APPENDIX 30: INTERVENTIONS FOR CHILDREN AND YOUNG PEOPLE – GRADE profiles

PHARMACOLOGICAL INTERVENTIONS FOR MANIA

Antipsychotics

Aripiprazole compared with placebo

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		
Response (assessed with: 50% reduction YMRS)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	122/215 (56.7%)	37/125 (29.6%)	RR 1.97 (1.5 to 2.61)	287 more per 1000 (from 148 more to 477 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	37/215 (17.2%)	25/125 (20%)	RR 0.77 (0.49 to 1.22)	46 fewer per 1000 (from 102 fewer to 44 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	12/215 (5.6%)	2/125 (1.6%)	RR 2.93 (0.76 to 11.32)	31 fewer per 1000 (from 4 fewer to 165 more)	⊕⊕OO LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	18	25	-	SMD 0.73 lower (1.61 lower to 0.15 higher)	⊕⊕OO LOW	CRITICAL

[1] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Olanzapine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Placebo for Acute Mania	Relative (95% CI)	Absolute		
Response (50% reduction in YMRS scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	51/105 (48.6%)	12/54 (22.2%)	RR 2.19 (1.28 to 3.74)	264 more per 1000 (from 62 more to 609 more)	⊕OOO VERY LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	105	54	-	SMD 0.91 lower (1.26 to 0.57 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	22/107 (20.6%)	19/54 (35.2%)	RR 0.58 (0.35 to 0.98)	148 fewer per 1000 (from 7 fewer to 229 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	3/107 (2.8%)	0/54 (0%)	RR 3.56 (0.19 to 67.79)	-	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Quetiapine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
Response (50% reduction in YMRS scores)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	117/203 (57.6%)	34/105 (32.4%)	RR 1.82 (1.36 to 2.43)	266 more per 1000 (from 117 more to 463 more)	⊕OOO VERY LOW	CRITICAL

Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	188	81	-	SMD 0.57 lower (0.83 to 0.31 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	41/203 (20.2%)	31/103 (30.1%)	RR 0.64 (0.38 to 1.1)	108 fewer per 1000 (from 187 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	22/203 (10.8%)	6/105 (5.7%)	RR 1.71 (0.70 to 4.17)	41 fewer per 1000 (from 17 fewer to 181 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Risperidone compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Risperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Response (50% reduction in YMRS scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	67/111 (60.4%)	16/58 (27.6%)	RR 2.18 (1.4 to 3.4)	326 more per 1000 (from 110 more to 662 more)	⊕OOO VERY LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	109	58	-	SMD 0.8 lower (1.13 to 0.47 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/111 (18%)	12/58 (20.7%)	RR 0.81 (0.34 to 1.95)	39 fewer per 1000 (from 137 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	8/111 (18%)	4/58 (20.7%)	RR 1.03 (0.32 to 3.31)	2 fewer per 1000 (from 47 fewer to 159 more)	⊕OOO VERY	CRITICAL

											LOW	

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Ziprasidone compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ziprasidone	Placebo	Relative (95% CI)	Absolute		
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	133	85	-	SMD 0.49 lower (0.76 to 0.21 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	17/150 (11.3%)	12/88 (13.6%)	RR 0.83 (0.42 to 1.66)	23 fewer per 1000 (from 79 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	53/150 (35.3%)	37/88 (42%)	RR 0.84 (0.61 to 1.17)	67 fewer per 1000 (from 164 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Risperidone compared with valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Valproate	Relative (95% CI)	Absolute		
Response (50% reduction in YMRS scores)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32/47 (68.1%)	19/47 (40.4%)	RR 1.70 (1.16 to 2.49)	283 more per 1000 (from 65 more to 602 more)	⊕OOO VERY	CRITICAL

