Q7: In individuals with bipolar mania, are a) antipsychotics, b) mood stabilizers (lithium carbonate, valproate, and carbamazepine) effective and safe?

Background

Mood stabilizers are the primary treatment for the manic phase of bipolar disorder. Of these, lithium carbonate, valproic acid, and carbamazepine are the most frequently prescribed worldwide and they are included in the World Health Organization List of Essential Medicines. Antipsychotic drugs are also used for the pharmacological treatment of bipolar mania. After the earliest antipsychotics, chlorpromazine and haloperidol, a wide range of antipsychotics have been developed and they are used as antimanic agents. Haloperidol and chlorpromazine are included in the World Health Organization List of Essential Medicines. A clear recommendation on mood stabilizers and antipsychotics use for bipolar mania is critical in clinical practice.

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

Population:	adults with bipolar mania
Interventions:	a) mood stabilizers; b) antipsychotics drugs
Comparisons:	placebo
Outcomes:	symptoms severity
	disability and functioning
	adverse effects of treatment
	quality of life
	mortality
	treatment adherence

users' and families' satisfaction with care

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Cipriani A, Rendell JM, Geddes J (2006). Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews* 2006(3):CD004362.

Macritchie K et al (2003). Valproate for acute mood episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*, (1):CD004052.

Smith LA et al (2007). Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disorders,* 9:551-60.

Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomizedcontrolled trials. *Archives of General Psychiatry*, 64:442-55.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Haloperidol/ Placebo	Symptoms severity	Cipriani et al, 2006	
		Disability and functioning	Cipriani et al, 2006	
		Adverse effects of treatment	Cipriani et al, 2006	
		Quality of life	No evidence available	
		Mortality	No evidence available	
		Treatment adherence	Cipriani et al, 2006	Total dropouts
		Users' and families' satisfaction with care	No evidence available	

II	Chlorpromazine / placebo	Symptoms severity Disability and functioning Adverse effects of treatment Quality of life Mortality Treatment adherence Users' and families' satisfaction with care	No evidence available No evidence available No evidence available No evidence available No evidence available No evidence available No evidence available No evidence available	
	Second generation antipsychotic drugs vs placebo	Symptoms severity Disability and functioning Adverse effects Treatment adherence User's and family's satisfaction	Scherk et al, 2007 No evidence Scherk et al, 2007 Scherk et al, 2007 (dropout rates) No evidence	
III	Lithium carbonate / placebo	Symptoms severity Disability and functioning Adverse effects of treatment Quality of life Mortality Treatment adherence Users' and families' satisfaction with care	Smith et al, 2007 No evidence available Smith et al, 2007 No evidence available No evidence available Smith et al, 2007 No evidence available	

IV	Valproic acid / placebo	Symptoms severity Disability and functioning Adverse effects of treatment Quality of life Mortality Treatment adherence Users' and families' satisfaction with care	Macritchie et al, 2003 Macritchie et al, 2003 Macritchie et al, 2003 No evidence available No evidence available No evidence available No evidence available	
V	Carbamazepine / placebo	Symptoms severity Disability and functioning Adverse effects of treatment Quality of life Mortality Treatment adherence Users' and families' satisfaction with care	Smith et al, 2007 No evidence available Smith et al, 2007 No evidence available No evidence available Smith et al, 2007 No evidence available	

Narrative description of the studies that went into the analysis

Cipriani et al, (2006) included 2 controlled trials randomizing 484 patients with acute mania to haloperidol or placebo. All participants had a diagnosis of DSM IV bipolar disorder and they were hospitalized for a manic episode. Inclusion criteria included a minimum score of 20 on the Young Mania Rating (YMRS). Smulevich et al, (2005) randomized 144 patients to 2-12 mg/day of haloperidol and 140 to placebo for 3 weeks. The mean (SD) modal doses were 8.0 (3.6) mg/day of haloperidol. Brecher & Huizar (2003) randomized 99 patients to 2-8 mg/day of haloperidol and 101 to placebo for 12 weeks.

Smith et al, (2007) included 2 controlled trials randomizing 305 patients with acute mania to lithium or placebo. All participants were hospitalized with a diagnosis of RDC criteria for manic disorder (SADS) or DSM-IV bipolar I, manic episode with or without psychotic symptoms. Bowden et al. (1994) randomized 36 patients to lithium (titrated from 900 mg/day to maximum target of 1.5 mmol/L) and 74 to placebo for 3 weeks. Bowden et al, (2005) randomized 98 patients to lithium (serum level 0.6–1.4 mEq/L) and 117 to placebo for 12 weeks.

Macritchie et al, (2003) included 3 controlled trials randomizing 315 patients with acute mania to valproic acid or placebo. All participants were hospitalized with a diagnosis of bipolar disorder, manic episode, according to DSM-IIIR, ICD-10, or RDC diagnostic criteria. The duration of all trials was 21 days, 2 were multicentre trials. Bowden et al, (1994) randomized 69 patients to valproic acid (increased from an initial 750mg/day to a dose allowing a maximum target level of 150 micrograms per ml) and 74 to placebo. Muller-Oerlinghausen et al, (2000) randomized 69 patients to valproic acid (fixed dose of 20mg/kg) and 67 to placebo. Pope et al, (1991) randomized 17 patients to valproic acid (adjusted to achieve serum levels of 50-100mg/litre) and 19 to placebo.

Smith et al, (2007) included 2 controlled trials randomizing 443 patients with acute mania to carbamazepine or placebo. All participants were hospitalized with a diagnosis of DSM-IV bipolar I, manic or mixed episode. The duration was 21 days. Weisler et al, (2004) randomized 101 patients to carbamazepine 200–1600 mg/day (mean serum level 8.9 lg/mL) and 103 to placebo. Weisler et al, (2005) randomized 122 patients to carbamazepine 200–1600 mg/day and 117 to placebo.

