APPENDIX 13: CLINICAL EVIDENCE -FOREST PLOTS

1.1 Psychosocial interventions aimed at core features of autism (overall autistic behaviours)
1.1.1 Behavioural interventions aimed at overall autistic behaviours as an indirect outcome
1.1.2 Educational interventions aimed at overall autistic behaviours as a direct outcome
1.1.3 Parent training interventions aimed at overall autistic behaviours as a direct or indirect outcome
1.1.4 Social-communication interventions aimed at overall autistic behaviours as an indirect outcome
1.2 Psychosocial interventions aimed at the core autism feature of impaired reciprocal social communication and interaction
1.2.1 AAC intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome
1.2.2 Animal-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome
1.2.3 Arts-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome
1.2.4 Behavioural intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome 13
1.2.5 Cognitive interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome
1.2.6 Educational interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome
1.2.7 Parent training interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome 20
1.2.8 Social-communication interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome 2.
1.3 Psychosocial interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours
1.3.1 Behavioural interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome
1.3.2 Cognitive intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome
1.3.3 Parent training intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

1.3.4 restrict	Social-communication intervention aimed at the core autism feature of ed interests and rigid and repetitive behaviours as an indirect outcome 43
	armacological interventions aimed at core features of autism (overall autistic
	,
1.4.1	Anticonvulsants for overall autistic behaviours as an indirect outcome 44
1.4.2	Antidepressants for overall autistic behaviours as an indirect outcome 44
1.4.3	Antihistamines for overall autistic behaviours as an indirect outcome 44
1.4.4	Antipsychotics for overall autistic behaviours as a direct or indirect outcome 45
1.4.5	SNRIs for overall autistic behaviours as an indirect outcome
	armacological interventions aimed at the core autism feature of impaired l social communication and interaction47
1.5.1 commı	Antioxidants for the core autism feature of impaired reciprocal social unication and interaction as an indirect outcome
	armacological interventions aimed at the core autism feature of restricted and repetitive behaviours48
1.6.1 and rep	Antidepressants for the core autism feature of restricted interests and rigid petitive behaviours as a direct outcome
	Antioxidants for the core autism feature of restricted interests and rigid and ive behaviours as an indirect outcome
1.6.3 repetiti	Antipsychotics for the core autism feature of restricted interests and rigid and ive behaviours as an indirect outcome
	omedical interventions aimed at core features of autism (overall autistic rs)
	Complementary therapies for overall autistic behaviours as a direct or toutcome
1.7.2	Hormones for overall autistic behaviours as a direct or indirect outcome 63
1.7.3 outcom	Medical procedures for overall autistic behaviours as a direct or indirect ne
1.7.4 outcom	Nutritional interventions for overall autistic behaviours as a direct or indirect ne77
1.7.5 outcon	Sensory interventions for overall autistic behaviours as a direct or indirect ne
	omedical interventions aimed at the core autism feature of impaired reciprocal nmunication and interaction
1.8.1 social o	Complementary therapies for the core autism feature of impaired reciprocal communication and interaction as an indirect outcome

	3.2 mmu	Hormones for the core autism feature of impaired reciprocal social unication and interaction as a direct outcome
	3.3 mmu	Medical procedures for the core autism feature of impaired reciprocal social inication and interaction as a direct or indirect outcome
	3.4 cial c	Nutritional interventions for the core autism feature of impaired reciprocal ommunication and interaction as a direct or indirect outcome
	3.5 mmu	Sensory interventions for the core autism feature of impaired reciprocal social inication and interaction as an indirect outcome
1.9 and		medical interventions aimed at the core autism feature of restricted interests and repetitive behaviours
	9.1 petiti	Hormones for the core autism feature of restricted interests and rigid and ve behaviours as an indirect outcome
	9.2 gid ar	Medical procedures for the core autism feature of restricted interests and nd repetitive behaviours as an indirect outcome
	9.3 .d rep	Motor intervention for the core autism feature of restricted interests and rigid petitive behaviours as a direct outcome
	9.4 .d rig	Nutritional interventions for the core autism feature of restricted interests id and repetitive behaviours as an indirect outcome
	9.5 gid ar	Sensory intervention for the core autism feature of restricted interests and nd repetitive behaviours as an indirect outcome
1.10	Psy	chosocial interventions aimed at behaviour that challenges98
	l0.1 itcom	Animal-based intervention for behaviour that challenges as an indirect ne98
	l0.2 itcom	Behavioural interventions for behaviour that challenges as a direct or indirect ne98
	l0.3 indir	Cognitive-behavioural interventions for behaviour that challenges as a direct rect outcome
1.1	10.4	Parent training for behaviour that challenges as a direct or indirect outcome 100
	l0.5 direct	Social-communication interventions for behaviour that challenges as an toutcome
1.11	Pha	armacological interventions aimed at behaviour that challenges107
1.1	11.1	Anticonvulsants for behaviour that challenges as a direct outcome 107
1.1	11.2	Antidepressants for behaviour that challenges as an indirect outcome 109
1.1	11.3	Antihistamines for behaviour that challenges as a direct outcome
1.1	11.4	Antioxidants for behaviour that challenges as a direct outcome

1.11.5	Antipsychotics for behaviour that challenges as a direct or indirect outcome 111	
1.11.6	Antivirals for behaviour that challenges as a direct outcome1	18
1.11.7	Cognitive enhancers for behaviour that challenges as a direct outcome 1	19
1.11.8	Methylxanthines for behaviour that challenges as a direct outcome 1	19
1.11.9	Opioid antagonists for behaviour that challenges as a direct outcome 1	20
1.11.10 challer	Selective noradrenaline reuptake inhibitors (SNRIs) for behaviour that nges as an indirect outcome	20
1.12 Bio	omedical interventions aimed at behaviour that challenges1	21
	Complementary therapies for behaviour that challenges as a direct or indire ne1	
1.12.2	Hormones for behaviour that challenges as an indirect outcome 1	25
1.12.3 outcor	Medical procedures for behaviour that challenges as a direct or indirect ne	27
1.12.4 outcor	Nutritional interventions for behaviour that challenges as a direct or indirect me	
1.12.5	Sensory interventions for behaviour that challenges as an indirect outcome 134	
1.13 Ps	ychosocial interventions aimed at adaptive behaviour1	36
	Behavioural interventions for adaptive behaviour as a direct or indirect ne1	36
	Cognitive-behavioural interventions for adaptive behaviour as an indirect ne1	38
1.13.3	Parent training for adaptive behaviour as a direct or indirect outcome 1	38
1.13.4 outcor	Social-communication interventions for adaptive behaviour as an indirect ne1	41
1.14 Bio	omedical interventions aimed at adaptive behaviour1	43
1.14.1	Complementary therapies for adaptive behaviour as an indirect outcome . 1-	44
1.14.2	Hormones for adaptive behaviour as an indirect outcome1	47
1.14.3	Medical procedures for adaptive behaviour as an indirect outcome 1	48
1.14.4	Nutritional interventions for adaptive behaviour as an indirect outcome 1	49
1.15 Ps	ychosocial interventions aimed at speech and language1	50
1.15.1	AAC interventions for speech and language as a direct outcome 1	50
1.15.2	Arts-based interventions for speech and language as a direct outcome 1	53
1.15.3	Behavioural interventions for speech and language as an indirect outcome 1	54

		Educational interventions for speech and language as a direct or indirect ne	156
1.	15.5	Parent training for speech and language as a direct or indirect outcome	159
	15.6 itcom	Social-communication interventions for speech and language as an indirective	t
1.16	Bio	medical interventions aimed at speech and language	163
	16.1 atcom	Complementary therapies for speech and language as a direct or indirect ne	163
1.	16.2	Hormones for speech and language as an indirect outcome	166
1.	16.3	Medical procedures for speech and language as an indirect outcome	167
1.	16.4	Nutritional interventions for speech and language as an indirect outcome.	168
1.	16.5	Sensory interventions for speech and language as an indirect outcome	170
1.17	Psy	chosocial interventions aimed at IQ and academic skills	173
	17.1 itcom	Behavioural interventions for IQ and/or academic skills as a direct or indi-	
1.	17.2	Educational interventions for IQ as an indirect outcome	174
1.	17.3	Parent training for IQ as an indirect outcome	174
1.	17.4	Social-communication interventions for IQ as an indirect outcome	175
1.18	Pha	armacological interventions aimed at academic skills	176
1.	18.1	Antipsychotics for academic skills as an indirect outcome	176
1.19	Bio	medical interventions aimed at IQ	176
1.	19.1	Complementary therapies for IQ as a direct outcome	176
1.	19.2	Hormones for IQ as an indirect outcome	177
1.	19.3	Nutritional intervention for IQ as an indirect outcome	178
1.	19.4	Sensory intervention for IQ as an indirect outcome	178
1.20	pS\	YCHOSOCIAL interventions aimed at SENSORY SENSITIVITIES	179
1.	20.1	Animal-based interventions for sensory sensitivities as an indirect outcome 179	e
1.	20.2	Educational interventions for sensory sensitivities as an indirect outcome.	179
1.21	Bio	medical interventions aimed at SENSORY SENSITIVITIES	180
1.	21.1	Complementary therapies for sensory sensitivities as a direct outcome	180
1.	21.2	Sensory interventions for sensory sensitivities as a direct outcome	180
1.22	Psy	chosocial interventions aimed at motor skills	182
1.	22.1	Animal-based interventions for motor skills as an indirect outcome	182

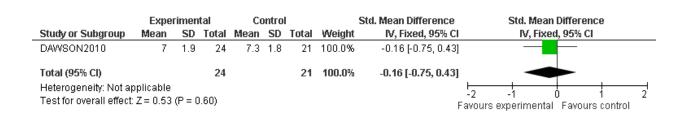
1.22.2	Behavioural interventions for motor skills as an indirect outcome	. 183
1.22.3	Educational interventions for motor skills as an indirect outcome	. 183
1.22.4	Parent training for motor skills as an indirect outcome	. 184
1.22.5	Social-communication interventions for motor skills as an indirect outcom 184	ne
1.23 Bio	omedical interventions aimed at motor skills	. 185
1.23.1	Hormones for motor skills as an indirect outcome	. 185
1.23.2	Nutritional interventions for motor skills as an indirect outcome	. 185
1.24 Psy	chosocial interventions aimed at coexisting mental health problems	. 186
1.24.1	Cognitive-behavioural interventions for anxiety as a direct outcome	. 186
1.25 Pha	armacological interventions aimed at coexisting mental health problems	. 190
1.25.1	SNRIs for ADHD as a direct outcome	. 190
1.26 Bio	omedical interventions aimed at coexisting mental health problems	. 192
1.26.1	Nutritional interventions for ADHD as an indirect outcome	. 192
1.26.2	Nutritional interventions for anxiety as an indirect outcome	. 192
1.26.3	Medical procedures for anxiety as an indirect outcome	. 193
-	vchosocial and pharmacological interventions aimed at coexisting medical of the problems	
1.27.1	Cognitive-behavioural interventions for sleep problems as a direct outcom	ne
1.27.2	Melatonin for sleep problems as a direct outcome	. 196
1.27.3 proble	Combined cognitive-behavioural intervention and melatonin for sleep ms as a direct outcome	. 202
	SNRIs for sleep problems as an indirect outcome	
	omedical interventions aimed at coexisting medical or functional problems.	
1.28.1	Nutritional interventions for sleep problems as an indirect outcome	
1.28.2	Hormones for gastrointestinal symptoms as an indirect outcome	
1.28.3 outcom	Nutritional interventions for gastrointestinal symptoms as a direct or indine	rect
	vchosocial interventions aimed at improving the impact of autism on the	. 214
1.29.1 as an ir	Behavioural interventions for improving the impact of autism on the fami	-
	Cognitive-behavioural interventions for improving the impact of autism on the impact of autism of the impact of	

