSRIs with placebo (Deshauner et al, 2008), included 8 studies and found that continuing antidepressant therapy significantly reduced the risk of relapse (OR 1.66, 95% CI 1.12 to 2.48).

[7] From page 1125 of Hansen et al (2008).

[8] Another systematic review and meta-analysis, which included only "classic" long-term randomized controlled trials comparing SSRIs with placebo (Deshauner et al, 2008), included 8 studies and found no difference between SSRIs and placebo in terms of overall acceptability (total dropouts).

Reference List

Barbui C et al (2007). Depression in adults: drug and physical treatments. *British Journal of Medicine Clinical Evidence*, 6:1003.

Deshauer D et al (2008). Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. *Canadian Medical Association Journal*, 178:293-1301.

Geddes JR et al (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*, 361:653-61.

Hansen R et al (2008). Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatric Services*, 59:1121-30.

Kaymaz N et al (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, 69:1423-36.

NICE (2004). Depression: Management of depression in primary and secondary care. National Clinical practice Guideline 23.

WHO (2009). Mental health systems in selected low- and middle-income countries: a WHO-AIMS cross-national analysis. Geneva, World Health Organization.

Zimmerman M, Thongy T (2007). How often do SSRIs and other new-generation antidepressants lose their effect during continuation treatment? Evidence suggesting the rate of true tachyphylaxis during continuation treatment is low. *Journal of Clinical Psychiatry*, 68:1271-6.

Zimmerman M, Posternak MA, Ruggero CJ (2007). Impact of study design on the results of continuation studies of antidepressants. *Journal of Clinical Psychopharmacology*, 27:177-81.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	There is consistent evidence that antidepressant continuation treatment significantly decreased the risk of relapse/recurrence at 3, 6, 9 and 12 months of follow up. The overall RR at study endpoint was 0.30 (0.25 to 0.35), suggesting a large protective effect. A similar effect was observed for TCAs(OR 0.29, 0.23 to 0.38) and SSRIs(OR 0.24, 0.20

<table>
<tr><td></td><td colspan="4">to 0.29).

In terms of treatment acceptability, there is evidence that more individuals continuing antidepressant treatment dropped out of the study in comparison with placebo (OR 1.30, 1.07 to 1.59).</td></tr>
<tr><td rowspan="4">Summary of the quality of evidence</td><td>Outcome</td><td>Antidepressants</td><td>TCAs</td><td>SSRIs</td></tr>
<tr><td>Response</td><td>MODERATE</td><td>HIGH</td><td>MODERATE</td></tr>
<tr><td>Functioning</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Acceptability</td><td>MODERATE</td><td>-</td><td>HIGH</td></tr>
<tr><td>Balance of benefits versus harms</td><td colspan="4">Continuation treatment with antidepressants as a group, TCAs and SSRIs, is associated with a large and clinically significant decreased risk of relapse. This beneficial effect has been shown for up to 12 months of treatment. Although individuals with recurrent episodes experienced less protection from antidepressants than individuals with a single episode (see footnote 13 in first GRADE Table 1), the beneficial effect of antidepressants was statistically significant in both subgroups of patients.

Long-term antidepressant use may be associated with additional adverse events, such as diabetes as a consequence of chronic weight gain.</td></tr>
<tr><td>Define the values and preferences including any variability and human rights issues.</td><td colspan="4">Maintenance treatment is sometimes continued for years without the person being re-evaluated and thus, in some instances, without benefit. This is inconsistent with the preference of only medicating where there is need and clinical oversight.</td></tr>
<tr><td>Define the costs and resource use and any other relevant feasibility issues</td><td colspan="4">Adherence is a major challenge

Discontinuities in drug availability (common in LAMIC) may interfere with continuation of treatment.

Costs accumulate with duration of prescription. Cost of daily dose of generic antidepressants varies from region to region throughout the world ranging from 3-9% of minimum wage, (WHO 2009).</td></tr>
<tr><td colspan="5">Final recommendation</td></tr>
</table>

Duration of antidepressant treatment

In adult individuals with depressive episode/disorders who have benefited from initial antidepressant treatment, the antidepressant treatment should not be stopped before 9 -12 months after recovery. Treatment should be regularly monitored, with special attention to treatment adherence. Frequency of contact should be determined by the adherence, severity and by local feasibility issues. Strength of recommendation: STRONG

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following new systematic review was 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.