Scherk et al, (2007) included 12 studies that compared second-generation antipsychotic drugs with placebo. The baseline mania scores were similar in all the trials except 2 studies that included more or less severely manic patients. The duration of most studies was 3 weeks; however, 3 studies investigated a 4-week period and a 6-week period. Four trials investigated a 12-week period but also evaluated treatment outcomes after 3 weeks. The 3-week data were used for the analysis. Four trials investigated purely manic patients, 4 studies did not report the types of manic episodes, and all the other trials examined patients with purely manic symptoms (45%-97%) and patients with mixed symptoms (3%-55%). Each of these trials was matched for episode type. Seven studies excluded patients with rapid cycling.

GRADE Tables

Table 1

Author(s): Andrea Cipriani, Jennifer M Rendell, John Geddes and Lorenzo Tarsitani (quality)
Date: 2009-07-17
Question: Should HALOPERIDOL vs PLACEBO be used for Acute Mania?
Settings: Hospital
Bibliography: Cipriani A, Rendell JM, Geddes J (2006). Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews* 2006(3):CD004362.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HALOPERIDOL	PLACEBO	Relative (95% CI)	Absolute		
Symptoms severity - YMRS - Mean change (LOCF) - at Week 1 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	reporting bias[3]	143	136	-	2 lower (4.01 lower to 0.01 higher)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - YMRS - Mean change (LOCF) - at Week 2 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	136	127	-	MD 3.6 lower (5.8 to 1.4 lower)	⊕⊕OO LOW	CRITICAL
Symptoms severity - YMRS - Mean change (LOCF) - at Week 3 - As monotherapy (Better indicated by lower values)												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	225	219	-	MD 5.36 lower (7.15 to 3.57 lower)	⊕⊕OO LOW	CRITICAL
Symptoms severity - YMRS - Mean change (LOCF) - at Week 3 endpoint - As monotherapy (Better indicated by lower values)												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243	239	-	MD 5.85 lower (7.69 to 4 lower)	⊕⊕OO LOW	CRITICAL
Symptoms severity - YMRS - Mean change - WITH psychotic symptoms at baseline - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[5]	reporting bias[3]	49	40	-	MD 7.3 lower (12.44 to 2.16 lower)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - YMRS - Mean change - WITHOUT psychotic symptoms at baseline - As monotherapy (Better indicated by lower values)												
1	randomised	no serious	no serious	serious[1]	serious[6]	reporting bias[3]	95	98	-	MD 3.7 lower (6.34 to 1.06	⊕OOO VERY	CRITICAL

	trials	limitations	inconsistency							lower)	LOW	
Symptoms severity - MADRS - at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[7]	reporting bias[3]	126	118	-	MD 0.1 lower (0.99 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - MADRS - endpoint data at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[8]	reporting bias[3]	144	138	-	MD 0.6 lower (1.54 lower to 0.34 higher)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - CGI - at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[9]	reporting bias[3]	128	119	-	MD 0.3 lower (0.55 to 0.05 lower)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - Change in CGI - endpoint data at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[8]	reporting bias[3]	144	138	-	MD 0.4 lower (0.67 to 0.13 lower)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - BPRS - at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[7]	reporting bias[3]	126	117	-	MD 0.2 lower (1.89 lower to 1.49 higher)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - BPRS - endpoint data at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[8]	reporting bias[3]	144	137	-	MD 1.3 lower (3.09 lower to 0.49 higher)	⊕OOO VERY LOW	CRITICAL

Symptoms severity - Failure to respond (YMRS) - As monotherapy												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	76/144 (52.8%)	94/140 (67.1%) 67.1%	RR 0.79 (0.65 to 0.95)	141 fewer per 1000 (from 34 fewer to 235 fewer) 141 fewer per 1000 (from 34 fewer to 235 fewer)	⊕⊕OO LOW	CRITICAL
Symptoms severity - Failure to complete treatment - due to lack of efficacy - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[1]	10/99 (10.1%)	29/101 (28.7%) 28.7%	RR 0.35 (0.18 to 0.68)	187 fewer per 1000 (from 92 fewer to 235 fewer) 187 fewer per 1000 (from 92 fewer to 235 fewer)	⊕OOO VERY LOW	CRITICAL
Disability and functioning - GAS - at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	123	116	-	MD 5.3 higher (1.79 to 8.81 higher)	⊕⊕OO LOW	CRITICAL
Disability and functioning - GAS - endpoint data at Week 3 - As monotherapy (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	131	130	-	MD 6.4 higher (2.73 to 10.07 higher)	⊕⊕OO LOW	CRITICAL
Adverse effects - Failure to complete treatment - due to side effects - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[11]	reporting bias[1]	10/99 (10.1%)	6/101 (5.9%) 5.9%	RR 1.7 (0.64 to 4.5)	42 more per 1000 (from 21 fewer to 208 more) 41 more per 1000 (from 21 fewer to 206 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Agitation - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[12]	reporting bias[3]	8/99 (8.1%)	9/101 (8.9%) 8.9%	RR 0.91 (0.36 to 2.26)	8 fewer per 1000 (from 57 fewer to 112 more) 8 fewer per 1000 (from 57 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL

Adverse effects - Akathisia - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	33/99 (33.3%)	6/101 (5.9%) 5.9%	RR 5.61 (2.46 to 12.8)	274 more per 1000 (from 87 more to 701 more) 272 more per 1000 (from 86 more to 696 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Depressive episode (MADRS equal to or more than 18) - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[12]	reporting bias[3]	8/99 (8.1%)	9/101 (8.9%) 8.9%	RR 0.91 (0.36 to 2.26)	8 fewer per 1000 (from 57 fewer to 112 more) 8 fewer per 1000 (from 57 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dry mouth - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[12]	reporting bias[3]	4/99 (4%)	4/101 (4%) 4%	RR 1.02 (0.26 to 3.97)	1 more per 1000 (from 29 fewer to 118 more) 1 more per 1000 (from 30 fewer to 119 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Extrapyramidal disorder - As monotherapy												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/243 (48.1%)	28/241 (11.6%) 12.2%	RR 4.17 (2.88 to 6.03)	368 more per 1000 (from 218 more to 584 more) 387 more per 1000 (from 229 more to 614 more)	⊕⊕OO LOW	CRITICAL
Adverse effects - Headache - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[11]	reporting bias[3]	8/99 (8.1%)	4/101 (4%) 4%	RR 2.04 (0.63 to 6.56)	41 more per 1000 (from 15 fewer to 220 more) 42 more per 1000 (from 15 fewer to 222 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Hyperkinesia - As monotherapy												
1	randomised	no serious	no serious	serious[1]	no serious	reporting bias[3]	22/144 (15.3%)	4/140	RR 5.35 (1.89 to	124 more per 1000 (from 25	⊕⊕OO	CRITICAL