	Parent training for improving the impact of autism on the family as a direct outcome	
	armacological interventions aimed at improving the impact of autism on the	
	SNRIs for improving the impact of autism on the family as an indirect ne	220
1.31 Bio 220	omedical interventions aimed at improving the impact of autism on the fami 0	ily
1.31.1 as an i	Complementary therapies for improving the impact of autism on the family andirect outcome	-
1.32 Ac	lverse events associated with pharmacological interventions	221
1.32.1	Adverse events associated with anticonvulsants	221
1.32.2	Adverse events associated with antidepressants	222
1.32.3	Adverse events associated with antihistamines	229
1.32.4	Adverse events associated with antioxidants	231
1.32.5	Adverse events associated with antipsychotics	235
1.32.6	Adverse events associated with antivirals	284
1.32.7	Adverse events associated with cognitive enhancers	285
1.32.8	Adverse events associated with melatonin	287
1.32.9	Adverse events associated with opioid antagonists	292
1.32.10	Adverse events associated with SNRIs	295
1.33 Ac	lverse events associated with biomedical interventions	299
1.33.1	Adverse events associated with medical procedures	299
1.33.2	Adverse events associated with nutritional interventions	300
FE	SYCHOSOCIAL INTERVENTIONS AIMED AT CORE EATURES OF AUTISM (OVERALL AUTISTIC EHAVIOURS)	

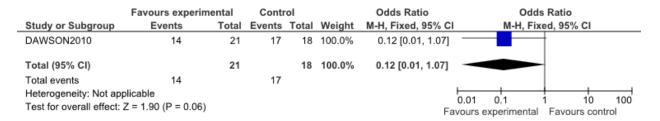
1.1.1 Behavioural interventions aimed at overall autistic behaviours as an indirect outcome

Early Start Denver Model versus treatment-as-usual for overall autistic behaviours as an indirect outcome

Overall autistic behaviours (ADOS severity)

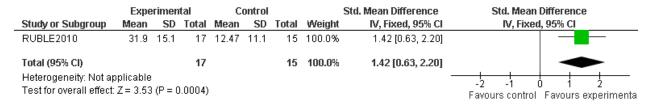


Autism DSM-IV diagnosis (improvement in diagnosis from autistic disorder to PDD-NOS)

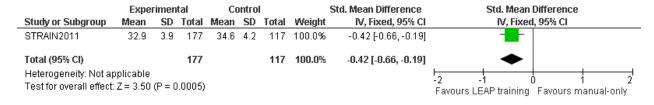


1.1.2 Educational interventions aimed at overall autistic behaviours as a direct outcome

COMPASS versus treatment-as-usual for overall autistic behaviours as a direct outcome



LEAP training versus manual-only control for overall autistic behaviours as a direct outcome



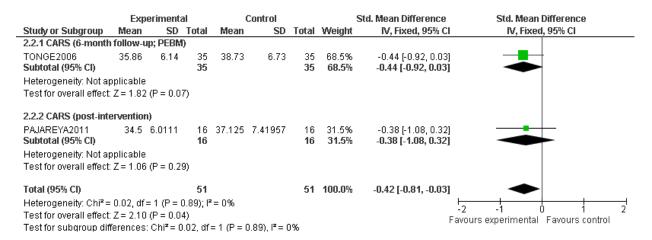
1.1.3 Parent training interventions aimed at overall autistic behaviours as a direct or indirect outcome

Parent training versus treatment-as-usual for overall autistic behaviours as an indirect outcome

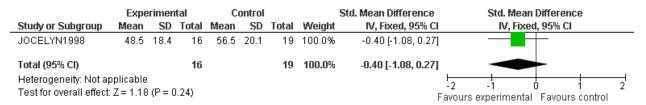
Overall autistic behaviours (DBC-ASA; 6-month follow-up; PEC+PEBM combined)

	Expe	erimental		(Control			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
TONGE2006	22.288971	8.662124	68	22.89	10.42	35	100.0%	-0.06 [-0.47, 0.34]	-	
Total (95% CI)			68			35	100.0%	-0.06 [-0.47, 0.34]	•	
Heterogeneity: Not ap Test for overall effect:	•	0.76)						F	-2 -1 0 1 avours experimental Favours control	2

Overall autistic behaviours (CARS)

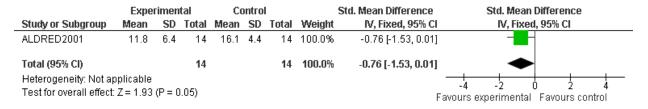


Parent and day-care staff training versus standard day-care for overall autistic behaviours as a direct outcome



1.1.4 Social-communication interventions aimed at overall autistic behaviours as an indirect outcome

Child's Talk versus treatment-as-usual for overall autistic behaviours as an indirect outcome



1.2 PSYCHOSOCIAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

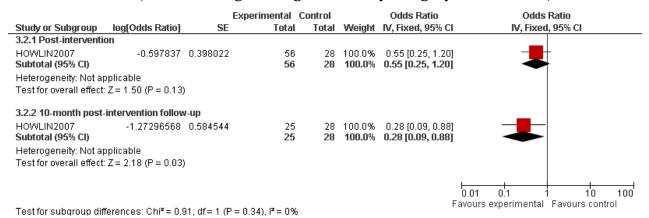
1.2.1 AAC intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

PECS training for teachers versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Communication (odds of being in a higher severity category on ADOS-G)

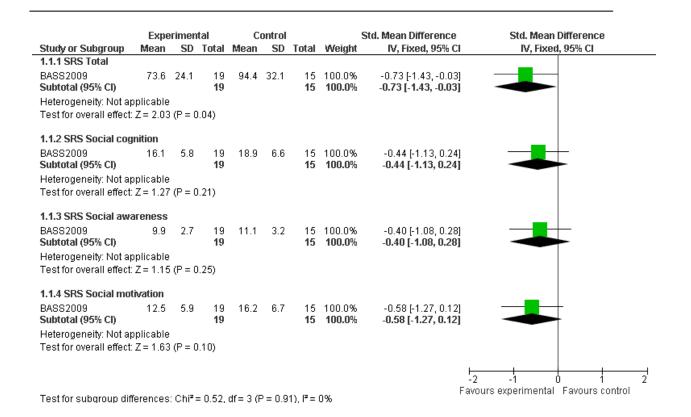
	ental	Contr	ol		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI			
DAWSON2010	17	24	23	24	100.0%	0.74 [0.56, 0.97]	_			
Total (95% CI)		24		24	100.0%	0.74 [0.56, 0.97]	•			
Total events	17		23							
Heterogeneity: Not ap Test for overall effect:					- Fav	0.5 0.7 1 1.5 2				

Social interaction (odds of being in a higher severity category on ADOS-G)



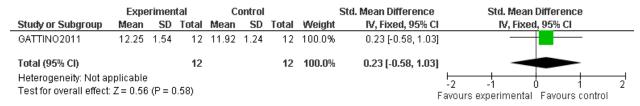
1.2.2 Animal-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Horseback riding versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome



1.2.3 Arts-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

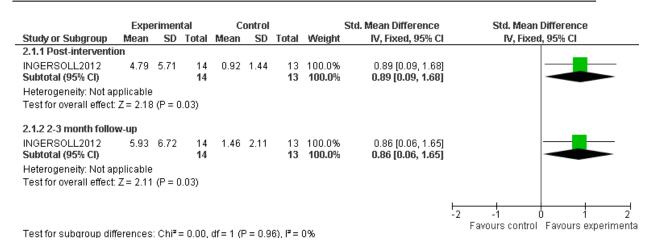
RMT versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



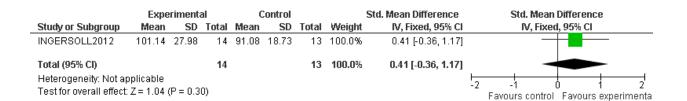
1.2.4 Behavioural intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

RIT versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Examiner-child joint/shared attention (ESCS IJA)

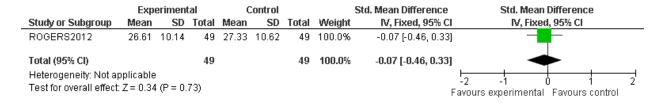


Social and emotional development (Bayley-Social-emotional subscale)

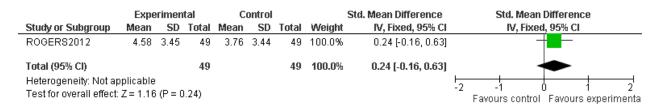


P-ESDM versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Social affect (ADOS-T)



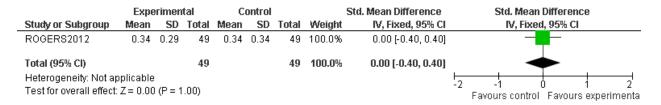
Imitation



Orienting to social stimuli

	Ехре	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ROGERS2012	0.47	0.28	49	0.43	0.35	49	100.0%	0.13 [-0.27, 0.52]	-
Total (95% CI)			49			49	100.0%	0.13 [-0.27, 0.52]	*
Heterogeneity: Not ap Test for overall effect:			1.54)						-2 -1 0 1 2 Favours control Favours experimenta

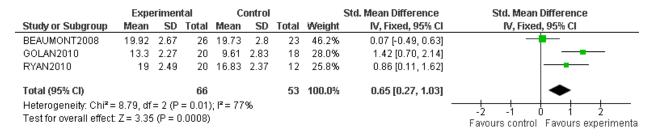
Orienting to joint attention



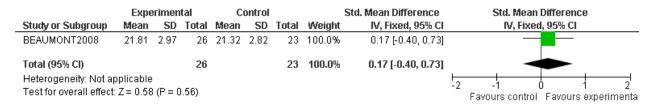
1.2.5 Cognitive interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

ERT versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Emotion recognition



Recognising emotion from posture



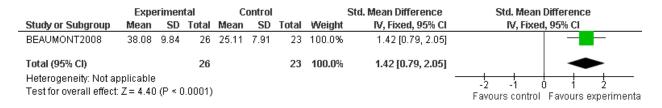
Emotion understanding (EmoVoc)

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
GOLAN2010	12.5	3.09	20	9.11	3.45	18	100.0%	1.02 [0.34, 1.70]	
Total (95% CI)			20			18	100.0%	1.02 [0.34, 1.70]	
Heterogeneity: Not ap Test for overall effect:	•).003)						-2 -1 0 1 2 Favours control Favours experimenta

