2. Depressione bipolare

Question: Should antidepressants vs placebo be used for bipolar depression?

Bibliography: Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. Journal of Clinical Psychiatry 2011; 72: 156-67.

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**		
Clinical response (follow-up 6-26 weeks; assessed with: HDRS, MADRS)												
5	randomised trials	no serious risk of bias	very serious[1]	serious[2]	serious[3]	none	142/341 (41.6%)	217/565 (38.4%)	RR 1.18 (0.99 to 1.4)[4,5]	69 more per 1000 (from 4 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up 10-26 weeks; assessed with: HDRS, MADRS)												
4	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[7]	none	106/334 (31.7%)	171/573 (29.8%)	RR 1.20 (0.98 to 1.47)	60 more per 1000 (from 6 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Total dropout												
0	No evidence available					none	-	-	-	-		CRITICAL
Hypomanic or manic switch (follow-up 6-26 weeks; assessed with: YMRS)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	32/416 (7.7%)	44/610 (7.2%)	RR 0.97 (0.62 to 1.53)[9]	2 fewer per 1000 (from 27 fewer to 38 more)	⊕⊕OO LOW	CRITICAL

[1] Visual inspection of forest plot suggests some degree of heterogeneity; I squared = 68.8 %
[2] One study with a large sample size compared the combination fluoxetine+olanzapine vs placebo
[3] 95% CI ranges from no effect to substantial benefit with antidepressants
[4] There is one additional randomized study comparing paroxetine with placebo that failed to detect a significant beneficial effect of paroxetine (WMD -1.16, 95% CI -5.00 to 2.68)
[5] There is one additional systematic review which included the old antidepressants imipramine and phenelzine. It found a statistically significant advantage for antidepressants over placebo (RR 1.43, 95% CI 1.11 to 1.84)
[6] Visual inspection of forest plot suggests some inconsistency; I squared = 50.8 %
[7] 95% CI ranges from no effect to substantial benefit with antidepressants
[8] 95% CI ranges from substantial benefit with antidepressants to substantial benefit with placebo
[9] There is one additional systematic review which included studies carried out not only in bipolar depression, but also in unipolar depression. It found a statistically significant increased risk of hypomanic or manic switch associeted with antidepressants; this risk is mainly explained by an increased risk with TCA (RR 1.92, 1.13 to 3.30), but not with SSRI (RR 1.70, 0.87 to 3.32)

Question: Should quetiapine 600 vs placebo be used for bipolar depression?

Bibliography: De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. Journal of Psychopharmacology 2012; 26: 603-17.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine 600	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 8 weeks; assessed with: MADRS)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	526/816 (64.5%)	269/580 (46.4%)	RR 1.33 (1.19 to 1.47)	153 more per 1000 (from 88 more to 218 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (follow-up 8 weeks; assessed with: MADRS)												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	513/816 (62.9%)	246/580 (42.4%)	RR 1.39 (1.19 to 1.63)	165 more per 1000 (from 81 more to 267 more)	⊕⊕⊕O MODERATE	CRITICAL
Total dropout (follow-up 8 weeks; assessed with: global dropout)												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	312/864 (36.1%)	219/608 (36%)	RR 1.05 (0.86 to 1.29)	18 more per 1000 (from 50 fewer to 104 more)	⊕⊕⊕O MODERATE	CRITICAL
Hypomanic or manic switch (assessed with: YMRS)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/863 (3%)	30/606 (5%)	RR 0.57 (0.33 to 0.98)	21 fewer per 1000 (from 1 fewer to 33 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Visual inspection of forest plot suggested some degree of heterogeneity

Question: Should quetiapine 300 vs placebo be used for bipolar depression?

Bibliography: De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. Journal of Psychopharmacology 2012; 26: 603-17.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine 300	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 8 weeks; assessed with: MADRS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	607/944 (64.3%)	328/717 (45.7%)	RR 1.36 (1.23 to 1.49)	165 more per 1000 (from 105 more to 224 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission (follow-up 8 weeks; assessed with: MADRS)												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	569/944 (60.3%)	300/717 (41.8%)	RR 1.36 (1.18 to 1.57)	151 more per 1000 (from 75 more to 238 more)	⊕⊕⊕O MODERATE	CRITICAL
Total dropout (follow-up 8 weeks; assessed with: global dropout)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	333/1002 (33.2%)	261/746 (35%)	RR 0.98 (0.82 to 1.16)	7 fewer per 1000 (from 63 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Hypomanic or manic switch (follow-up 8 weeks; assessed with: YMRS)												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	32/997 (3.2%)	39/746 (5.2%)	RR 0.62 (0.26 to 1.47)	20 fewer per 1000 (from 39 fewer to 25 more)	⊕⊕OO LOW	CRITICAL

[1] Visual inspection of forest plot suggested some degree of heterogeneity

[2] 95%CI ranges from substantial benefit with quetiapine 300 to substantial benefit with placebo

Question: Should olanzapine vs placebo be used for bipolar depression?

Bibliography: De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. Journal of Psychopharmacology 2012; 26: 603-17.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 8 weeks; assessed with: MADRS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/351 (39%)	108/355 (30.4%)	RR 1.28 (1.05 to 1.57)	85 more per 1000 (from 15 more to 173 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (follow-up 8 weeks; assessed with: MADRS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115/351 (32.8%)	87/355 (24.5%)	RR 1.34 (1.06 to 1.69)	83 more per 1000 (from 15 more to 169 more)	⊕⊕OO LOW	CRITICAL
Total dropout (follow-up 8 weeks; assessed with: global dropout)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	191/370 (51.6%)	232/377 (61.5%)	RR 0.84 (0.74 to 0.95)	98 fewer per 1000 (from 31 fewer to 160 fewer)	⊕⊕OO LOW	CRITICAL
Hypomanic or manic switch (follow-up 8 weeks; assessed with: YMRS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/335 (5.7%)	23/345 (6.7%)	RR 0.85 (0.47 to 1.53)	10 fewer per 1000 (from 35 fewer to 35 more)	⊕OOO VERY LOW	CRITICAL

[1] Dropout rate is higher than 50%

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

Question: Should aripiprazole vs placebo be used for bipolar depression?