	trials	limitations	inconsistency		imprecision			(2.9%) 2.9%	15.12)	more to 403 more) 126 more per 1000 (from 26 more to 409 more)	LOW	
Adverse effects - Hypertonia - As monotherapy												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	13/144 (9%)	0/140 (0%) 0%	RR 26.26 (1.58 to 437.47)	0 more per 1000 (from 0 more to 0 more) 0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	CRITICAL
Adverse effects - Insomnia - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[13]	reporting bias[3]	14/99 (14.1%)	20/101 (19.8%) 19.8%	RR 0.71 (0.38 to 1.33)	57 fewer per 1000 (from 123 fewer to 65 more) 57 fewer per 1000 (from 123 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Postural hypotension - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	serious[12]	reporting bias[3]	2/99 (2%)	1/101 (1%) 1%	RR 2.04 (0.19 to 22.14)	10 more per 1000 (from 8 fewer to 209 more) 10 more per 1000 (from 8 fewer to 211 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Somnolence - As monotherapy												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[11]	none	14/243 (5.8%)	7/241 (2.9%) 3.2%	RR 2.01 (0.83 to 4.87)	29 more per 1000 (from 5 fewer to 112 more) 32 more per 1000 (from 5 fewer to 124 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Tremor - As monotherapy												
2	randomised trials	very serious[4]	serious[14]	no serious indirectness	no serious imprecision	none	46/243 (18.9%)	14/241 (5.8%) 5.8%	RR 3.28 (1.86 to 5.79)	132 more per 1000 (from 50 more to 278 more) 132 more per 1000 (from 50	⊕OOO VERY LOW	CRITICAL

										more to 278 more)		
Adverse effects - Weight gain mean change (Kg) - As monotherapy (Better indicated by lower values)												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[15]	none	198	182	-	MD 0.38 higher (0.17 lower to 0.92 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Use of rescue medication (for sedation) - As monotherapy												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	60/144 (41.7%)	42/140 (30%) 30%	RR 1.39 (1.01 to 1.91)	117 more per 1000 (from 3 more to 273 more) 117 more per 1000 (from 3 more to 273 more)	⊕⊕OO LOW	CRITICAL
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment adherence - Failure to complete treatment - total dropouts - according to text - As monotherapy												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/243 (24.3%)	80/241 (33.2%) 36.7%	RR 0.74 (0.57 to 0.96)	86 fewer per 1000 (from 13 fewer to 143 fewer) 95 fewer per 1000 (from 15 fewer to 158 fewer)	⊕⊕OO LOW	IMPORTANT
Treatment adherence - Failure to complete treatment - total dropouts - according to figure - As monotherapy												
2	randomised	very serious[4]	no serious	no serious	no serious	none	59/243 (24.3%)	80/241	RR 0.74 (0.57 to	86 fewer per 1000 (from 13	⊕⊕OO	IMPORTANT

	trials		inconsistency	indirectness	imprecision			(33.2%) 36.7%	0.96)	fewer to 143 fewer) 95 fewer per 1000 (from 15 fewer to 158 fewer)	LOW	
Treatment adherence - Failure to complete treatment - due to other reasons - As monotherapy												
1	randomised trials	very serious[10]	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[3]	25/99 (25.3%)	24/101 (23.8%) 23.8%	RR 1.06 (0.65 to 1.73)	14 more per 1000 (from 83 fewer to 173 more) 14 more per 1000 (from 83 fewer to 174 more)	⊕OOO VERY LOW	IMPORTANT
Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] Only one study contributed to the analisys.
[2] The 95% confidence interval includes both no effect and appreciable benefit.
[3] Only one study reported this outcome measure.
[4] One of two studies (Brecher & Huizar, 2003) has a dropout rate of 52%.
[5] One study; sample size is 89.
[6] Sample size is 193.
[7] CI crosses 0 and 0.5 in both directions.
[8] CI crosses 0 and -0.5.
[9] CI crosses 0 and -0.5.
[10] Only one study (Brecher & Huizar, 2003) with a dropout rate of 52%.
[11] CI crosses 1 and a risk of 2.
[12] CI crosses 1 and a risk of both 0.5 and 2.
[13] CI crosses 1 and a risk of 0.5.
[14] I-squared test = 62.4%
[15] CI crosses 0 and 0.5.

Table 2
Author(s): Corrado Barbui and Andrea Cipriani
Date: 2009-09-08
Question: Should aripiprazole vs placebo be used for acute mania?
Settings: Hospital

Bibliography: Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomizedcontrolled trials. *Archives of General Psychiatry*, 64:442-55.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aripiprazole	placebo	Relative (95% CI)	Absolute		
symptom severity (Young Mania Rating Scale) (Better indicated by lower values)												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	0[4]	0[4]	-	SMD 0.25 lower (0.5 to 0.01 lower)	⊕⊕OO LOW	CRITICAL
response rate												
2[5]	randomised trials	serious[2]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	0/0 (0%)[4,6]	0%	RR 1.82 (1.43 to 2.32)[7]	0 more per 1000 (from 0 more to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
treatment acceptability (total dropouts)												
2[5]	randomised trials	serious[2]	no serious inconsistency[4]	no serious indirectness	serious[8]	none	0/0 (0%)[4,6]	0%	RR 0.82 (0.65 to 1.04)[9]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (extrapyramidal symptoms)												
1[10]	randomised trials	serious[2]	no serious inconsistency	serious[11]	no serious imprecision	none	0/0 (0%)[4]	0%	RR 4.95 (2.38 to 10.28)[9]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (sedation)												
1[12]	randomised trials	serious[2]	no serious inconsistency	serious[11]	no serious imprecision	none	0/0 (0%)[4]	0%	RR 1.75 (1.19 to 2.57)[9]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT

