APPENDIX 29: INTERVENTIONS FOR CHILDREN AND YOUNG PEOPLE - FOREST PLOTS

1.1	Pharmacological interventions for mania	2
	.1 Antipsychotics	
	.2 Anticonvulsants	
	.3 Acute depression	
	.4 Psychological interventions	

Abbreviations

CI confidence interval M-H Mantel-Haenszel SE standard error

1.1 PHARMACOLOGICAL INTERVENTIONS FOR MANIA

1.1.1 Antipsychotics

Outcomes for antipsychotics compared with placebo

Response (50% reduction in manic symptoms) at post-treatment

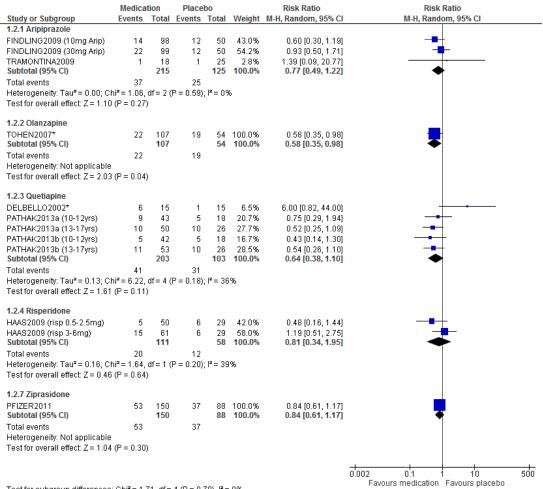
	Medica	tion	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Aripiprazole							
FINDLING2009 (10mg Arip)	43	98	12	50	26.1%	1.83 [1.06, 3.14]	
FINDLING2009 (30mg Arip)	63	99	12	50	28.8%	2.65 [1.58, 4.44]	
TRAMONTINA2009	16	18	13	25	45.1%	1.71 [1.13, 2.58]	
Subtotal (95% CI)		215		125	100.0%	1.97 [1.50, 2.61]	•
Total events	122		37				
Heterogeneity: Tau² = 0.00; Ch	i * = 2.02,	df = 2 (F	P = 0.36);	$ I^2 = 19 $	6		
Test for overall effect: Z = 4.80	(P < 0.000	001)					
1.1.2 Olanzapine							
TOHEN2007*	51	105	12	54	100.0%	2.19 [1.28, 3.74]	—
Subtotal (95% CI)		105		54	100.0%	2.19 [1.28, 3.74]	-
Total events	51		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.86	(P = 0.004)	4)					
1.1.3 Quetiapine							
DELBELLO2002*	13	15	8	15	31.6%	1.63 [0.97, 2.72]	
PATHAK2013 (400mg Quet)	51	93	13	45	34.1%	1.90 [1.16, 3.11]	
PATHAK2013 (600mg Quet)	53	95	13	45	34.4%	1.93 [1.18, 3.16]	
Subtotal (95% CI)		203		105	100.0%	1.82 [1.36, 2.43]	•
Total events	117		34				
Heterogeneity: Tau ^z = 0.00; Ch	$i^2 = 0.30$,	df = 2 (F	P = 0.86);	$I^2 = 0\%$	6		
Test for overall effect: Z = 4.06	(P < 0.000	01)					
1.1.4 Risperidone							
HAAS2009 (risp 0.5-2.5mg)	29	50	8	29	48.9%	2.10 [1.11, 3.97]	
HAAS2009 (risp 3-6mg)	38	61	8	29	51.1%	2.26 [1.21, 4.20]	
Subtotal (95% CI)		111		58	100.0%	2.18 [1.40, 3.40]	-
Total events	67		16				
Heterogeneity: Tau² = 0.00; Ch	$i^2 = 0.02$,	df = 1 (F	P = 0.87);	I ² = 0%	6		
Test for overall effect: Z = 3.44	(P = 0.00)	06)					
							0.2 0.5 1 2 5
							Favours placebo Favours medication