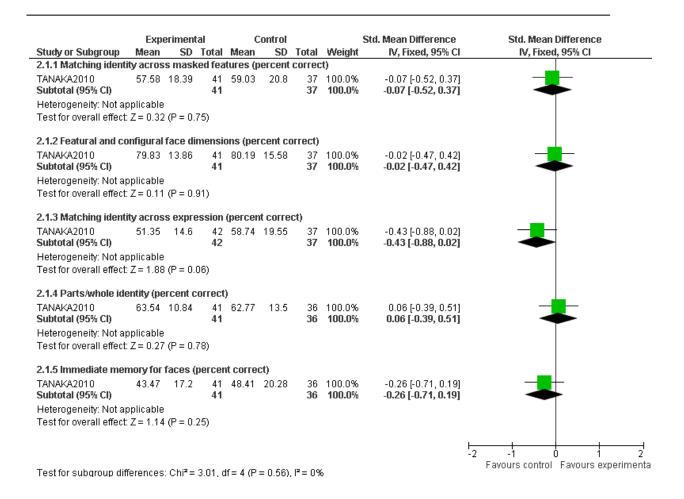
Emotion regulation

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 Emotion regulat	tion and	socia	skills	(ERSSQ)				
BEAUMONT2008 Subtotal (95% CI)	57.38	13.4	26 26	40.14	10.69	23 23	100.0% 100.0 %	1.39 [0.76, 2.02] 1.39 [0.76, 2.02]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 4.32	(P < 0).0001)						
1.4.2 Anxiety coping	skills (Ja	ames	and the	e Maths	Test)				
BEAUMONT2008 Subtotal (95% CI)	5.08	2.23	26 26	2.64	1.56	23 23	100.0% 100.0 %	1.23 [0.62, 1.85] 1.23 [0.62, 1.85]	
Heterogeneity: Not ap Test for overall effect:			1 00011						
restroi overali ellect.	2-5.55	() -0	,.0001)						
1.4.3 Bullying coping	skills (D	ylan is	s Being	Tease	I)				
BEAUMONT2008 Subtotal (95% CI)	3.81	1.58	26 26	2	1.11	23 23	100.0% 100.0 %	1.29 [0.67, 1.91] 1.29 [0.67, 1.91]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 4.07	(P < 0	0.0001)						
		-	·						
								-	-2 -1 0 1 2
Test for subgroup diff	erences	: Chi²:	= 0.12,	df = 2 (F	9 = 0.94), I² = 0'	%		Favours control Favours experimen

Social skills (SSQ)

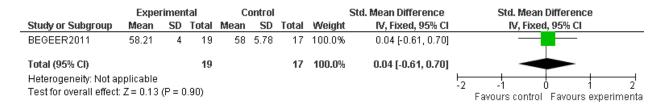


FRT versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

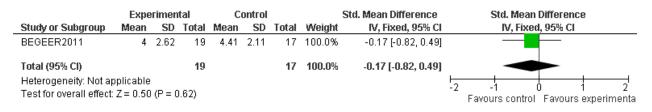


ToM versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

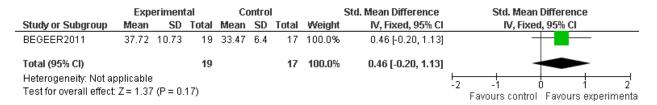
Theory of Mind (ToM test, total score)



Empathy (Index of Empathy for Children and Adolescents)



Emotional awareness (LEAS-C)

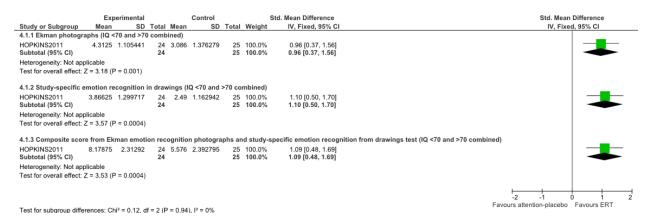


Maladaptive social behaviour (CSBQ)

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Me	an Differ	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ked, 95%	CI	
BEGEER2011	34.8	17.6	19	40	14.54	17	100.0%	-0.31 [-0.97, 0.35]					
Total (95% CI)			19			17	100.0%	-0.31 [-0.97, 0.35]					
Heterogeneity: Not ap Test for overall effect:).35)					F	-2 avours	-1 experimen	0 tal Favo	urs contro	

Computer-based ERT versus software training (attention-placebo) for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

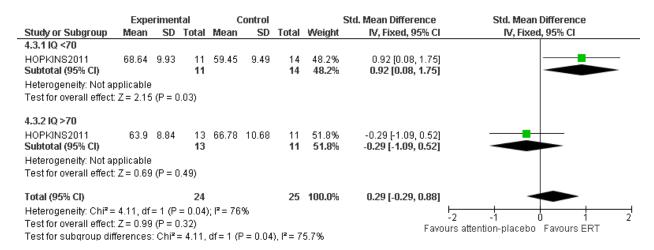
Emotion recognition



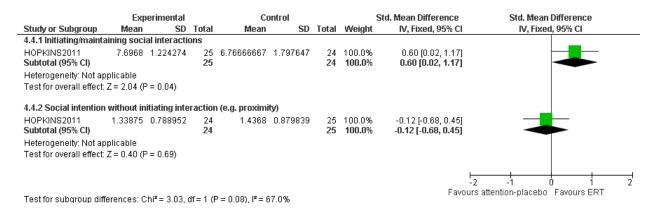
Face recognition

	Expe	rimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.2.1 Benton short fo	rm (IQ <70 aı	nd >70 com	bined)						
HOPKINS2011 Subtotal (95% CI)	17.245417	4.596495	24 24	13.476	3.819834	25 25	100.0% 100.0 %	0.88 [0.29, 1.47] 0.88 [0.29, 1.47]	
Heterogeneity: Not ap Test for overall effect:	•	0.003)							
4.2.2 Benton long for	m (IQ <70 an	d >70 comb	ined)						
HOPKINS2011 Subtotal (95% CI)	36.973333	6.733997	24 24	30.1828	4.973625	25 25	100.0% 100.0 %	1.13 [0.53, 1.74] 1.13 [0.53, 1.74]	
Heterogeneity: Not ap Test for overall effect:	•	0.0003)							
								<u>⊢</u> -2	-1 0 1

Social skills (SSRS standardised score)



Positive social interaction (behavioural observation)

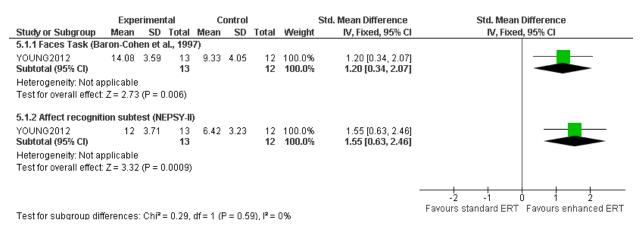


Negative social interaction (behavioural observation)

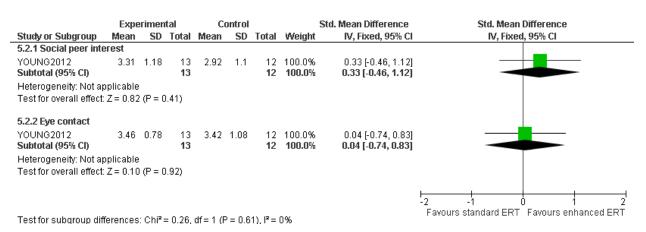
	Exp	erimental			Control			Std. Mean Difference		Std. Mean	Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CL		
HOPKINS2011	0.63125	0.863339	24	1.5348	1.131922	25	100.0%	-0.88 [-1.47, -0.29]					
Total (95% CI)			24			25	100.0%	-0.88 [-1.47, -0.29]		~			
Heterogeneity: Not ap Test for overall effect		P = 0.003)							-2	-1 Favours ERT	0 Favours	1 attentio	n-plac

Enhanced ERT versus standard ERT for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Emotion recognition



Positive social behaviours



Gaze aversion

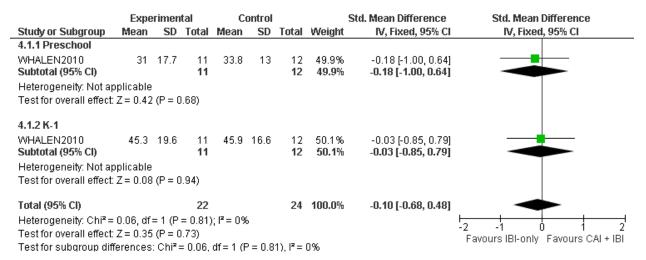
	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
YOUNG2012	2.85	0.8	13	3	1.21	12	100.0%	-0.14 [-0.93, 0.64]	
Total (95% CI)			13			12	100.0%	-0.14 [-0.93, 0.64]	
Heterogeneity: Not a Test for overall effect		(P = 0	1.72)						-2 -1 0 1 2 Favours enhanced ERT Favours standard ERT

1.2.6 Educational interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

LEAP training versus manual-only control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
STRAIN2011	42.1	12.6	177	32.7	11.9	117	100.0%	0.76 [0.52, 1.00]	-
Total (95% CI) Heterogeneity: Not ap Test for overall effect:			177).00001	1)		117	100.0%	0.76 [0.52, 1.00]	-2 -1 0 1 2 Favours manual-only Favours LEAP training

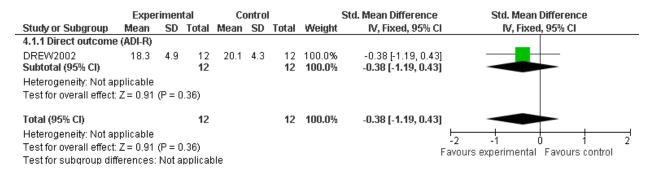
Combined TeachTown and IBI versus IBI-only for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



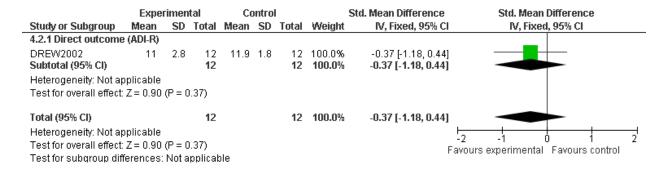
1.2.7 Parent training interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

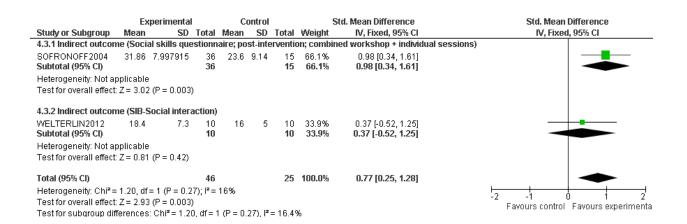
Reciprocal social interaction



Nonverbal communication



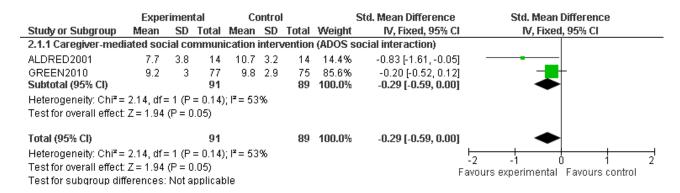
Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