adverse effects (weight gain) (Better indicated by lower values)											
2[5]	randomised trials	serious[2]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	0[4]	0[4,13]	-	SMD 0.16 higher (0.02 lower to 0.33 higher)	⊕⊕⊕O MODERATE	IMPORTANT
disability and functioning (Better indicated by lower values)											
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)											
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Figure 1 of Scherk et al, 2007.
[2] Loss to follow-up exceeds 30%.
[3] Inspection of the forest plot reveals only a partial overlap of confidence intervals.
[4] Not reported.
[5] From Table 2 of Scherk et al, 2007.
[6] The total number of included patients was 534.
[7] RR > 1 favors second-generation antipsychotic drugs.
[8] Confidence interval ranges from appreciable benefit to no difference.
[9] RR > 1 favors placebo.
[10] From Figure 3 of Scherk et al, 2007.
[11] Only one study contributed to the analysis.
[12] From Figure 2 of Scherk et al, 2007.
[13] The total number of included patients was 514.

Table 3
Author(s): Corrado Barbui and Andrea Cipriani
Date: 2009-09-08
Question: Should olanzapine vs placebo be used for acute mania?
Settings: Hospital
Bibliography: : Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomizedcontrolled trials. *Archives of General Psychiatry*, 64:442-55.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	olanzapine	placebo	Relative (95% CI)	Absolute		
symptom severity (Young Mania Rating Scale) (Better indicated by lower values)												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	SMD 0.47 lower (0.72 to 0.22 lower)	⊕⊕OO LOW	CRITICAL
response rate												
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 1.76 (1.31 to 2.36)[6]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	CRITICAL
treatment acceptability (total dropouts)												
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 0.62 (0.48 to 0.8)[7]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	IMPORTANT
adverse effects (extrapyramidal symptoms)												
0	no evidence available					none	0/0 (0%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
adverse effects (sedation)												
2[8]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[3]	0%	RR 2.76 (1.16 to 6.58)[7]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (weight gain) (Better indicated by lower values)												
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0[3,9]	0[3]	-	SMD 0.75 higher (0.49 to 1.01 higher)	⊕⊕OO LOW	IMPORTANT

disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Figure 1 of Scherk et al, 2007.
[2] Loss to follow-up exceeds 30% and dropouts are not equally distributed between treatment arms.
[3] Not repoted.
[4] From Table 2 of Scherk et al, 2007.
[5] The total number of included patients was 254.
[6] RR > 1 favors second-generation antipsychotic drugs.
[7] RR > 1 favors placebo.
[8] From Figure 2 of Scherk et al, 2007.
[9] The total number of included patients was 246.

Table 4

Author(s): Corrado Barbui and Andrea Cipriani
Date: 2009-09-08
Question: Should quetiapine vs placebo be used for acute mania?
Settings: Hospital
Bibliography: Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of General Psychiatry,* 64:442-55.

Quality assessment							**Summary of findings**					**Importance**
							No of patients		**Effect**		**Quality**	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**quetiapine**	**placebo**	**Relative (95% CI)**	**Absolute**		
symptom severity (Young Mania Rating Scale) (Better indicated by lower values)												

2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	SMD 0.40 lower (0.6 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
response rate												
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 1.46 (0.81 to 2.64)[6]	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
treatment acceptability (total dropouts)												
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	serious[7]	none	0/0 (0%)[3,5]	0%	RR 0.54 (0.18 to 1.59)[8]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
adverse effects (extrapyramidal symptoms)												
2[9]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	0/0 (0%)[3]	0%	RR 1.25 (0.66 to 2.37)[8]	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
adverse effects (sedation)												
2[10]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[3]	0%	RR 3.82 (1.57 to 9.29)[8]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (weight gain) (Better indicated by lower values)												
1[4]	randomised trials	serious[2]	no serious inconsistency[3]	serious[11]	no serious imprecision	none	0[3]	0[3,12]	-	SMD 0.44 higher (0.17 to 0.72 higher)	⊕⊕OO LOW	IMPORTANT
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												

0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Figure 1 of Scherk et al, 2007.
[2] High rates of dropouts were recorded, and dropouts were not equally distributed between treatment arms.
[3] Not reported.
[4] From Table 2 of Scherk et al, 2007.
[5] The total number of included patients was 407.
[6] RR > 1 favors second-generation antipsychotic drugs.
[7] Confidence interval ranges from appreciable benefit to appreciable harm.
[8] RR > 1 favors placebo.
[9] From Figure 3 of Scherk et al, 2007.
[10] From Figure 2 of Scherk et al, 2007.
[11] Only one study contributed to the analysis.
[12] The total number of included patients was 203.

Table 5

Author(s): Corrado Barbui and Andrea Cipriani
Date: 2009-09-08
Question: Should risperidone vs placebo be used for acute mania?
Settings: Hospital
Bibliography: Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of General Psychiatry,* 64:442-55.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	risperidone	placebo	Relative (95% CI)	Absolute		
symptom severity (Young Mania Rating Scale) (Better indicated by lower values)												
3[1]	randomised trials	very	no serious	no serious	no serious	none	0[3]	0[3]	-	SMD 0.66 lower (0.84 to 0.48	⊕⊕OO	CRITICAL

		serious[2]	inconsistency	indirectness	imprecision					lower)	LOW	
response rate												
3[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 1.75 (1.41 to 2.18)[6]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	CRITICAL
treatment acceptability (total dropouts)												
3[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 0.61 (0.38 to 0.95)[7]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	IMPORTANT
adverse effects (extrapyramidal symptoms)												
2[8]	randomised trials	very serious[2]	serious[9]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3]	0%	RR 3.32 (1.17 to 9.36)[7]	0 more per 1000 (from 0 more to 0 more)	⊕OOO VERY LOW	IMPORTANT
adverse effects (sedation)												
2[10]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[3]	0%	RR 3.80 (2.03 to 7.12)[7]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (weight gain) (Better indicated by lower values)												
3[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	serious[11]	none	0[3,12]	0[3]	-	SMD 0.29 higher (0.19 lower to 0.78 higher)	⊕OOO VERY LOW	IMPORTANT
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