Test for subgroup differences: Chi² = 0.64, df = 3 (P = 0.89), l² = 0%

Symptoms of mania at post-treatment

			Medication	Placebo		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 Aripiprazole							
FINDLING2009 (10mg Arip)	-0.68822692	0.14958078	96	46	73.5%	-0.69 [-0.98, -0.40]	
FINDLING2009 (30mg Arip)	-0.31121187	0.41435252	99	46	9.6%	-0.31 [-1.12, 0.50]	
TRAMONTINA2009 (12-17yrs)	-1.21186584	0.47119446	9	14	7.4%	-1.21 [-2.14, -0.29]	
TRAMONTINA2009 (8-11yrs)	-0.31121187	0.41435252		11	9.6%	-0.31 [-1.12, 0.50]	
Subtotal (95% CI)			213	117	100.0%	-0.65 [-0.91, -0.40]	•
Heterogeneity: Tau² = 0.00; Chi² =		= 0%					
Test for overall effect: Z = 5.11 (P	< 0.00001)						
1.4.3 Quetiapine							
DELBELLO2002*	0.08722867	0.16592846	15	15	24.7%	0.09 [-0.24, 0.41]	
PATHAK2013a (10-12yrs)	-0.42115315	0.27976036	43	9	17.8%	-0.42 [-0.97, 0.13]	
PATHAK2013a (13-17yrs)	-0.53675643	0.24035193	50	14	20.0%	-0.54 [-1.01, -0.07]	
PATHAK2013b (10-12yrs)	-0.89455145	0.28980261	42	9	17.2%	-0.89 [-1.46, -0.33]	
PATHAK2013b (13-17yrs)	-0.49014007	0.23734594		14	20.2%	-0.49 [-0.96, -0.02]	
Subtotal (95% CI)			203	61	100.0%	-0.41 [-0.76, -0.06]	•
Heterogeneity: Tau² = 0.10; Chi² : Test for overall effect: Z = 2.31 (P); I²= 65%					
1.4.4 Risperidone							
HAAS2009 (risp 0.5-2.5mg)	-0.91438034	0.24324661	49	15	47.3%	-0.91 [-1.39, -0.44]	
HAAS2009 (risp 3-6mg)	-0.69820744	0.23023368		15	52.7%	-0.70 [-1.15, -0.25]	
Subtotal (95% CI)			109	30	100.0%	-0.80 [-1.13, -0.47]	•
Heterogeneity: Tau² = 0.00; Chi² : Fest for overall effect: Z = 4.79 (P		I² = 0%					
1.4.7 Ziprasidone							
PFIZER2011	-0.48528045	0.14032034			100.0%	-0.49 [-0.76, -0.21]	
Subtotal (95% CI)			133	85	100.0%	-0.49 [-0.76, -0.21]	•
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.46 (P	= 0.0005)						
1.4.8 Olanzapine							_
FOHEN2007*	-0.91277921	0.17434059	105		100.0%	-0.91 [-1.25, -0.57]	
Subtotal (95% CI)			105	54	100.0%	-0.91 [-1.25, -0.57]	•
Heterogeneity: Not applicable Fest for overall effect: Z = 5.24 (P	< 0.00001)						
							-2 -1 0 1 2
Test for subaroup differences: Cl	ni²= 6.19 df= 4 (P = 0.1	19) 12= 35.4%					Favours medication Favours placeb

Number of participants withdrawing (for any reason)



Test for subgroup differences: Chi² = 1.71, df = 4 (P = 0.79), I² = 0%

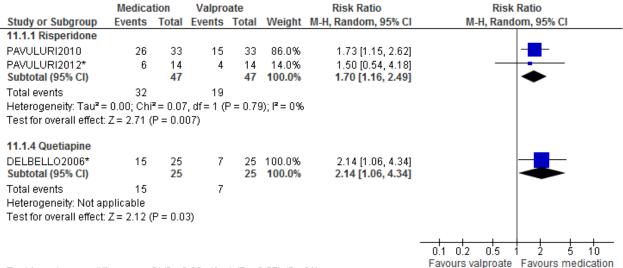
Number of participants withdrawing because of side effects

