3. Depressione unipolare

Depressione unipolare con mancata risposta al trattamento con SSRI

Question: Should switching from SSRIs to another antidepressant class vs switching within class (SSRIs) be used for patients with unipolar depression not responding to SSRIs?

Bibliography: Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biological Psychiatry 2008; 63:699-704.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from SSRIs to another antidepressant class	Switching within class (SSRIs)	Relative (95% CI)	Absolute		
Response (follow-up 4-14 weeks; assessed with: HDRS, MADRS, QIDS-C)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	RR 1.05 (0.9 to 1.23)	-	⊕⊕OO LOW	CRITICAL
Remission (follow-up 4-14 weeks; assessed with: HDRS, MADRS, QIDS-C)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	RR 1.29 (1.07 to 1.56)	-	⊕⊕OO LOW	CRITICAL
Dropout due to intolerance (follow-up 4-14 weeks)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	RR 1.23 (0.95 to 1.59)	-	⊕OOO VERY LOW	CRITICAL
Remission -switching to SSRI vs switching to venlafaxine (follow-up 4-14 weeks; assessed with: HDRS, MADRS, QIDS-C)												
3	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	RR 1.31 (1.02 to 1.67)	-	⊕⊕OO LOW	CRITICAL
Dropout due to intolerance -SSRI vs venlafaxine- (follow-up 4-14 weeks)												
3	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	0%	RR 1.03 (0.71 to 1.5)	-	⊕OOO VERY	IMPORTANT

											LOW	
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] Only total sample size provided (n=1496 patients)
[2] 95% CI ranges from no difference to substantial benefit associated with switching within class
[3] No information about studies characteristics such as: allocation concealment, blinding and drop-out rates
[4] 95% CI ranges from substantial benefit associated with switching to another class to substantial benefit associated with switching within class

Question: Should switching within class (SSRI) vs switching to venlafaxine be used for patients with unipolar depression not responding to SSRIs?

Bibliography: Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biological Psychiatry 2008; 63:699-704.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching within class (SSRI)**	**Switching to venlafaxine**	**Relative (95% CI)**	**Absolute**		
Remission												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	RR 1.31 (1.02 to 1.67)	-	⊕⊕OO LOW	CRITICAL
Total dropouts												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	0%	RR 1.03 (0.71 to 1.5)	-	⊕OOO VERY LOW	IMPORTANT

[1] No information about study characteristics such as: allocation concealment, blinding and dropout rates

[2] 95% CI ranges from substantial benefit associated with switching to another class to substantial benefit associated with switching within class

Question: Should switching strategy vs continuation be used for patients with unipolar depression not responding to antidepressant monotherapy?

Bibliography: Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. Acta Psychiatrica Scandinavica 2010;121:174-9.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching strategy	Continuation	Relative (95% CI)	Absolute		
Response (follow-up 4-14 weeks; assessed with: HDRS, MADRS, QIDS-C)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/231 (17.7%)	32/164 (19.5%)	RR 0.99 (0.59 to 1.67)	2 fewer per 1000 (from 80 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
Remission (follow-up 4-14 weeks; assessed with: HDRS, MADRS, QIDS-C)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76/231 (32.9%)	64/164 (39%)	RR 0.85 (0.55 to 1.3)	59 fewer per 1000 (from 176 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
Dropout due to intolerance												
0	no evidence available					none	-	-	-	-		CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] Drop-out rates were not reported

[2] 95% CI ranges from substantial benefit associated with switching strategy to substantial benefit associated with continuation strategy

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Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. Acta Psychiatrica Scandinavica 2010; 121: 174-9.

Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 2011; 71: 43-64.

Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biological Psychiatry 2008; 63: 699-704.

Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. New England Journal of Medicine 2006; 354 : 1231-42.

Depressione unipolare resistente al trattamento

Question: Should lithium (augmentation) vs placebo be used for treatment resistant depression?

Bibliography: Bauer M, Adli M, Baethge C, Berghöfer A, Sasse J, Heinz A, Bschor T. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. Canadian Journal of Psychiatry 2003; 48:440-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium (augmentation)	Placebo	Relative (95% CI)	Absolute		
Response (assessed with: HDRS, MADRS, QIDS-C)												
9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/113 (44.2%)	21/121 (17.4%)	RR 2.50 (1.6 to 3.8)	260 more per 1000 (from 104 more to 486 more)	⊕⊕⊕O MODERATE	CRITICAL
Remission												
0	no evidence available					none	-	-	-	-		CRITICAL
Total dropouts												
0	no evidence available					none	-	-	-	-		CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] Drop-out rates were not reported

Question: Should olanzapine (augmentation) vs placebo be used for treatment resistant depression?