	available											

[1] From Figure 1 of Leucht 2007.
[2] High dropout rates were recorded, and dropouts were not equally distributed between treatment arms.
[3] Not reported.
[4] From Table 2 of Leucht 2007.
[5] The total number of included patients was 844.
[6] RR >1 favors second-generation antipsychotic drugs.
[7] RR > 1 favors placebo.
[8] From Figure 3 of Leucht 2007.
[9] Only partial overlap between confidence intervals (heterogeneity test revealed statistically significant heterogeneity) .
[10] From Figure 2 of Leucht 2007.
[11] Confidence interval ranges from no difference to appreciable harm.
[12] The total number of included patients was 824.

Table 6

Author(s): Corrado Barbui and Andrea Cipriani
Date: 2009-09-08
Question: Should ziprasidone vs placebo be used for acute mania?
Settings: Hospital
Bibliography: Scherk H, Pajonk FG, Leucht S (2007). Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of General Psychiatry,* 64:442-55.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ziprasidone	placebo	Relative (95% CI)	Absolute		
symptom severity (Young Mania Rating Scale) (Better indicated by lower values)												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	SMD 0.44 lower (0.65 to 0.23 lower)	⊕⊕OO LOW	CRITICAL

response rate											
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/0 (0%)[3,5]	0%	RR 1.49 (1.13 to 1.98)[6]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	CRITICAL
treatment acceptability (total dropouts)											
2[4]	randomised trials	very serious[2]	no serious inconsistency[3]	no serious indirectness	serious[7]	none	0/0 (0%)[3,5]	0%	RR 0.85 (0.68 to 1.05)[8]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
adverse effects (extrapyramidal symptoms)											
1[9]	randomised trials	very serious[2]	no serious inconsistency	serious[10]	serious[11]	none	0/0 (0%)[3]	0%	RR 7.07 (0.95 to 52.41)[8]	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
adverse effects (sedation)											
2[12]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[3]	0%	RR 3.10 (1.8 to 5.34)[8]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	IMPORTANT
adverse effects (weight gain) (Better indicated by lower values)											
1[4]	randomised trials	very serious[2]	no serious inconsistency[3]	serious[10]	serious[13]	none	0[3,14]	0[3]	-	SMD 0.0 higher (0.29 lower to 0.29 higher)	⊕OOO VERY LOW	IMPORTANT
disability and functioning (Better indicated by lower values)											
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)											
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Figure 1 of Leucht 2009.
[2] High dropout rates, and dropouts were not equally distributed between treatment arms.
[3] Not reported.
[4] From Table 2 of Leucht 2009.
[5] The total number of included patients was 416.
[6] RR > 1 favors second-generation antipsychotic drugs.
[7] Confidence interval ranges from appreciable benefit to no difference.
[8] RR > 1 favors placebo.
[9] From Figure3 of Leucht 2009.
[10] Only one study was included in the analysis.
[11] Confidence interval ranges from no difference to appreciable harm.
[12] From Figure 2 of Leucht 2009.
[13] Confidence interval ranges from appreciable benefit to appreciable harm.
[14] The total number of included patients was 203.

Table 7

Author(s): Lorenzo Tarsitani
Date: 2009-07-26
Question: Should LITHIUM CARBONATE vs PLACEBO be used for Acute mania?
Settings: Hospital
Bibliography: Smith LA et al (2007). Pharmacological interventions for acute bipolar mania: a systematic review of randomized, placebo-controlled trials. *Bipolar disorders,* 9:551-60.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	LITHIUM CARBONATE	PLACEBO	Relative (95% CI)	Absolute		
Symptoms severity - Response (at least 50% improvement in Young Mania Rating Scale score) (YMRS)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/133 (51.1%)	45/169 (26.6%)	RR 1.89 (1.40 to 2.57)	237 more per 1000 (from 107 more to 418 more)	⊕⊕OO LOW	CRITICAL

Symptoms severity - Withdrawal for lack of efficacy												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/134 (11.9%)	59/171 (34.5%)	RR 0.38 (0.11 to 1.33)	214 fewer per 1000 (from 307 fewer to 114 more)	⊕OOO VERY LOW	CRITICAL
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse effects - Withdrawal for adverse event												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/134 (7.5%)	6/171 (3.5%)	RR 2.14 (0.80 to 5.75)	40 more per 1000 (from 7 fewer to 167 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment adherence/acceptability - Withdrawal any reason												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/134 (38.1%)	107/171 (62.6%)	RR 0.67 (0.36 to 1.23)	206 fewer per 1000 (from 400 fewer to 144 more)	⊕OOO VERY LOW	IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer		IMPORTANT

										to 0 fewer)		
Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] Dropout rate was > 30% in both trials included in the analysis.
[2] CI crosses 1 and 0.5.
[3] CI crosses 1 and 2.

Table 8

Author(s): Lorenzo Tarsitani
Date: 2009-07-17
Question: Should VALPROATE vs PLACEBO be used for Acute Mania?
Settings: Hospital
Bibliography: Macritchie K et al (2003). Valproate for acute mood episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*, (1):CD004052.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VALPROATE**	**PLACEBO**	**Relative (95% CI)**	**Absolute**		
Symptoms severity - Failure to respond by end of study - <50% reduction on YMRS or SADS-C mania scale (YMRS or SADS-C mania scale)												
3	randomised trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/155 (42.6%)	111/161 (68.9%)	RR 0.62 (0.51 to 0.77)	262 fewer per 1000 (from 159 fewer to 338 fewer)	⊕⊕OO LOW	CRITICAL
Symptoms severity - Failure to respond by end of trial - CGI change score of 3+ (CGI)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	reporting bias[3]	22/67 (32.8%)	33/66 (50%)	RR 0.66 (0.43 to 1)	170 fewer per 1000 (from 285 fewer to 0 more)	⊕OOO VERY	CRITICAL