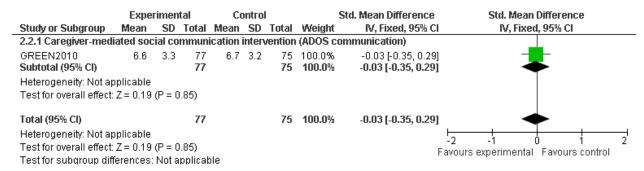
1.2.8 Social-communication interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Caregiver- or preschool-teacher- mediated social-communication interventions versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

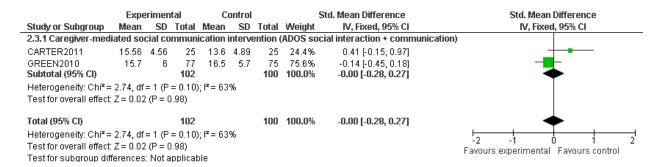
Social interaction



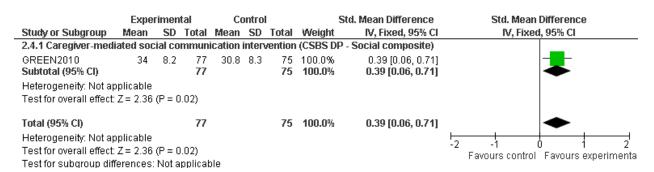
Communication



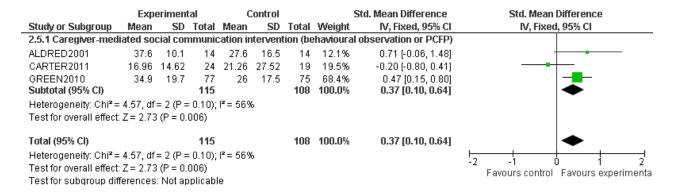
Social interaction and communication



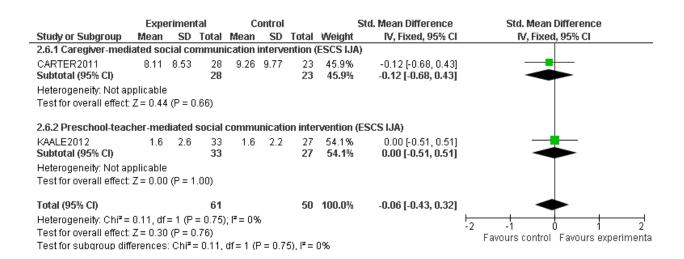
Parent-rated social-communication



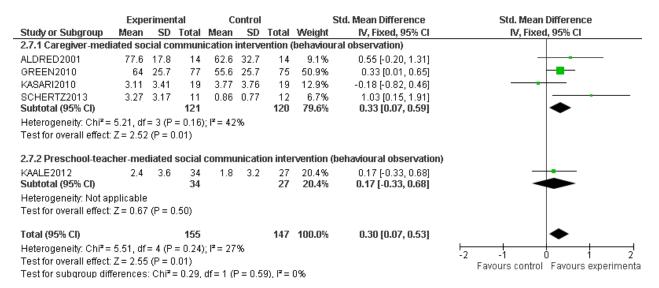
Communication acts



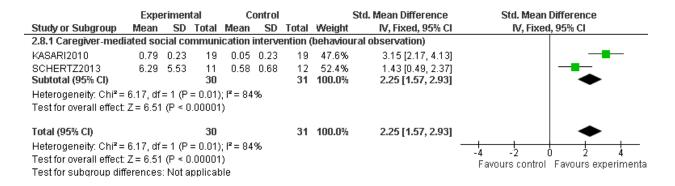
Examiner-child joint/shared attention



Parent-child joint/shared attention



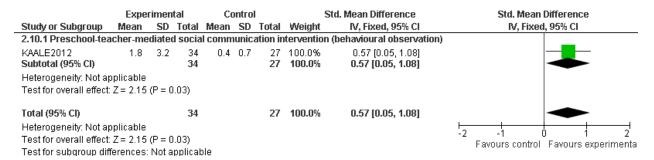
Parent-child joint attention responses



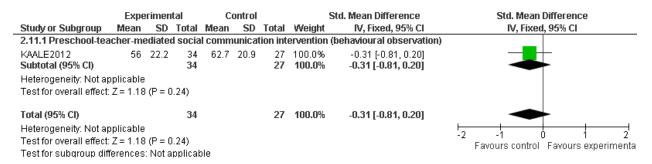
Parent-child joint engagement

	Exp	erimen	tal	(ontrol		9	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.9.1 Caregiver-med	liated so	cial cor	nmuni	cation ir	iterven	tion (be	havioural	observation)	
KASARI2010 Subtotal (95% CI)	42.85	19.96	19 19	27.87	14.01	19 19	36.9% 36.9 %	0.85 [0.18, 1.52] 0.85 [0.18, 1.52]	
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z = 2.50	P = 0	01)						
2.9.2 Preschool-tead	cher-med	diated s	ocial c	ommur	nication	interv	ention (be	havioural observation)	
KAALE2012 Subtotal (95% CI)	57.3	22.8	34 34	49.2	19.9	27 27	63.1% 63.1 %	0.37 [-0.14, 0.88] 0.37 [-0.14, 0.88]	
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z=1.43	(P = 0.	15)						
Total (95% CI)			53			46	100.0%	0.55 [0.14, 0.95]	•
Heterogeneity: Chi² =	= 1.25, df	= 1 (P =	0.26);	l²= 209	6				-2 -1 0 1 2
Test for overall effect	: Z = 2.65	(P = 0.	008)						Favours control Favours experiment
Test for subgroup di	fferences	Chi²=	1.25 0	f=1/P	= 0.26)	$I^2 = 20$	3%		ravours control ravours experimen

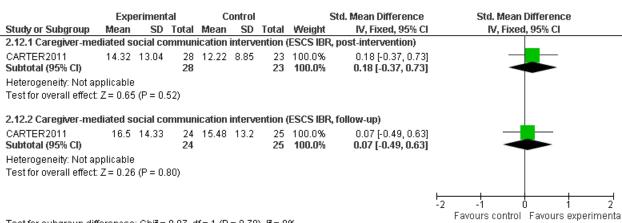
Teacher-child joint/shared attention



Teacher-child joint engagement

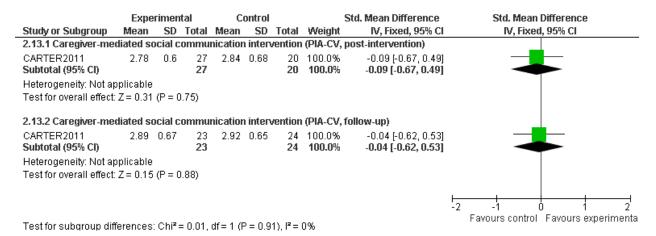


Behaviour requests

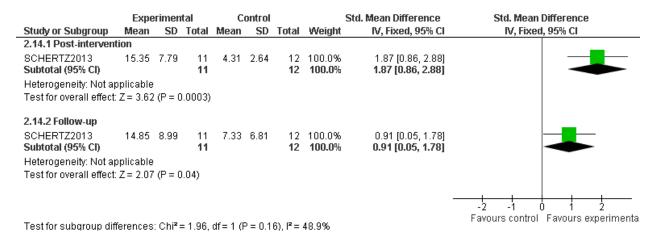


Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I^2 = 0%

Non-verbal communication

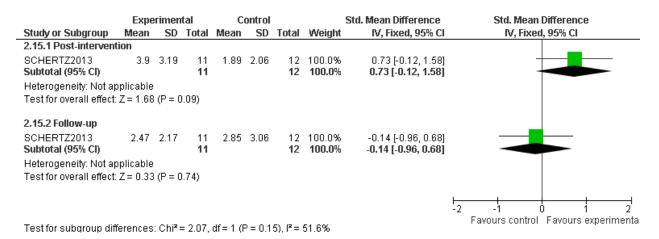


Focusing on faces (behavioural observation; caregiver-mediated)



Autism: the management and support of children and young people on the autism spectrum

Turn-taking (behavioural observation; caregiver-mediated)



Peer-mediated (and/or therapist-mediated) social-communication interventions versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

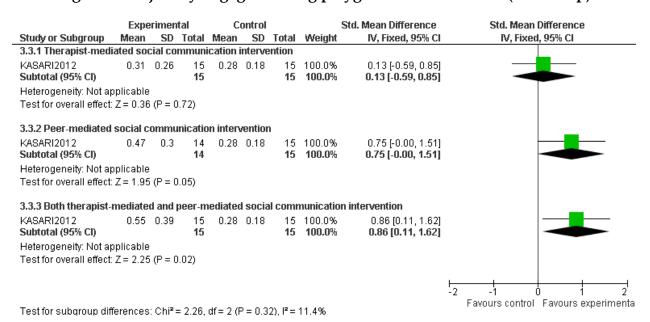
Peer-child joint engagement

	Expe	eriment	al	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 Peer-mediated	social c	ommur	nication	n interv	ention/	(beha	vioural o	servations of social interactions with unfamiliar TD peer or % time in joi	nt engagement in playground)
KASARI2012	0.46	0.36	15	0.42	0.31	14	27.7%	0.12 [-0.61, 0.84]	
ROEYERS1996	20.24	10.5	48	11	9.19	37	72.3%	0.92 [0.47, 1.37]	-
Subtotal (95% CI)			63			51	100.0%	0.70 [0.31, 1.08]	•
Heterogeneity: Chi² =	: 3.38, df	= 1 (P =	0.07);	$ ^2 = 70$	%				
Test for overall effect	Z= 3.56	(P = 0.	0004)						
Total (95% CI)			63			51	100.0%	0.70 [0.31, 1.08]	•
Heterogeneity: Chi²=	: 3.38, df	= 1 (P =	0.07);	$I^2 = 70$	%				2 1 1 2
Test for overall effect	Z= 3.58	i (P = 0.	0004)						Fayours control Fayours experimenta
Test for subgroup dif	ferences	: Not ap	plicab	e					, around contact if around experimenta

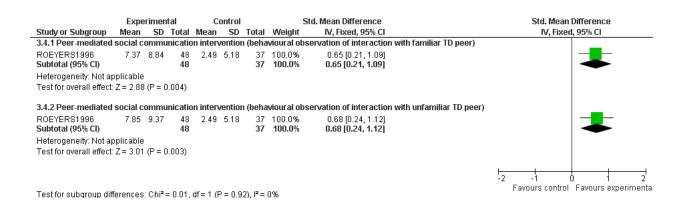
Percentage of time jointly engaged during playground observations (post-intervention)