	Medica	tion	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.5.1 Aripiprazole							
FINDLING2009 (10mg Arip)	4	98	1	50	38.9%	2.04 [0.23, 17.78]	
FINDLING2009 (30mg Arip)	7	99	1	50	42.7%	3.54 [0.45, 27.95]	
TRAMONTINA2009	1	18	0	25	18.4%	4.11 [0.18, 95.37]	_
Subtotal (95% CI)		215		125	100.0%	2.93 [0.76, 11.32]	-
Total events	12		2				
Heterogeneity: Tau² = 0.00; Cl		,	P = 0.91)	$ \mathbf{r} = 0$	6		
Test for overall effect: $Z = 1.56$	i (P = 0.12)	1					
1.5.2 Olanzapine							<u>_</u>
TOHEN2007*	3	107	0	54	100.0%	3.56 [0.19, 67.79]	-
Subtotal (95% CI)		107		54	100.0%	3.56 [0.19, 67.79]	
Total events	3		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.85	(P = 0.40)	1					
1.5.3 Quetiapine							
DELBELLO2002*	0	15	0	15		Not estimable	
PATHAK2013a (10-12yrs)	7	43	1	18	19.3%	2.93 [0.39, 22.13]	
PATHAK2013a (13-17yrs)	8	50	2	27	36.2%	2.16 [0.49, 9.46]	
PATHAK2013b (10-12yrs)	1	42	1	18	10.7%	0.43 [0.03, 6.48]	-
PATHAK2013b (13-17yrs)	6	53	2	27	33.7%	1.53 [0.33, 7.07]	- -
Subtotal (95% CI)		203		105	100.0%	1.71 [0.70, 4.17]	◆
Total events	22		6				
Heterogeneity: Tau ² = 0.00; Cl Test for overall effect: Z = 1.19		,	P = 0.71)	I= 09	6		
restroi overali ellect. Z = 1.13	r (r = 0.23)	'					
1.5.5 Risperidone							
HAAS2009 (risp 0.5-2.5mg)	3	50	2	29	45.5%	0.87 [0.15, 4.91]	<u> </u>
HAAS2009 (risp 3-6mg)	5	61	2	29	54.5%	1.19 [0.25, 5.77]	_
Subtotal (95% CI)		111		58	100.0%	1.03 [0.32, 3.31]	—
Total events			4				
Heterogeneity: Tau ² = 0.00; Cl Test for overall effect: Z = 0.05		,	P = 0.79)	; I*= U9	6		
restroi overali ellect. Z = 0.03	r (r = 0.80)	'					
1.5.7 Ziprasidone					400		<u> </u>
PFIZER2011	17	150	12		100.0%	0.83 [0.42, 1.66]	The state of the s
Subtotal (95% CI)		150		88	100.0%	0.83 [0.42, 1.66]	₹
Total events	17		12				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.53$	i (P = 0.60)	1					
							0.002 0.1 1 10 500
Test for subgroup differences	: Chi² = 3.9	35. df=	4 (P = 0 -	41). I² =	: 0%		Favours medication Favours placebo

Test for subgroup differences: $\mathrm{Chi^2} = 3.95$, $\mathrm{df} = 4$ (P = 0.41), $\mathrm{I^2} = 0\%$

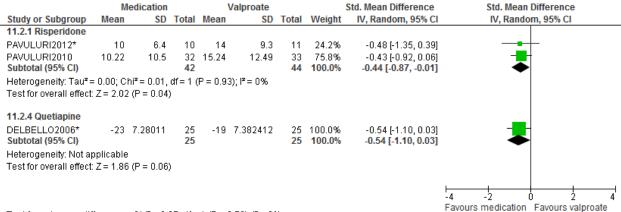
Outcomes for antipsychotics compared with valproate

Response (50% reduction of manic symptoms) at post-treatment



Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I^2 = 0%

Symptoms of mania at post-treatment



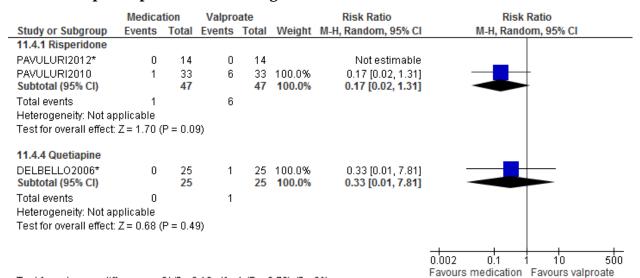
Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79), $I^2 = 0\%$

Number of participants withdrawing (for any reason)

	Medica	tion	Valproate			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
11.3.1 Risperidone									
PAVULURI2012*	0	14	0	14		Not estimable			
PAVULURI2010 Subtotal (95% CI)	6	33 47	16	33 47	100.0% 100.0%	0.38 [0.17, 0.84] 0.38 [0.17, 0.84]	-		
Total events	6		16						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.39 (P = 0.0	2)						
11.3.4 Quetiapine									
DELBELLO2006* Subtotal (95% CI)	6	25 25	6	25 25	100.0% 100.0%	1.00 [0.37, 2.68] 1.00 [0.37, 2.68]	-		
Total events	6		6						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.00 (P = 1.0	0)						
							0.01 0.1 1 10 100		
							Favours medication Favours valproate		