Bibliography: De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. Journal of Psychopharmacology 2012; 26: 603-17.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aripiprazole	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 8 weeks; assessed with: MADRS)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	148/337 (43.9%)	147/353 (41.6%)	RR 1.05 (0.88 to 1.25)	21 more per 1000 (from 50 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (follow-up 8 weeks; assessed with: MADRS)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94/337 (27.9%)	100/353 (28.3%)	RR 0.99 (0.78 to 1.25)	3 fewer per 1000 (from 62 fewer to 71 more)	⊕⊕OO LOW	CRITICAL
Total dropout (follow-up 8 weeks; assessed with: global dropout)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	164/373 (44%)	122/376 (32.4%)	RR 1.35 (1.13 to 1.63)	114 more per 1000 (from 42 more to 204 more)	⊕⊕⊕O MODERATE	CRITICAL
Hypomanic or manic switch (follow-up 8 weeks; assessed with: YMRS)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/360 (3.1%)	6/367 (1.6%)	RR 1.88 (0.7 to 5.03)	14 more per 1000 (from 5 fewer to 66 more)	⊕⊕OO LOW	CRITICAL

[1] Dropout rate higher than 40% and not similarly distributed between treatment arms

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

Question: Should carbamazepine vs placebo be used for bipolar depression?

Bibliography: Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. British Journal of Psychiatry 2010; 196: 266-273.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbamazepine	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 3-26 weeks; assessed with: MADRS, HRSD)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/47 (63.8%)	8/23 (34.8%)	RR 1.84 (1.01 to 3.34)	292 more per 1000 (from 3 more to 814 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (assessed with: MADRS, HRSD)												
0	No evidence available					none	-	-	-	-		CRITICAL
Total dropout												
0	No evidence available					none	-	-	-	-		CRITICAL
Hypomanic or manic switch												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Dropout rate is substially high

[2] 95% CI ranges from no effect to substantial benefit with carbamazepine; number of patients less than 100

Question: Should lamotrigine vs placebo be used for bipolar depression?

Bibliography: Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. British Journal of Psychiatry 2010; 196: 266-273.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 3-26 weeks; assessed with: MADRS, HRSD)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	288/587 (49.1%)	211/507 (41.6%)	RR 1.17 (1.01 to 1.36)	71 more per 1000 (from 4 more to 150 more)	⊕⊕OO LOW	CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Total dropout												
0	No evidence available					none	-	-	-	-		CRITICAL
Hypomanic or manic switch												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Dropout rate is substantially high

[2] 95% CI ranges from no effect to substantial benefit with lamotrigine

Question: Should valproic acid vs placebo be used for bipolar depression?

Bibliography: Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. British Journal of Psychiatry 2010; 196: 266-273.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproic acid	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 3-26 weeks; assessed with: MADRS, HRSD)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/9 (33.3%)	1/7 (14.3%)	RR 2.33 (0.3 to 17.88)	190 more per 1000 (from 100 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical remission (follow-up 3-26 weeks; assessed with: MADRS, HRSD)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/13 (46.2%)	3/12 (25%)	RR 1.85 (0.59 to 5.79)	213 more per 1000 (from 103 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Total dropout												
0	No evidence available					none	-	-	-	-		CRITICAL
Hypomanic or manic switch												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Dropout rate is substantially high

[2] 95% CI ranges from substantial benefit with valproic acid to substantial benefit with placebo; number of patients less than 50

Question: Should lithium vs placebo be used for bipolar depression?

Bibliography: Vieta E, Locklear J, Günther O, Ekman M, Miltenburger C, Chatterton ML, Aström M, Paulsson B. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. Journal of Clinical Psychopharmacology 2010; 30: 579-590.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Placebo	Relative (95% CI)	Absolute		
Clinical response (follow-up 8 weeks; assessed with: MADRS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	85/136 (62.5%)	72/129 (55.8%)	RR 1.12 (0.92 to 1.37)	67 more per 1000 (from 45 fewer to 207 more)	⊕⊕OO LOW	CRITICAL
Clinical remission (follow-up 8 weeks; assessed with: MADRS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	85/136 (62.5%)	71/129 (55%)	RR 1.14 (0.93 to 1.39)	77 more per 1000 (from 39 fewer to 215 more)	⊕⊕OO LOW	CRITICAL
Total dropout (follow-up 8 weeks; assessed with: all cause treatment discontinuation)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/136 (25%)	37/133 (27.8%)	RR 0.90 (0.6 to 1.34)	28 fewer per 1000 (from 111 fewer to 95 more)	⊕⊕OO LOW	CRITICAL
Hypomanic or manic switch												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Allocation concealment is unclear

[2] 95% CI ranges from no effect to substantial benefit with lithium; only one study included in the analysis

Bibliografia

De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. Journal of Psychopharmacology 2012; 26: 603-17.

Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. Journal of Clinical Psychiatry 2011; 72: 156-67.

Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. British Journal of Psychiatry 2010; 196: 266-273.

Vieta E, Locklear J, Günther O, Ekman M, Miltenburger C, Chatterton ML, Aström M, Paulsson B. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. Journal of Clinical Psychopharmacology 2010; 30: 579-590.