	Eunc	erimen	ıtal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean	SD		Weight		IV, Fixed, 95% CI
3.2.1 Therapist-medi							weight	IV, I IAGU, 33 /II CI	10,11AGG, 53/8 CI
KASARI2012		0.28	15		0.31		100.0%	0.001.070.070	
Subtotal (95% CI)	0.43	0.20	15	0.42	0.31	14 14	100.0%		
Heterogeneity: Not ap	nlicabla		13				100.074	0.03 [-0.10, 0.10]	
Test for overall effect:			0.93)						
3.2.2 Peer-mediated	social c	ommu	ınicatio	n interv	/entio	n			
KASARI2012	0.46	0.36	15	0.42	0.31	14	100.0%	0.12 [-0.61, 0.84]	
Subtotal (95% CI)			15			14	100.0%	0.12 [-0.61, 0.84]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.31	(P = 0)	0.76)						
3.2.3 Both therapist-	mediate	d and	peer-m	ediated	l socia	al com	nunicatio	on intervention	
KASARI2012	0.42	0.27	15	0.42	0.31	14	100.0%	0.00 [-0.73, 0.73]	
Subtotal (95% CI)			15			14	100.0%	0.00 [-0.73, 0.73]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.00	(P = 1	.00)						
									-2 -1 0 1
Test for subgroup diff	ferences	: Chi²:	= 0.05,	df = 2 (F	o = 0.9	(7), I ² =	0%		Favours control Favours experime

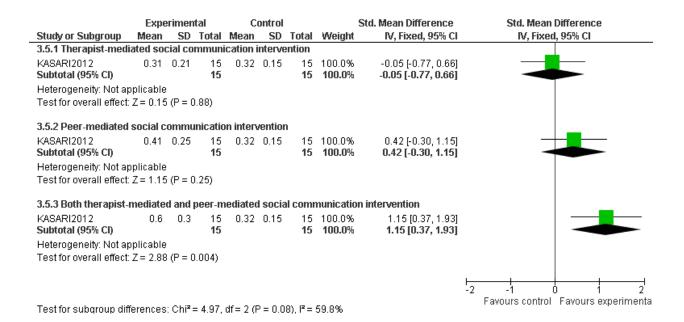
Percentage of time jointly engaged during playground observations (follow-up)



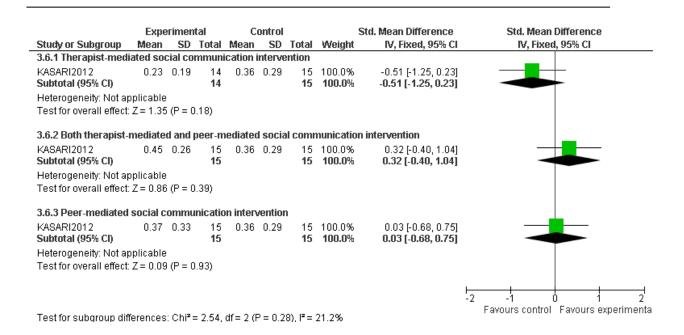
Child-initiated social interactions



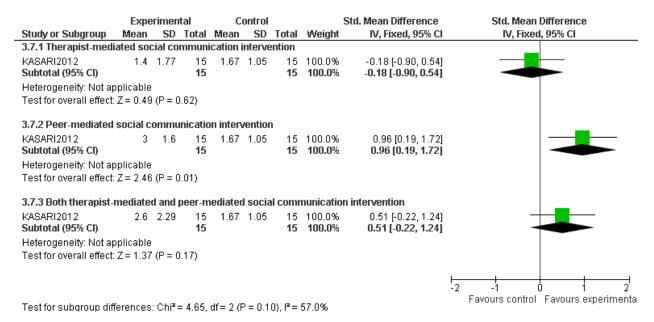
Social network salience (SNS; post-intervention)



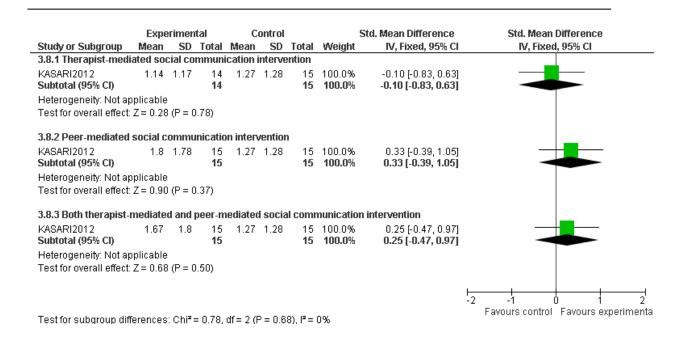
Social network salience (SNS; follow-up)



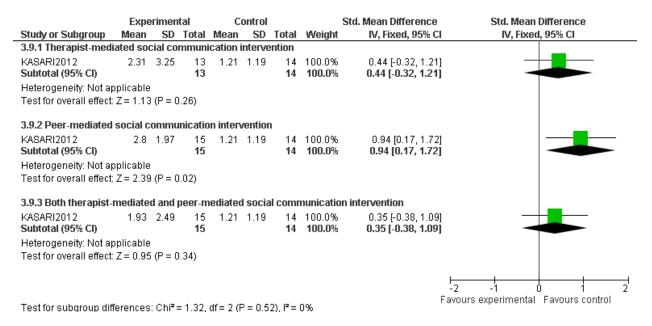
Number of received friendship nominations (SNS; post-intervention)



Number of received friendship nominations (SNS; follow-up)



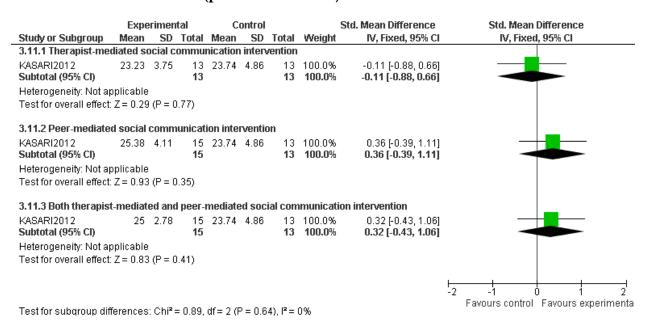
Number of times child identified as someone other children don't like to 'hang out with' (SNS; post-intervention)



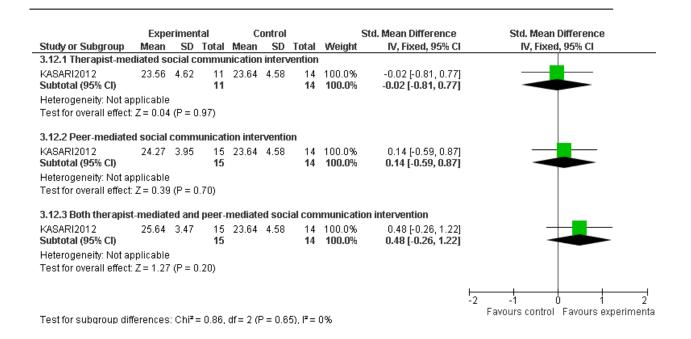
Number of times child identified as someone other children don't like to 'hang out with' (SNS; follow-up)

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD		Mean	SD	Total	Weight		
3.10.1 Therapist-med	diated so	ocial c	ommu	nication	inter	rention			
KASARI2012	1.42	2.5	12	1.79	1.81	14	100.0%	-0.17 [-0.94, 0.61]	1 —
Subtotal (95% CI)			12			14	100.0%	-0.17 [-0.94, 0.61]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.42	(P = 0)	1.67)						
3.10.2 Peer-mediated	d social	comm	unicati	ion inte	rventio	on			
KASARI2012	2.07	2.05	15	1.79	1.81	14	100.0%	0.14 [-0.59, 0.87]	1 —
Subtotal (95% CI)			15			14	100.0%	0.14 [-0.59, 0.87]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.38	(P = 0)	1.71)						
3.10.3 Both therapist	-mediate	ed and	I реег-ı	mediate	ed soc	ial con	nmunicat	ion intervention	
KASARI2012	2.73	2.49	15	1.79	1.81	14	100.0%		
Subtotal (95% CI)			15			14	100.0%	0.42 [-0.32, 1.15]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.11	(P = 0)	1.27)						
									2 -1 0 1
Test for subgroup diff	erences	· Chi² :	= 1 15	df = 2 / F	2=05	6) I ² =	n%		Favours experimental Favours contro

Teacher-rated social skills (post-intervention)

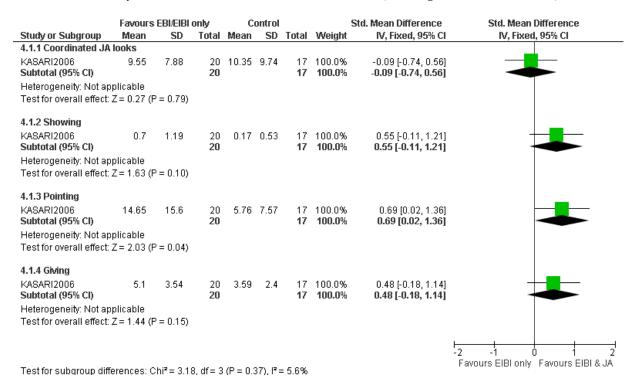


Teacher-rated social skills (follow-up)

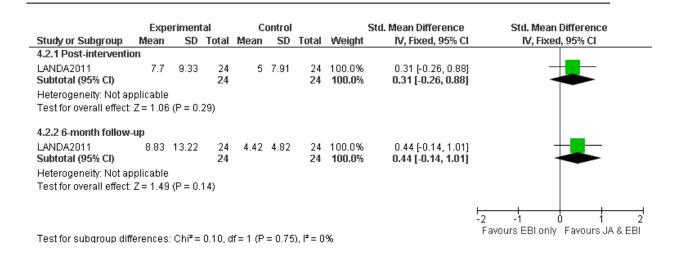


Joint attention training and EBI/EIBI versus EBI/EIBI only for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

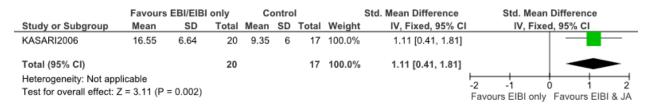
Examiner-child joint attention - Child-initiated JA (EScs, post-intervention)



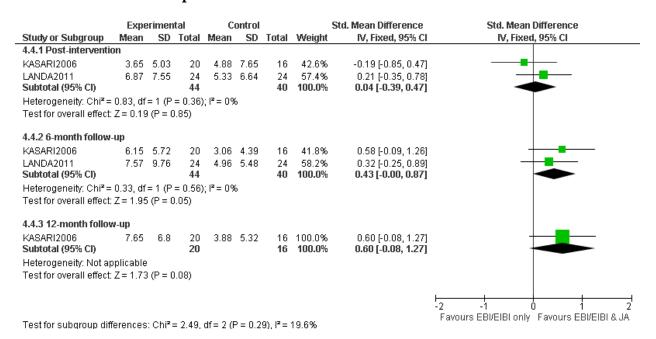
Examiner-child joint attention- Child-initiated JA (CSBSDP)



Examiner-child joint attention - Child responding to JA (EScs, post-intervention)