Test for subgroup differences: $Chi^2 = 2.28$, df = 1 (P = 0.13), $I^2 = 56.1\%$

Number of participants withdrawing because of side effects

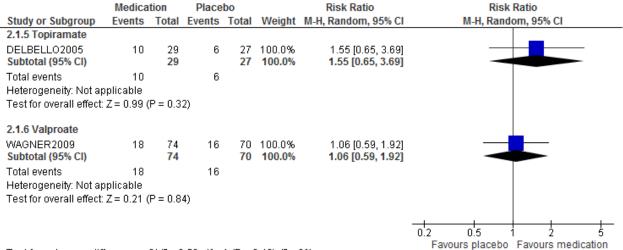


Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

1.1.2 Anticonvulsants

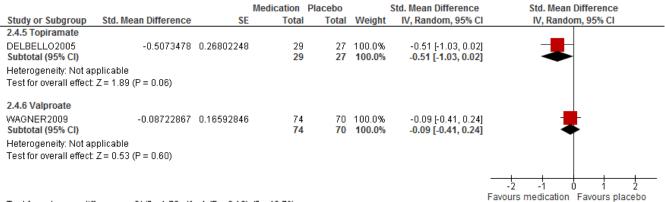
Outcomes for anticonvulsants compared with placebo

Response (50% reduction in manic symptoms) at post-treatment



Test for subgroup differences: $Chi^2 = 0.50$, df = 1 (P = 0.48), $I^2 = 0\%$

Symptoms of mania at post-treatment



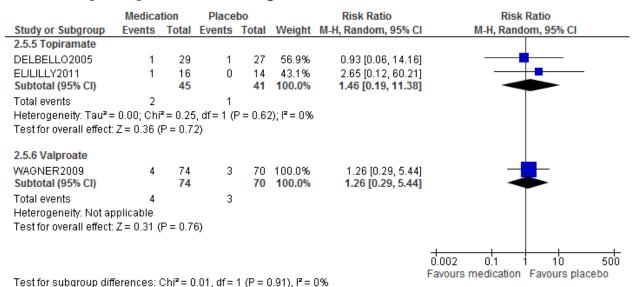
Test for subgroup differences: $Chi^2 = 1.78$, df = 1 (P = 0.18), $I^2 = 43.7\%$

Number of participants withdrawing (for any reason)

	Medica	tion	Placebo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
2.2.5 Topiramate								
DELBELLO2005	8	29	3	27	86.8%	2.48 [0.73, 8.40]	+	
ELILILLY2011	1	16	0	14	13.2%	2.65 [0.12, 60.21]	- •	
Subtotal (95% CI)		45		41	100.0%	2.50 [0.80, 7.79]	•	
Total events	9		3					
Heterogeneity: Tau ² =	0.00; Chř	z = 0.00), df = 1 (F	P = 0.97	7); I² = 0%			
Test for overall effect: 2	Z = 1.58 (I	P = 0.1	1)					
2.2.6 Valproate								
WAGNER2009	20	74	13	70	100.0%	1.46 [0.79, 2.70]	•	
Subtotal (95% CI)		74		70	100.0%	1.46 [0.79, 2.70]	▼	
Total events	20		13					
Heterogeneity: Not app	plicable							
Test for overall effect: 2	Z = 1.19 (I	P = 0.2	3)					
							0.002 0.1 1 10 500	
T16							Favours medication Favours placebo	

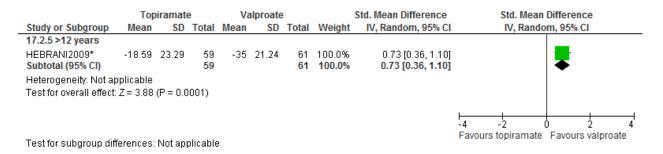
Test for subgroup differences: $Chi^2 = 0.68$, df = 1 (P = 0.41), $I^2 = 0\%$