Bibliography: Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166:980-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine (augmentation)	Placebo	Relative (95% CI)	Absolute		
Response (follow-up 8-12 weeks; assessed with: HDRS, MADRS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/586 (38.6%)	122/414 (29.5%)	RR 1.39 (1.05 to 1.84)	115 more per 1000 (from 15 more to 248 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Remission (follow-up 8-12 weeks; assessed with: HDRS, MADRS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/586 (26.3%)	64/414 (15.5%)	RR 1.83 (1.3 to 2.56)	128 more per 1000 (from 46 more to 241 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	143/599 (23.9%)	84/418 (20.1%)	RR 1.23 (0.9 to 1.69)	46 more per 1000 (from 20 fewer to 139 more)	⊕⊕⊕O MODERATE	CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] 95% CI ranges from no effect to substantial harm with olanzapine treatment

Question: Should risperidone (augmentation) vs placebo be used for treatment resistant depression?

Bibliography: Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166:980-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone (augmentation)	Placebo	Relative (95% CI)	Absolute		
Response (follow-up 4-8 weeks; assessed with: HDRS, MADRS)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	89/211 (42.2%)	48/175 (27.4%)	RR 1.83 (1.18 to 2.82)	228 more per 1000 (from 49 more to 499 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Remission (follow-up 4-8 weeks; assessed with: HDRS, MADRS)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/211 (29.4%)	22/175 (12.6%)	RR 2.63 (1.51 to 4.57)	205 more per 1000 (from 64 more to 449 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	35/215 (16.3%)	27/177 (15.3%)	RR 1.08 (0.63 to 1.86)	12 more per 1000 (from 56 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] Visual inspection of forest plots suggests some degree of heterogeneity, I squared= 63%

[2] 95% CI ranges from substantial benefit associated with risperidone to substantial benefit associated with placebo

Question: Should quetiapine (augmentation) vs placebo be used for treatment resistant depression?

Bibliography: Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166:980-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine (augmentation)	Placebo	Relative (95% CI)	Absolute		
Response (follow-up 6-8 weeks; assessed with: HDRS, MADRS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	374/677 (55.2%)	151/352 (42.9%)	RR 1.60 (1.24 to 2.08)	257 more per 1000 (from 103 more to 463 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Remission (follow-up 6-8 weeks; assessed with: HDRS, MADRS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	245/677 (36.2%)	80/352 (22.7%)	RR 1.89 (1.41 to 2.54)	202 more per 1000 (from 93 more to 350 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	144/688 (20.9%)	55/358 (15.4%)	RR 1.59 (1.12 to 2.25)	91 more per 1000 (from 18 more to 192 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

Question: Should aripiprazole (augmentation) vs placebo be used for treatment resistant depression?

Bibliography: Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166:980-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aripiprazole (augmentation)	Placebo	Relative (95% CI)	Absolute		
Response (follow-up mean 6 weeks; assessed with: HDRS, MADRS)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	202/540 (37.4%)	118/525 (22.5%)	RR 2.07 (1.58 to 2.72)	240 more per 1000 (from 130 more to 387 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Remission (assessed with: HDRS, MADRS)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	158/540 (29.3%)	87/525 (16.6%)	RR 2.09 (1.55 to 2.81)	181 more per 1000 (from 91 more to 300 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts (follow-up mean 6 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	81/550 (14.7%)	66/538 (12.3%)	RR 1.24 (0.87 to 1.76)	29 more per 1000 (from 16 fewer to 93 more)	⊕⊕⊕O MODERATE	CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

[1] 95% CI ranges from no effect to substantial harm with aripiprazole augmentation

Question: Should atypical antipsychotics (augmentation) be used for treatment resistant depression?

Bibliography: Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166:980-91.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical antipsychotics (augmentation)	Control	Relative (95% CI)	Absolute		
Response (follow-up 4-12 weeks; assessed with: HDRS, MADRS)												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	891/2014 (44.2%)	439/1466 (29.9%)	RR 1.69 (1.46 to 1.95)	207 more per 1000 (from 138 more to 284 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Remission (follow-up 4-12 weeks; assessed with: HDRS, MADRS)												
16	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	619/2014 (30.7%)	253/1466 (17.3%)	RR 2.0 (1.69 to 2.37)	173 more per 1000 (from 119 more to 236 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts (follow-up 4-12 weeks)												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	403/2052 (19.6%)	232/1491 (15.6%)	RR 1.30 (1.09 to 1.57)	47 more per 1000 (from 14 more to 89 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Side effects												
0	no evidence available					none	-	-	-	-		IMPORTANT

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Bauer M, Adli M, Baethge C, Berghöfer A, Sasse J, Heinz A, Bschor T. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. Canadian Journal of Psychiatry 2003; 48: 440-8.

Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009; 166: 980-91.