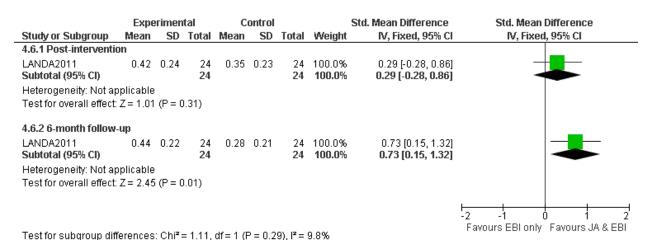
Examiner-child shared positive affect



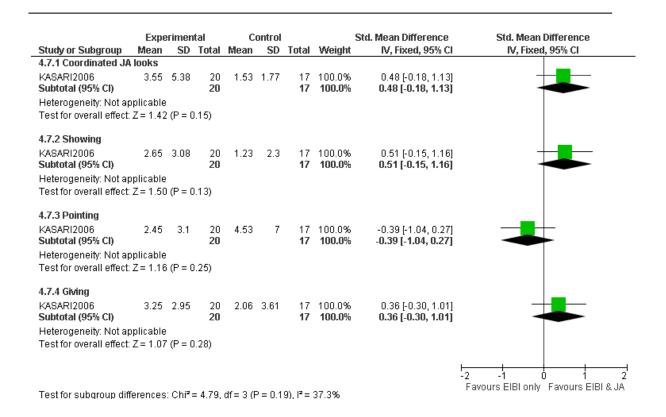
Examiner-child joint attention, shared positive affect & utterance (EScs)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.5.1 Post-interventio	n								
KASARI2006	1.8	2.57	20	1.68	3.09	16	100.0%	0.04 [-0.62, 0.70]	
Subtotal (95% CI)			20			16	100.0%	0.04 [-0.62, 0.70]	-
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.12	(P = 0)	.90)						
4.5.2 6-month follow-	up								
KASARI2006	4.1	4.64	20	1.75	3.38	16	100.0%	0.56 [-0.12, 1.23]	+-
Subtotal (95% CI)			20			16	100.0%	0.56 [-0.12, 1.23]	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 1.62	(P = 0)	.10)						
4.5.3 12-month follow	/-up								
KASARI2006	5.3	5.68	20	1.56	3.1	16	100.0%	0.77 [0.09, 1.46]	—
Subtotal (95% CI)			20			16	100.0%	0.77 [0.09, 1.46]	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 2.22	(P = 0)	.03)						
									-2 -1 0 1
Test for subgroup differ		OL:2 -	0.44 -4	f = 0 /D	- 0.00	N 12 - 4	10.40/		Favours EIBI only Favours EIBI &

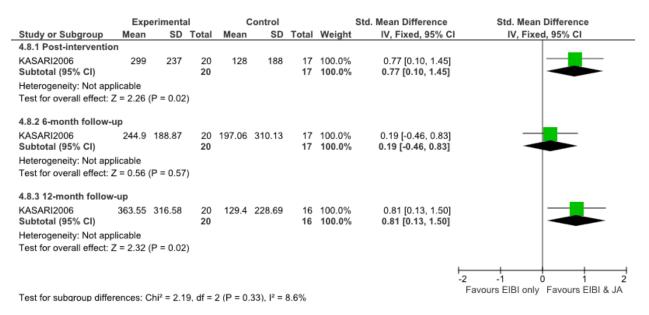
Examiner-child socially engaged imitation (SEI)



Mother-child joint attention - Child-initiated JA (post-intervention)



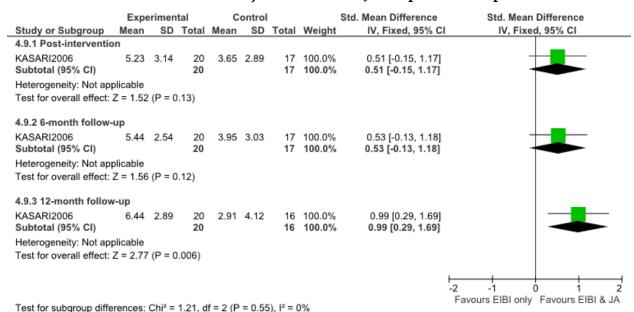
Mother-child joint attention: Child-initiated JA (duration in seconds)



Examiner-child and mother-child joint attention: JA initiation composite

	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
4.9.1 Post-interventio	n								
KASARI2006	5.23	3.14	20	3.65	2.89	17	100.0%	0.51 [-0.15, 1.17]	+
Subtotal (95% CI)			20			17	100.0%	0.51 [-0.15, 1.17]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 1.52	(P = 0	.13)						
4.9.2 6-month follow-	up								
KASARI2006	5.44	2.54	20	3.95	3.03	17	100.0%	0.53 [-0.13, 1.18]	+-
Subtotal (95% CI)			20			17	100.0%	0.53 [-0.13, 1.18]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 1.56	(P = 0	.12)						
4.9.3 12-month follow	/-up								
KASARI2006	6.44	2.89	20	2.91	4.12	16	100.0%	0.99 [0.29, 1.69]	
Subtotal (95% CI)			20			16	100.0%	0.99 [0.29, 1.69]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 2.77	(P = 0	.006)						
									-2 -1 0 1
Test for subgroup diffe	rencee.	Chi2 -	121 4	f = 2 (P	- 0.54	S) 12 - 0	19/-		Favours EIBI only Favours EIBI & J

Examiner-child and mother-child joint attention: JA responses composite

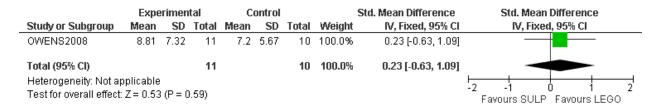


LEGO® therapy versus SULP for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

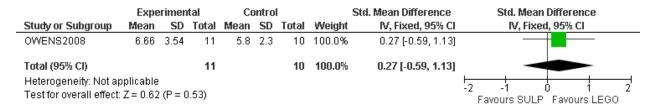
Social interaction (GARS)

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
OWENS2008	7.44	2.2	16	9.27	2.66	15	100.0%	-0.73 [-1.46, -0.00]	
Total (95% CI)			16			15	100.0%	-0.73 [-1.46, -0.00]	
Heterogeneity: Not a Test for overall effect	•).05)						-2 -1 0 1 2 Favours LEGO Favours SULP

Frequency of child-initiated social interactions with TD peers (behavioural observation)

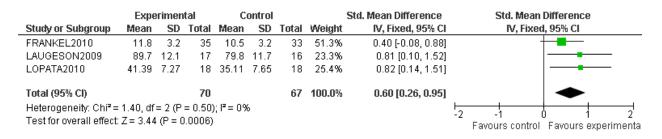


Duration of all social interactions with TD peers (behavioural observation)



Social skills group versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

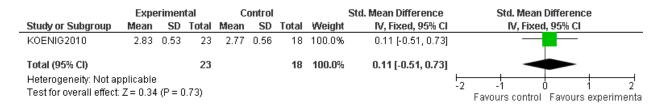
Social skills (SSRS Assertion/Social skills standardized score or BASC-2-PRS)



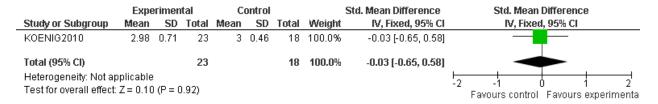
Social impairment (SRS total)

	Exp	erimen	tal	(Control			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
LOPATA2010	73.67	11.42	18	82.53	13.77	17	100.0%	-0.69 [-1.37, -0.00]	_		
Total (95% CI)			18			17	100.0%	-0.69 [-1.37, -0.00]	-		
Heterogeneity: Not ap Test for overall effect			05)					F	-2 -1 avours experimental	D 1 Favours contr	——— rol

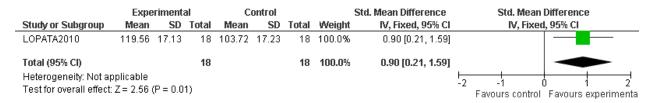
Adaptive social behaviour (SCI Pro-social index)



Capacity for social interactions (SCI Social initiation index)



Study-specific targeted social skills (ASC)



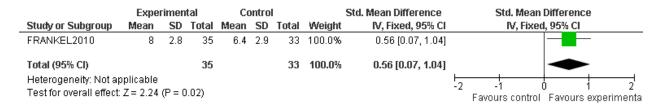
Social skills knowledge

	Expe	rimen	tal	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
6.6.1 Self-rated (TAS	SSK)								
LAUGESON2009	19.6	1.4	17	13.3	3.8	16	39.7%	2.17 [1.29, 3.06]	
Subtotal (95% CI)			17			16	39.7%	2.17 [1.29, 3.06]	•
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Z= 4.83	(P < 0	0.00001)					
6.6.2 Researcher-ra	ted (SKA)							
LOPATA2010	58.83	11.5	18	43.31	13.86	18	60.3%	1.19 [0.48, 1.91]	
Subtotal (95% CI)			18			18	60.3%	1.19 [0.48, 1.91]	•
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Z = 3.26	(P = 0	0.001)						
Total (95% CI)			35			34	100.0%	1.58 [1.03, 2.14]	•
Heterogeneity: Chi ^z =	: 2.87, df:	= 1 (P	= 0.09)	; I² = 65	%			_	-4 -2 0 2 4
Test for overall effect	: Z = 5.58	(P < 0).00001)					-4 -2 U 2 4 Favours control Favours experimer
Test for subgroup dif	ferences	: Chi²:	= 2.87.	df = 1 (F	o.09), $I^2 = 6$	5.1%		ravouis connoi Favours experimer

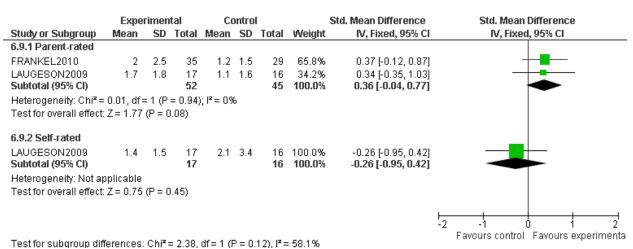
Feelings of loneliness (Loneliness Scale)

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Differe	ence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95%	CI
FRANKEL2010	31.4	8.5	35	38.9	13.3	32	100.0%	-0.67 [-1.16, -0.18]	_	
Total (95% CI)			35			32	100.0%	-0.67 [-1.16, -0.18]	-	
Heterogeneity: Not ap Test for overall effect:	•		0.008)					F	-2 -1 0 avours experimental Favo	1 2

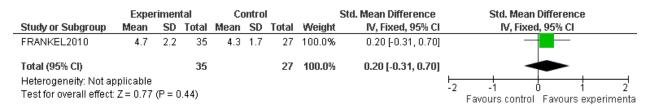
Popularity (self-rated PHS popularity)



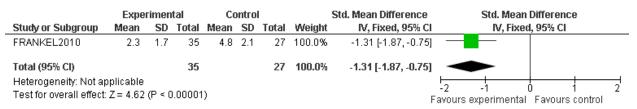
Number of times child invited to a play date (QPQ Guest)