											LOW	
Symptoms severity - Withdrawal because patient no longer needed hospital admission												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5,6]	none	7/89 (7.9%)	2/96 (2.1%)	RR 3.24 (0.8 to 13.17)	47 more per 1000 (from 4 fewer to 254 more)	⊕OOO VERY LOW	CRITICAL
Symptoms severity - Withdrawal due to lack of treatment response												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/158 (17.1%)	46/163 (28.2%)	RR 0.63 (0.43 to 0.92)	104 fewer per 1000 (from 23 fewer to 161 fewer)	⊕⊕OO LOW	IMPORTANT
Disability and functioning - Clinical response -general health and social functioning (Better indicated by higher values)												
2	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	84	85	-	MD 7.77 higher (2.54 to 13 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Withdrawal due to adverse events												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[10]	none	9/158 (5.7%)	5/163 (3.1%)	RR 1.91 (0.66 to 5.51)	28 more per 1000 (from 10 fewer to 138 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects - Constipation												
2	randomised trials	very serious[4]	serious[11]	no serious indirectness	serious[12]	none	7/89 (7.9%)	8/96 (8.3%)	RR 0.95 (0.37 to 2.45)	4 fewer per 1000 (from 53 fewer to 121 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Diarrhoea												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[13]	none	9/89 (10.1%)	15/96 (15.6%)	RR 0.65 (0.3 to 1.4)	55 fewer per 1000 (from 109 fewer to 62 more)	⊕OOO VERY LOW	CRITICAL

Adverse effects - Nausea												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[14]	none	23/158 (14.6%)	17/165 (10.3%)	RR 1.45 (0.82 to 2.56)	46 more per 1000 (from 19 fewer to 161 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Vomiting												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[15]	none	11/89 (12.4%)	5/96 (5.2%)	RR 2.37 (0.85 to 6.61)	71 more per 1000 (from 8 fewer to 292 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Twitching												
1	randomised trials	very serious[16]	no serious inconsistency	serious[1]	serious[17,18]	reporting bias[3]	2/69 (2.9%)	0/74 (0%)	RR 5.36 (0.26 to 109.65)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Headache												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[19,20]	none	15/70 (21.4%)	24/75 (32%)	RR 0.67 (0.38 to 1.17)	106 fewer per 1000 (from 198 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Sedation												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[21]	none	18/158 (11.4%)	12/163 (7.4%)	RR 1.58 (0.81 to 3.08)	43 more per 1000 (from 14 fewer to 153 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Anorexia												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[23]	reporting bias[3]	1/20 (5%)	0/22 (0%)	RR 3.29 (0.14 to 76.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dizziness												

2	randomised trials	very serious[24]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/138 (9.4%)	4/141 (2.8%)	RR 3.17 (1.13 to 8.88)	62 more per 1000 (from 4 more to 224 more)	⊕⊕OO LOW	CRITICAL
Adverse effects - Asthenia												
2	randomised trials	very serious[24]	no serious inconsistency	no serious indirectness	serious[25]	none	15/138 (10.9%)	10/141 (7.1%)	RR 1.55 (0.72 to 3.34)	39 more per 1000 (from 20 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Fever												
1	randomised trials	very serious[16]	no serious inconsistency	serious[1]	serious[26]	reporting bias[3]	1/69 (1.4%)	3/74 (4.1%)	RR 0.36 (0.04 to 3.36)	26 fewer per 1000 (from 39 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Agitation												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	0/22 (0%)	RR 3.29 (0.14 to 76.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Ataxia												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	2/20 (10%)	0/22 (0%)	RR 5.48 (0.28 to 107.72)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Diplopia												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	1/22 (4.5%)	RR 1.10 (0.07 to 16.45)	5 more per 1000 (from 42 fewer to 702 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dysarthria												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	0/22 (0%)	RR 3.29 (0.14 to 76.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY	CRITICAL

											LOW	
Adverse effects - Pain												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5,28]	none	14/89 (15.7%)	17/96 (17.7%)	RR 0.89 (0.47 to 1.68)	19 fewer per 1000 (from 94 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dysuria												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	0/20 (0%)	2/22 (9.1%)	RR 0.22 (0.01 to 4.3)	71 fewer per 1000 (from 90 fewer to 300 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Palpitations												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	1/22 (4.5%)	RR 1.10 (0.07 to 16.45)	5 more per 1000 (from 42 fewer to 702 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Chest tightness												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	0/22 (0%)	RR 3.29 (0.14 to 76.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Tremor												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	1/69 (1.4%)	4/67 (6%)	RR 0.24 (0.03 to 2.12)	45 fewer per 1000 (from 58 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Akathisia												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	4/69 (5.8%)	2/67 (3%)	RR 1.94 (0.37 to 10.25)	28 more per 1000 (from 19 fewer to 276 more)	⊕OOO VERY LOW	CRITICAL

Adverse effects - Hypersalivation												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	4/69 (5.8%)	2/67 (3%)	RR 1.94 (0.37 to 10.25)	28 more per 1000 (from 19 fewer to 276 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Extra-pyramidal side-effects												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	7/69 (10.1%)	7/67 (10.4%)	RR 0.97 (0.36 to 2.62)	3 fewer per 1000 (from 67 fewer to 169 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dyskinesia												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	2/69 (2.9%)	2/67 (3%)	RR 0.97 (0.14 to 6.7)	1 fewer per 1000 (from 26 fewer to 170 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Blood dyscrasio												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[29]	reporting bias[3]	2/69 (2.9%)	0/67 (0%)	RR 4.86 (0.24 to 99.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects - Dry eyes												
1	randomised trials	very serious[22]	no serious inconsistency	serious[1]	very serious[27]	reporting bias[3]	1/20 (5%)	0/22 (0%)	RR 3.29 (0.14 to 76.33)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Treatment adherence												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		

Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] Only one study contributed to the analysis.
[2] On study, sample size is 133.
[3] Only one study reported this outcome measure.
[4] Two trails included (Bowden et al, 1994; Pope et al, 1991), both with a drop out rate >30%
[5] Sample size is 185.
[6] Sample size is 185 and CI crosses 1 and 2.
[7] Two trials (Bowden et al, 1994; Pope et al, 1991) out of three have a dropout rate > 30%.
[8] One (Pope et al, 1991) out of two trials has a doprout rate >30.
[9] Sample size is 169.
[10] CI crosses 1 and 2.
[11] I-squared test is 53%.
[12] Sample size is 185 and CI crosses 1 and both 0.5 and 2.
[13] Sample size is 185 and CI crosses 1 and 0.5.
[14] CI crosses 1 and 2.
[15] Sample size is 185 and CI crosses 1 and 2.
[16] Only one study (Bowden et al, 1994) with a dropout rate >30%.
[17] Sample size is 143.
[18] Sample size is 143 and CI crosses 1, 0.5 and 2.
[19] Sample size is 145.

[20] Sample size is 145 and CI crosses 1 and 0.5.
[21] CI crosses 1 and 2.
[22] Only one study (Pope et al, 1991) with a dropout rate >30%.
[23] Sample size is very low (N=42) and CI crosses 1, 0.5 an 2.
[24] One (Bowden et al, 1994) out of two trials has a dropout rate >30%.
[25] CI crosses 1 and 2.
[26] Sample size is 143 and CI 1, 0.5 and 2.
[27] Sample size is very low (N=42) and CI crosses 1, 0.5 and 2.
[28] Sample size is 185 and CI crosses 1 and 0.5
[29] Sample size is 136 and CI crosses 1, 0.5 and 2.

Table 9

Author(s): Lorenzo Tarsitani
Date: 2009-07-17
Question: Should CARBAMAZEPINE vs PLACEBO be used in Acute Mania?
Settings: Hospital
Bibliography: Smith LA et al (2007). Pharmacological interventions for acute bipolar mania: a systematic review of randomized, placebo-controlled trials. *Bipolar disorders,* 9:551-60.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CARBAMAZEPINE	PLACEBO	Relative (95% CI)	Absolute		
Symptoms severity - Change from baseline Young Mania Rating Scale scores (measured with: YMRS; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	214	213	-	MD 5.82 lower (10.23 to 1.41 lower)	⊕⊕OO LOW	CRITICAL
Symptoms severity - Response (at least 50% improvement in Young Mania Rating Scale score) (YMRS)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/223 (51.1%)	56/220 (25.5%)	RR 2.00 (1.55 to 2.59)	255 more per 1000 (from 140 more to 405 more)	⊕⊕OO LOW	CRITICAL

Symptoms severity - Withdrawal for lack of efficacy												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/214 (10.3%)	50/213 (23.5%)	RR 0.45 (0.19 to 1.03)	129 fewer per 1000 (from 190 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse effects - Withdrawal for adverse event												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/214 (11.2%)	12/213 (5.6%)	RR 2.00 (1.03 to 3.9)	56 more per 1000 (from 2 more to 163 more)	⊕⊕OO LOW	CRITICAL
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment adherence/acceptability - Withdrawal any reason												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93/223 (41.7%)	110/220 (50%)	RR 0.85 (0.69 to 1.04)	75 fewer per 1000 (from 155 fewer to 20 more)	⊕⊕OO LOW	IMPORTANT

Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] Dropout rate is >30% in both trials included in the analysis.
[2] CI crosses 1 and 0.5.

Additional information that was not GRADEd

COST

Rosenheck et al, 2008a; 2008b: The cost of second-generation antipsychotics is about $10 per day, more than ten times the cost of generic first-generation antipsychotics.

Waraich PS et al (2002): This review selected studies with people being treated for acute schizophrenia, randomised to two or more dose ranges of haloperidol. Using low doses (>3-7.5mg/day) did not clearly result in loss of efficacy (no clinically important improvement in global state, versus >7.5-15mg/day n=48, 1 RCT, RR 1.09 CI 0.7 to 1.8; versus >15-35mg/day n=81, 2 RCTs, 0.95 CI 0.8 to 1.2). Doses of haloperidol in the range of >3-7.5 mg/day had a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses (clinically significant extrapyramidal adverse effects, versus >7.5-15mg/day n=64, 2 RCTs, RR 0.12 CI 0.01 to 2.1; versus >15-35mg/day n=144, 3 RCTs RR 0.59 CI 0.5 to 0.8, NNH 3 CI 2 to 6; versus >35mg/day n=86, 2 RCTs, RR 0.70 CI 0.5 to 1.1).

USE AMONG PREGNANT AND LACTATING WOMEN

National Collaborating Centre for Mental Health (NCCMH) 2007: Valproate should not be routinely prescribed to women of child-bearing potential. If there is no effective alternative, the risks of taking valproate during pregnancy, and the importance of using adequate contraception, should be explained.

Lithium should not be routinely prescribed for pregnant women, particularly in the first trimester of pregnancy (because of the risk of cardiac malformations in the fetus) or during breastfeeding (because of the high levels in breast milk).

If a woman who needs antimanic medication plans to become pregnant, a low-dose typical or atypical antipsychotic should be the treatment of choice.

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Cipriani A, Rendell JM, Geddes J (2006). Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews* 2006(3):CD004362.

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Waraich PS et al (2002). Haloperidol dose for the acute phase of schizophrenia. *Cochrane Database of Systematic Reviews,* (3):CD001951.

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Weislar RH et al (2005). Extended release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry,* 66:323-30.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	In terms of proportion of patients showing an improvement in manic symptoms, there is evidence that haloperidol (Failure to respond: RR 0.79; 0.65 to 0.95, absolute risk difference 14.1%), lithium (Response: RR 1.89; 1.40 to 2.57, absolute risk difference 23.7%), valproate (Failure to respond RR 0.62; 0.51 to 0.77, absolute risk difference 26.2%), carbamazepine (Response: RR 2.00; 1.55 to 2.59, absolute risk difference 25.5%) were significantly more effective than placebo in bipolar mania.In terms of symptom reduction (change from baseline to endpoint score on the YMRS), compared to placebo, haloperidol (MD -5.85, -7.69 to -4.00) and carbamazepine (MD -5.82, -10.23 to -1.41) were more effective at reducing manic symptoms. No evidence on lithium and valproate was available for this outcome.