Number of participants withdrawing because of side effects



Outcomes for anticonvulsants compared with valproate

Symptoms of mania at post-treatment

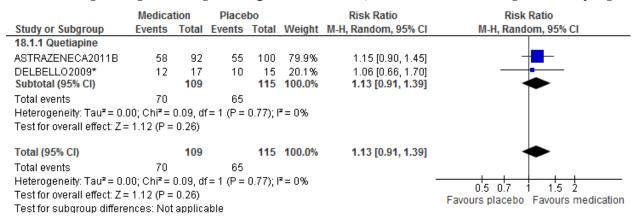


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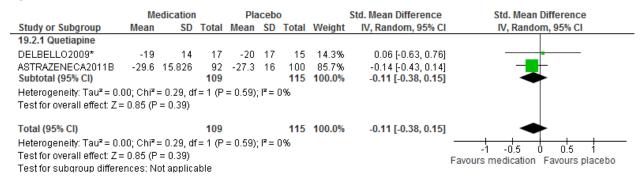
1.1.3 Acute depression

Outcomes for quetiapine compared with placebo

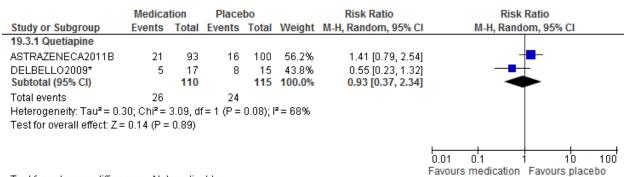
Number of participants responding to treatment (50% reduction in depressive symptoms)



Symptoms of depression at post-treatment



Number of participants withdrawing (for any reason)



Test for subgroup differences: Not applicable

Number of participants withdrawing because of side effects

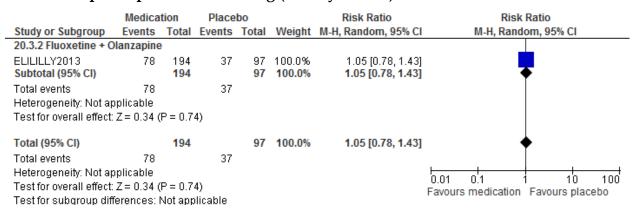
	Medica	tion	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
19.4.1 Quetiapine							
ASTRAZENECA2011B	1	93	2	100	55.9%	0.54 [0.05, 5.83]	
DELBELLO2009* Subtotal (95% CI)	1	17 110	1	15 115	44.1% 100.0%	0.88 [0.06, 12.91] 0.67 [0.11, 3.98]	-
Total events Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			3 f=1 (P=	0.79); I	²= 0%		
Test for subaroup differe	nces: Not	applica	able				0.01 0.1 10 100 Favours medication Favours placebo

Outcomes for olanzapine and fluoxetine combination compared with placebo

Symptoms of depression at post-treatment

	Me	edication		F	Placebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
20.2.2 Fluoxetine + C	Olanzapin	ie							
ELILILLY2013	-28.43	14.733	170	-23.4	13.656	84	100.0%	-0.35 [-0.61, -0.09]	
Subtotal (95% CI)			170			84	100.0%	-0.35 [-0.61, -0.09]	•
Heterogeneity: Not ap	pplicable								
Test for overall effect	Z = 2.60	(P = 0.00)	9)						
Total (95% CI)			170			84	100.0%	-0.35 [-0.61, -0.09]	•
Heterogeneity: Not a	pplicable								
Test for overall effect	Z= 2.60	(P = 0.00)	9)						-1 -0.5 0 0.5 1 Favours medication Favours placebo
Test for subgroup dif	ferences:	Not appl	licable						Tavours medication Tavours placebo

Number of participants withdrawing (for any reason)



Number of participants withdrawing because of side effects

	Medica	tion	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
20.4.2 Fluoxetine + 0	Olanzapine)					<u> </u>
ELILILLY2013 Subtotal (95% CI)	20	194 194	5	97 97	100.0% 100.0%	2.00 [0.77, 5.17] 2.00 [0.77, 5.17]	
Total events Heterogeneity: Not a Test for overall effect		'P = 0 1	5 5)				
Total (95% CI)		194	٠,	97	100.0%	2.00 [0.77, 5.17]	•
Total events Heterogeneity: Not a Test for overall effect Test for subgroup dit	: Z=1.43 (•					0.01 0.1 1 10 100 Favours medication Favours placebo

1.1.4 Psychological interventions

Outcomes for family focused therapy compared with TAU

Number of participants withdrawing (for any reason)