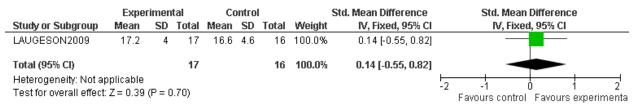
Time spent in interactive activities (QPQ Engage)



Time spent in minimally interactive activities (QPQ Disengage)



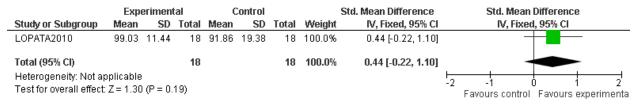
Quality of friendships (self-rated FQS)



Positive treatment response ('much improved/very improved' on CGI-improvement)

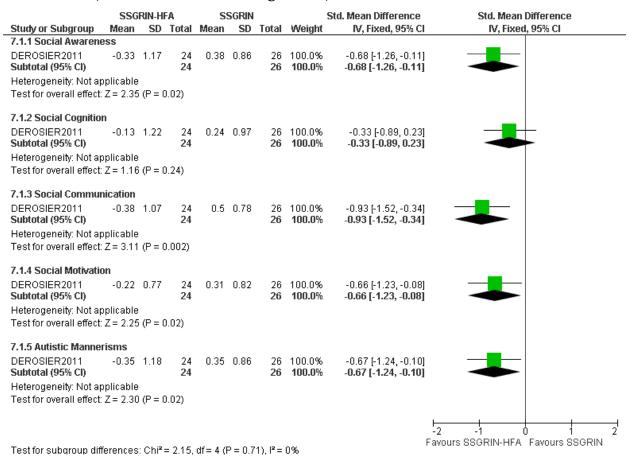
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
KOENIG2010	16	23	0	18	100.0%	26.13 [1.67, 407.99]	
Total (95% CI)		23		18	100.0%	26.13 [1.67, 407.99]	
Total events	16		0				
Heterogeneity: Not as	pplicable						0.005 0.1 1 10 200
Test for overall effect	Z = 2.33 (F	P = 0.02)				Favours control Favours experimen

Emotion recognition (DANVA2)

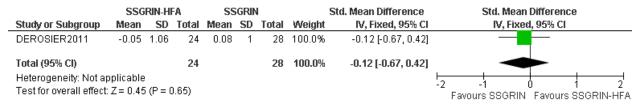


Social skills group modified for autism versus standard social skills group for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Social skills (SRS standardized change score)



Social self-efficacy (self-rated Social Self-efficacy Scale; standardized change score)



Feelings of loneliness (Social Dissatisfaction Questionnaire; standardized change score)

	SSG	RIN-HI	Α	S	SGRIN			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
DEROSIER2011	0.08	1.23	24	-0.07	0.79	28	100.0%	0.15 [-0.40, 0.69]	_
Total (95% CI)			24			28	100.0%	0.15 [-0.40, 0.69]	
Heterogeneity: Not ap Test for overall effect:).60)						-2 -1 0 1 2 Favours SSGRIN Favours SSGRIN-HFA

1.3 PSYCHOSOCIAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

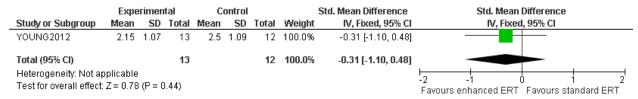
1.3.1 Behavioural interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

ESDM or P-ESDM versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Expe	erimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.1.1 ESDM (RBS)									
DAWSON2010 Subtotal (95% CI)	16.7	13.1	24 24	22	16.3	21 21	31.0% 31.0 %	-0.35 [-0.95, 0.24] - 0.35 [-0.95, 0.24]	
Heterogeneity: Not as	nnlicable						0 110 11	5155 [5155, 512.7]	
Test for overall effect:	•		0.24)						
4.1.2 P-ESDM (ADOS	-T)								
ROGERS2012 Subtotal (95% CI)	3.96	1.86	49 49	3.82	2.04	49 49	69.0% 69.0 %	0.07 [-0.32, 0.47] 0.07 [-0.32, 0.47]	<u> </u>
Heterogeneity: Not ag	nlicable		40			-10	00.07	0.01 [-0.02, 0.41]	\top
Test for overall effect:	•).72)						
Total (95% CI)			73			70	100.0%	-0.06 [-0.39, 0.27]	•
Heterogeneity: Chi² = Test for overall effect:		•); I² = 27	%			 -2 	the second secon
Test for subgroup diff				df = 1 (F	o = 0.2	4), l²=	27.4%	ravi	Juis experimental Favours control

1.3.2 Cognitive intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Enhanced ERT versus standard ERT for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



1.3.3 Parent training intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Combined parent training and antipsychotic versus antipsychotic-only for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Comb. ris	peridone	+ PT	Risper	idone d	only		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
AMAN2009	10.11	3.83	55	11.86	4.47	40	100.0%	-0.42 [-0.83, -0.01	
Total (95% CI)			55			40	100.0%	-0.42 [-0.83, -0.01]	•
Heterogeneity: Not ap Test for overall effect:	•	= 0.04)							-2 -1 0 1 2 Comb. risperidone + PT Risperidone only

1.3.4 Social-communication intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

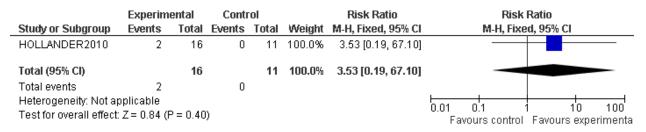
Caregiver-mediated social-communication intervention (PACT) versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Diffe	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95	% CI	
GREEN2010	3	1.7	77	3.5	1.6	75	100.0%	-0.30 [-0.62, 0.02]	-		
Total (95% CI)			77			75	100.0%	-0.30 [-0.62, 0.02]	•		
Heterogeneity: Not ap Test for overall effect:	•).06)					F	-2 -1 0 avours experimental Fav	/ours contro	

1.4 PHARMACOLOGICAL INTERVENTIONS AIMED AT CORE FEATURES OF AUTISM (OVERALL AUTISTIC BEHAVIOURS)

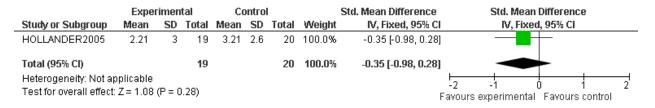
1.4.1 Anticonvulsants for overall autistic behaviours as an indirect outcome

Divalproex sodium versus placebo for overall autistic behaviours as an indirect outcome



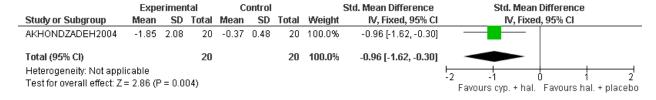
1.4.2 Antidepressants for overall autistic behaviours as an indirect outcome

Fluoxetine versus placebo for overall autistic behaviours as an indirect outcome



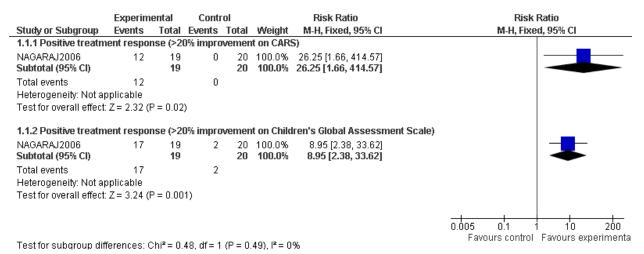
1.4.3 Antihistamines for overall autistic behaviours as an indirect outcome

Cyproheptadine and haloperidol versus placebo and haloperidol for overall autistic behaviours as an indirect outcome

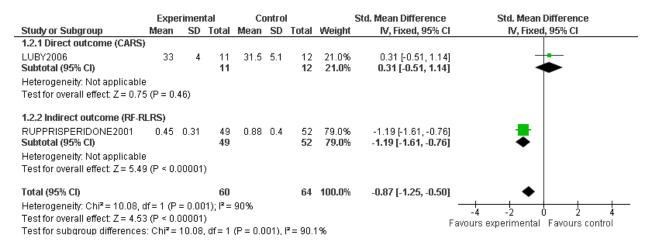


1.4.4 Antipsychotics for overall autistic behaviours as a direct or indirect outcome

Risperidone versus placebo for overall autistic behaviours as a direct outcome

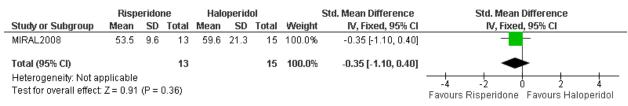


Risperidone versus placebo for overall autistic behaviours as a direct or indirect outcome

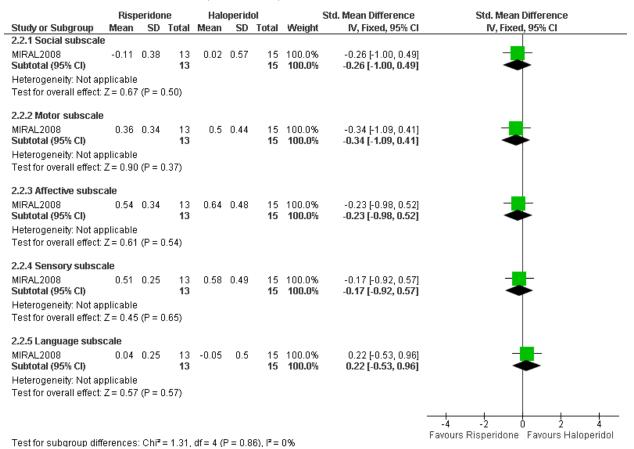


Risperidone versus haloperidol for overall autistic behaviours as a direct outcome

Overall autistic behaviours (Turgay DSM-IV PDD Rating Scale)

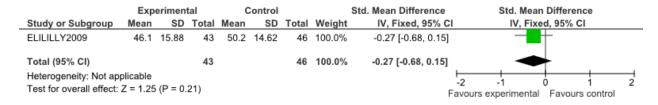


Overall autistic behaviours (RF-RLRS)



1.4.5 SNRIs for overall autistic behaviours as an indirect outcome

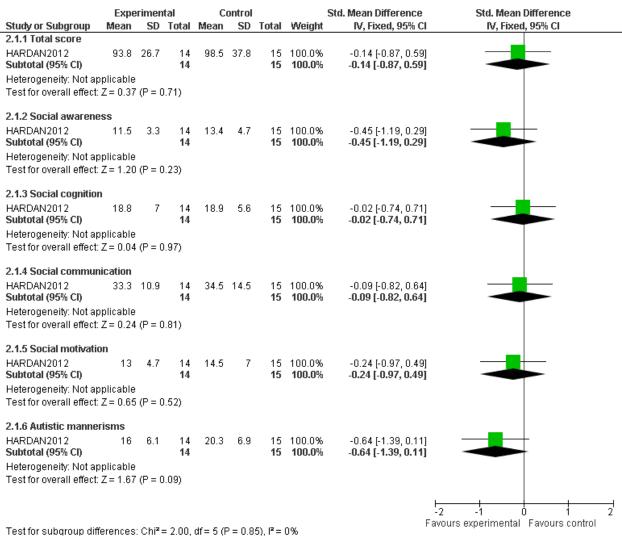
Atomoxetine versus placebo for overall autistic behaviours as an indirect outcome