	In terms of symptom reduction, all second-generation antipsychotic drugs (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) were more effective than placebo (overall SMD = -0.45, 95% confidence interval -0.57 to -0.32). In terms of proportion of patients showing an improvement in manic symptoms, all second-generation antipsychotic drugs (aripiprazole, olanzapine, risperidone, ziprasidone) with the exception of quetiapine (see GRADE table) were more effective than placebo (overall RR = 1.67, 95% confidence interval 1.48 to 1.89, significantly in favor of second-generation antipsychotic drugs). In terms of functioning (GAS), compared to placebo, haloperidol (MD 6.4, 1.79 to 8.81) and valproate (MD 7.77, 2.54 to 13) were more effective in increasing functioning. No evidence on lithium and valproate was available for this outcome. There is limited evidence that haloperidol (RR 1.7, 0.64 to 4.5), lithium (RR 2.14, 0.80 to 5.75), valproate (1.91, 0.66 to 5.51). carbamazepine (RR 2.00, 1.03 to 3.9), significantly increased the risk of withdrawal for adverse events. There is evidence that haloperidol significantly increased the risk of extrapyramidal disorder (RR 4.17, 2.88 to 6.03), akathisia (RR 5.61, 2.46 to 12.8), hyperkinesia (RR 5.35, 1.89 to 15.12), tremor (RR 3.28, 1.86 to 5.79) compared to placebo (all events > 10% and > placebo). Some second-generation antipsychotic drugs (see GRADE tables) seemed to induce more extrapyramidal symptoms and weight gain than placebo. All second-generation antipsychotic drugs were also associated with higher rates of somnolence than placebo. In terms of treatment acceptability, some second-generation antipsychotic drugs (see GRADE tables) were better than placebo (overall RR = 0.72, 95% confidence interval 0.62 to 0.83, significantly in favor of second-generation antipsychotic drugs). No evidence exists for chlorpromazine compared to placebo in bipolar mania.

Summary of the quality of evidence	For haloperidol, the quality of evidence was LOW or VERY LOW for symptom reduction, LOW for functioning, LOW or VERY LOW for adverse events, and LOW or VERY LOW for treatment adherence For lithium, the quality of evidence was LOW for symptom reduction (response), VERY LOW for withdrawal for lack of efficacy, VERY LOW for adverse events, and VERY LOW for treatment adherence For valproate, the quality of evidence was LOW and VERY LOW for symptom reduction, VERY LOW for functioning, and LOW or VERY LOW for adverse events. For carbamazepine, the quality of evidence was LOW for symptoms reduction and response, VERY LOW for withdrawal for lack of efficacy, LOW for adverse events and treatment adherence. For second-generation antipsychotic drugs the quality of evidence was LOW for most critical and important outcomes.
Balance of benefits versus harms	In studies carried out in individuals with bipolar mania, haloperidol, lithium, valproate, and carbamazepine are associated with a beneficial effect. In addition to these drugs, a similar beneficial effect was observed for second-generation antipsychotic drugs (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) In terms of tolerability, haloperidol is associated with a large increase in the risk of movement disorders. This risk is dose related. In schizophrenia, low doses of haloperidol (3 to 7.5 mg/day) have a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses. Second-generation antipsychotic drugs are associated with extrapyramidal symptoms, sedation and weight gain. The long-term metabolic consequences associated with some second-generation antipsychotic drugs have not been captured by randomized trials. Mood stabilizers (especially lithium) have a narrow therapeutic index and can be toxic to

	multiple organ systems.
Values and preferences including any variability and human rights issues	Important issues are the short and long term consequences of disability, lack of functioning, and discrimination associated with manic symptoms. In addition, mania can be a life threatening condition. However, there are significant concerns about safety and tolerability associated with antipsychotic medications and mood stabilizers. A further important issue is the burden of taking mood stabilizers that requires regular blood monitoring. Additionally, extrapyramidal symptoms may lead to easy identification of people treated for a mental disorder.
Costs and resource use and any other relevant feasibility issues	Haloperidol, lithium, valproate, and carbamazepine are associated with low acquisition costs. Lithium, valproate, and carbamazepine requires regular blood monitoring. The cost of second generation antipsychotics in the treatment of schizophrenia is more than ten times the cost of generic first-generation antipsychotics. In many LAMICs continuous availability of antipsychotic in non specialized health care is a challenge. Haloperidol, lithium, valproate, and carbamazepine are available in WHO Essential Medicine List as antipsychotic medicines. Lithium treatment requires periodic blood level monitoring, that may not be available except in secondary care settings and adds costs. Treatment with valproate and carbamazepine also requires periodic blood tests, that may not be available except in secondary care settings and adds costs.
Recommendation(s) Haloperidol is recommended in individuals with bipolar mania.	

Strength of recommendation: STRONG

Second-generation antipsychotics may be considered as an alternative to haloperidol in individuals with bipolar mania if availability can be assured and cost is not a constraint.
Strength of recommendation: STANDARD

Lithium, valproate, or carbamazepine should be offered to individuals with bipolar mania.
Strength of recommendation: STRONG

In individuals with bipolar mania, treatment with lithium should be initiated only in those settings where personnel and facilities for close clinical and laboratory monitoring are available.
Strength of recommendation: STRONG

In women with bipolar mania planning a pregnancy or pregnant or breastfeeding, lithium and valproate should be avoided. In this group, low dose haloperidol should be considered with caution.
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 systematic reviews were found to be relevant without changing the recommendation:

Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR. Comparative effi cacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011; 378: 1306–15. DOI:10. 1016/S0140- 6736(11)60873-8

McKnight R, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profi le: a systematic review and meta-analysis. Lancet 2012; 379: 721–28. DOI:10.1016/S0140-6736(11)61516-X