Durata del trattamento con antidepressivi nella depressione unipolare

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

Bibliography: Kaymaz N, van Os J, Looner AJM, Nolen WA. 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 2008; 69: 1423-1436. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653-661. NICE. The treatment and management of depression in adults (updated edition). National Clinical Practice Guideline 90. National Institute for Health & Clinical Excellence 2009.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antidepressants**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Loss of response (relapse/recurrence) at three months												
23[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	strong association[4]	-[5]	0%	OR 0.25 (0.17 to 0.36)	-	⊕⊕⊕O MODERATE	CRITICAL
Loss of response (relapse/recurrence) at six months												
21[6]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	strong association[4]	-[5]	0%	OR 0.19 (0.13 to 0.29)	-	⊕⊕⊕O MODERATE	CRITICAL
Loss of response (relapse/recurrence) at 9 months												
15[7]	randomised trials	serious[2]	serious[8]	no serious indirectness	no serious imprecision	strong association[4]	-[5]	0%	OR 0.29 (0.21 to 0.4)	-	⊕⊕⊕O MODERATE	CRITICAL
Loss of response (relapse/recurrence) at 12 months												
7[9]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	-[5]	0%	OR 0.27 (0.12 to 0.6)[10]	-	⊕⊕OO LOW	CRITICAL
Loss of response (relapse/recurrence) at endpoint												
30[11]	randomised trials	serious[2]	serious[8]	no serious indirectness	no serious imprecision	strong association[4]	-	0%	OR 0.30 (0.25 to 0.35)[12,13]	-	⊕⊕⊕O MODERATE	IMPORTANT
Total dropouts												

32[14]	randomised trials	serious[2]	no serious inconsistency[15]	no serious indirectness	no serious imprecision	none	-[5]	0%	OR 1.30 (1.07 to 1.59)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] From Figure 3 of Kaymaz 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 2008
[7] From Figure 5 of Kaymaz 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 2008
[10] A previous systematic review and meta-analysis (Geddes 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 2008
[12] NICE 2004, which 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 2008 estimate. The updated NICE guidance (2009) confirmed this finding.
[13] Kaymaz and colleagues 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 2003
[15] Inconsistency not assessed because data from individual studies were not reported

Question: Should Tricyclic and related antidepressants vs placebo be used for the long-term treatment of major depression?

Bibliography: Kaymaz N, van Os J, Looner AJM, Nolen WA. 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 2008; 69: 1423-1436. NICE. The treatment and management of depression in adults (updated edition). National Clinical Practice Guideline 90. National Institute for Health & Clinical Excellence 2009.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tricyclic and related antidepressants	Placebo	Relative (95% CI)	Absolute		
Loss of response (relapse/recurrence)												
15[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	strong association[4]	-[5]	0%	OR 0.29 (0.23 to 0.38)[6]	-	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts												
0	No evidence available					none	-	0%	-	-		CRITICAL

[1] From Table 1 of Kaymaz 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, which 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 2008 estimate. The updated NICE guidance (2009) confirmed this finding.

Question: Should Selective serotonin reuptake inhibitors vs placebo be used for the long-term treatment of major depression?

Bibliography: Kaymaz N, van Os J, Looner AJM, Nolen WA. 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 2008; 69: 1423-1436. Hansen R, Gaynes B, Thieda P, Gartlehner G, Deveaugh-Geiss A, Krebs E, Lohr K. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatric Services 2008; 59: 1121-1130. Deshauer D, Moher D, Fergusson D, Moher E, Sampson M, Grimshaw J. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. CMAJ 2008; 178: 1293-1301. NICE. The treatment and management of depression in adults (updated edition). National Clinical Practice Guideline 90. National Institute for Health & Clinical Excellence 2009.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Selective serotonin reuptake inhibitors**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Loss of response (relapse/recurrence)												
15[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	strong association[4]	-[5]	0%	OR 0.24 (0.2 to 0.29)[6]	-	⊕⊕⊕⊕ HIGH	CRITICAL
Total dropouts												
17[7]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	-[5]	0%	RR 0.75 (0.69 to 0.83)[8]	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Table 1 from Kaymaz 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, which 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 2008 estimate. The updated NICE guidance (2009) confirmed this finding. Another systematic review and meta-analysis, which included only "classic" long-term randomized controlled trials comparing selective serotonin reuptake inhibitors with placebo (Deshauer 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 2008

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

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Deshauer D, Moher D, Fergusson D, Moher E, Sampson M, Grimshaw J. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. CMAJ 2008; 178: 1293-1301.

Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653-661.

Hansen R, Gaynes B, Thieda P, Gartlehner G, Deveaugh-Geiss A, Krebs E, Lohr K. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatric Services 2008; 59: 1121-1130.

Kaymaz N, van Os J, Looner AJM, Nolen WA. 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 2008; 69: 1423-1436.

NICE. The treatment and management of depression in adults (updated edition). National Clinical Practice Guideline 90. National Institute for Health & Clinical Excellence 2009.