											LOW	
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	42	44	-	SMD 0.44 lower (0.87 to 0.01 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/47 (12.8%)	16/47 (34%)	RR 0.38 (0.17 to 0.84)	211 fewer per 1000 (from 54 fewer to 283 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/47 (2.1%)	6/47 (12.8%)	RR 0.17 (0.02 to 1.31)	106 fewer per 1000 (from 125 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Quetiapine compared with valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quetiapine**	**Valproate**	**Relative (95% CI)**	**Absolute**		
Response (50% reduction in YMRS scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	15/25 (60%)	7/25 (28%)	RR 2.14 (1.06 to 4.34)	319 more per 1000 (from 17 more to 935 more)	⊕OOO VERY LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	25	25	-	SMD 0.54 lower (1.1 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	6/25 (24%)	6/25 (24%)	RR 1 (0.37 to 2.68)	0 fewer per 1000 (from 151 fewer to 403 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	reporting bias[2]	0/25 (0%)	1/25 (4%)	RR 0.33 (0.01 to 7.81)	27 fewer per 1000 (from 40 fewer to 272 more)	⊕OOO VERY LOW	CRITICAL

[1] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Anticonvulsants

Topiramate compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute		
Response (50% reduction in YMRS scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/29 (34.5%)	6/27 (22.2%)	RR 1.55 (0.65 to 3.69)	122 more per 1000 (from 78 fewer to 598 more)	⊕OOO VERY LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	29	27	-	SMD 0.51 lower (1.04 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	9/45 (20%)	3/41 (7.3%)	RR 2.5 (0.8 to 7.79)	110 more per 1000 (from 15 fewer to 497 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	2/45 (4.4%)	1/41 (2.4%)	RR 1.26 (0.29 to 5.44)	6 more per 1000 (from 17 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Valproate compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Placebo	Relative (95% CI)	Absolute		
Response (50% reduction in YMRS scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	18/74 (24.3%)	16/70 (22.9%)	RR 1.06 (0.59 to 1.92)	14 more per 1000 (from 94 fewer to 210 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/74 (27%)	13/70 (18.6%)	RR 1.46 (0.79 to 2.7)	85 more per 1000 (from 39 fewer to 316 more)	⊕OOO VERY LOW	CRITICAL
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	74	70	-	SMD 0.09 lower (0.41 lower to 0.24 higher)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	4/74 (27%)	3/70 (18.6%)	RR 1.26 (0.29 to 5.44)	11 more per 1000 (from 30 fewer to 190 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Topiramate compared with valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topimarate	Valproate	Relative (95% CI)	Absolute		
Symptoms of mania (clinician rated) (measured with: YMRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	59	61	-	SMD 0.73 higher (0.36 to 1.1 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies

PHARMACOLOGICAL INTERVENTIONS FOR ACUTE DEPRESSION

Medication compared with placebo

Fluoxetine and olanzapine combination compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine and olazapine	Placebo	Relative (95% CI)	Absolute		
Symptoms of depression (clinician rated) (measured with: CDRS; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	170	84	-	SMD 0.35 lower (0.61 to 0.09 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/194 (10.3%)	5/97 (5.2%)	RR 2.00 (0.77 to 5.17)	52 more per 1000 (from 12 fewer to 215 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	78/194 (40.2%)	37/97 (38.1%)	RR 1.05 (0.78 to 1.43)	19 more per 1000 (from 84 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

Quetiapine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
Symptoms of depression (clinician rated) (measured with: CDRS; better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	109	115	-	SMD 0.11 lower (0.38 lower to 0.15 higher)	⊕OOO VERY LOW	CRITICAL

Response (50% reduction in CDRS scores)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	70/109 (64.2%)	65/115 (56.5%)	RR 1.13 (0.91 to 1.39)	73 more per 1000 (from 51 fewer to 220 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	26/110 (23.6%)	24/115 (20.9%)	RR 0.93 (0.37 to 2.34)	15 fewer per 1000 (from 131 fewer to 280 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	2/110 (1.8%)	3/115 (2.6%)	RR 0.67 (0.11 to 3.98)	9 fewer per 1000 (from 23 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.

PSYCHOLOGICAL INTERVENTIONS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological therapies	Control	Relative (95% CI)	Absolute		
Discontinuation (for any reason)												
2	randomised trials	serious[1]	serious[2]	serious[3]	serious[4]	reporting bias[5]	15/109 (13.8%)	40/115 (34.8%)	RR 0.49 (0.17 to 1.39)	177 fewer per 1000 (from 289 fewer to 136 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains
[2] Substantial and significant heterogeneity
[3] Different interventions
[4] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Few trials were identified, trials in this area have not been registered, and previous reviews of medication for children and young people find evidence of important differences between published and unpublished studies.