1.5 PHARMACOLOGICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

1.5.1 Antioxidants for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

N-acetylcysteine versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



1.6 PHARMACOLOGICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

1.6.1 Antidepressants for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

SSRIs versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

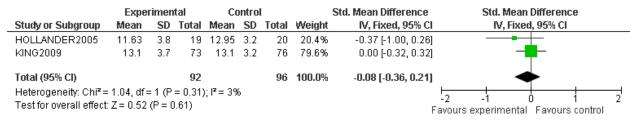
Global positive treatment response ('much improved/very improved' on CGI-improvement)

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2009	24	73	26	76	100.0%	0.96 [0.61, 1.51]	-
Total (95% CI)		73		76	100.0%	0.96 [0.61, 1.51]	•
Total events	24		26				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.86)				0.1 0.2 0.5 1 2 5 10 Favours control Favours experimenta

Global positive treatment response (>25% improvement on CYBOCS-PDD & 'much improved/very improved' on CGI-improvement)

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2009	15	73	10	76	100.0%	1.56 [0.75, 3.25]	+
Total (95% CI)		73		76	100.0%	1.56 [0.75, 3.25]	
Total events	15		10				
Heterogeneity: Not as	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.19 (F	P = 0.23)				Favours control Favours experimenta

Compulsions (CYBOCS-PDD)

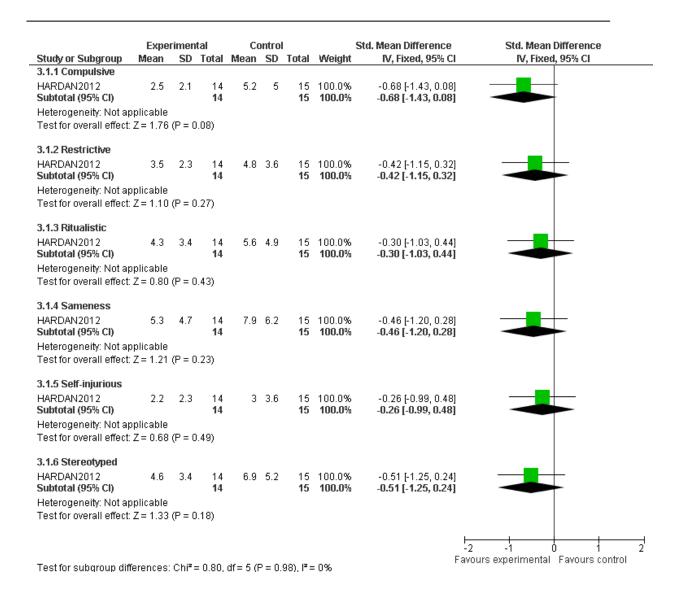


Repetitive behaviour (RBS)

	Expe				ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.4.1 Compulsive									<u> </u>
KING2009 Subtotal (95% CI)	5.2	4.4	73 73	4.8	4.1	76 76	100.0% 100.0 %	0.09 [-0.23, 0.42] 0.09 [-0.23, 0.42]	
Heterogeneity: Not ap	nlicable		73			70	100.070	0.09 [-0.23, 0.42]	
Test for overall effect:		(P = 1	1 57)						
restror everan enect.	2-0.01	(i – c	,						
2.4.2 Restrictive									<u>_</u>
KING2009	4.2	3.1	73	3.2	2.8		100.0%	0.34 [0.01, 0.66]	H
Subtotal (95% CI)			73			76	100.0%	0.34 [0.01, 0.66]	-
Heterogeneity: Not ap									
Test for overall effect:	Z = 2.04	(P = t	1.04)						
2.4.3 Ritualistic									
KING2009	5.3	3.8	73	5.3	4.4	76	100.0%	0.00 [-0.32, 0.32]	-
Subtotal (95% CI)			73			76	100.0%	0.00 [-0.32, 0.32]	•
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.00	(P = 1)	.00)						
2.4.4 Sameness									
KING2009	0.4	0.5	72	7.0	6.2	70	100.00	0.05 (0.07 0.07)	
Subtotal (95% CI)	8.1	6.5	73 73	7.0	6.2	76	100.0% 100.0 %	0.05 [-0.27, 0.37] 0.05 [-0.27, 0.37]	
Heterogeneity: Not ap	nlicable							5.55 [5.5. , 5.5.]	T
Test for overall effect:	•	(P = 0	1.77)						
2.4.5 Self-injurious				_				0.454047.047	_
KING2009 Subtotal (95% CI)	2.4	2.7	73 73	2	2.6	76 76	100.0% 100.0 %	0.15 [-0.17, 0.47] 0.15 [-0.17, 0.47]	
Heterogeneity: Not ap	nlicable		13			70	100.078	0.13[-0.17, 0.47]	
Test for overall effect:	•	(P = f	136)						
			,						
2.4.6 Stereotyped									<u>L</u>
KING2009	5.5	4	73	5	3.9		100.0%	0.13 [-0.20, 0.45]	
Subtotal (95% CI)			73			76	100.0%	0.13 [-0.20, 0.45]	-
Heterogeneity: Not ap									
Test for overall effect:	∠= 0.77	(P = 0	1.44)						
									-2 -1 0 1
Test for subgroup diff	oroncoe.	Chi²:	= 2.52	df = 5.0	o = ∩	77) l² =	: n%	Fa	avours experimental Favours control

1.6.2 Antioxidants for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

N-acetylcysteine versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

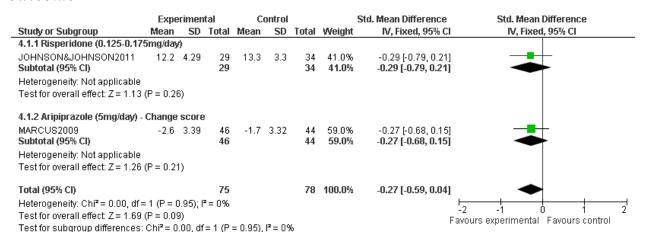


1.6.3 Antipsychotics for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Expe	erimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
3.1.1 Risperidone									
RUPPRISPERIDONE2001	11.65	4.02	49	14.21	4.81	52	30.7%	-0.57 [-0.97, -0.17	n ———
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	11.6	4.57857	58 107	13.3	3.3	34 86	26.7% 57.4 %		
Heterogeneity: Chi ² = 0.31, df = Test for overall effect: $Z = 3.32$		•							
3.1.2 Aripiprazole									
MARCUS2009 Subtotal (95% CI)	-2.721622	3.256739	148 148	-1.7	3.32	44 44	42.6% 4 2.6 %		
Heterogeneity: Not applicable Test for overall effect: Z = 1.80	(P = 0.07)								
Total (95% CI)			255			130	100.0%	-0.42 [-0.64, -0.20	ı •
Heterogeneity: Chi ² = 0.96, df =	= 2 (P = 0.62)	; I² = 0%							<u> </u>
Test for overall effect: $Z = 3.70$	(P = 0.0002)								-2 -1 U 1 Favours experimental Favours control
Test for subgroup differences:			0.42), I ^z	= 0%					ravours experimental Favours control

Low-dose antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



1.7 BIOMEDICAL INTERVENTIONS AIMED AT CORE FEATURES OF AUTISM (OVERALL AUTISTIC BEHAVIOURS)

1.7.1 Complementary therapies for overall autistic behaviours as a direct or indirect outcome

Acupressure versus waitlist for overall autistic behaviours as a direct outcome

		erimen			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 Total score									
CHAN2009	0.97	0.73	16	0.41	0.41		100.0%	0.92 [0.19, 1.66]	
Subtotal (95% CI)			16			16	100.0%	0.92 [0.19, 1.66]	-
Heterogeneity: Not ap	•								
Test for overall effect:	Z = 2.46	i (P = 0	1.01)						
1.1.2 Language									
CHAN2009	1.21	0.73	16	0.43	0.35	16	100.0%	1.33 [0.55, 2.10]	 _
Subtotal (95% CI)			16			16	100.0%	1.33 [0.55, 2.10]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 3.36	6 (P = 0	.0008)						
1.1.3 Social interaction	on								
CHAN2009		0.77	16	0.42	0.49	16	100.0%	0.98 [0.24, 1.72]	
Subtotal (95% CI)	1.07	0.77	16	0.42	0.49	16	100.0%	0.98 [0.24, 1.72]	
Heterogeneity: Not ap	nlicable							510 g (512 1, 111 2)	
Test for overall effect:			.009)						
1.1.4 Stereotyped be	haviour								
CHAN2009		1.08	16	0.24	0.67	16	100.0%	0.23 [-0.47, 0.92]	
Subtotal (95% CI)	0.55	1.00	16	0.34	0.07	16		0.23 [-0.47, 0.92]	
Heterogeneity: Not ap	nlicable						1001011	oleo [or rr, olee]	
Test for overall effect:	•		152)						
			,						
1.1.5 Motor functioning	ng								<u></u>
CHAN2009	1.03	1.15	16	0.59	0.71		100.0%	0.45 [-0.25, 1.15]	
Subtotal (95% CI)			16			16	100.0%	0.45 [-0.25, 1.15]	
Heterogeneity: Not ap	•								
Test for overall effect:	∠=1.25	(P=0	1.21)						
								_	
									2 -1 0 1 2
Test for subgroup diff		. Obiz-	- 5 00	de		0) 17 -	20.50		Favours control Favours experime

Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only for overall autistic behaviours as a direct outcome

Overall autistic behaviours (ATEC)

		erimenta			ontrol			Std. Mean Difference	Std. Mean Difference
, , ,	lean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1 Total score /ONG2008 6 ubtotal (95% CI)	.167	17.504	18 18	1.44	19.8	18 18	100.0% 100.0 %	0.25 [-0.41, 0.90] 0.25 [-0.41, 0.90]	
eterogeneity: Not appli est for overall effect: Z=		(P = 0.46	6)						
1.2 Communication ar	nd spe	ech							
ONG2008 0 ubtotal (95% Cl)	.444	2.617	18 18	0.67	4.537	18 18	100.0% 100.0 %	-0.06 [-0.71, 0.59] - 0.06 [-0.71, 0.59]	-
eterogeneity: Not appli est for overall effect: Z =		(P = 0.86	6)						
1.3 Sociability									
ONG 2008 1 ubtotal (95% CI)	.944	7.28	18 18	0.89	7.045	18 18	100.0% 100.0%	0.14 [-0.51, 0.80] 0.14 [-0.51, 0.80]	
eterogeneity: Not appli est for overall effect: Z=		(P = 0.67	7)					,,	
1.4 Sensory and cogni	itive a	warenes	ss						_
ONG 2008 1 ubtotal (95% CI)	.611	6.572	18 18	-0.89	4.922	18 18	100.0% 100.0%	0.42 [-0.24, 1.08] 0.42 [-0.24, 1.08]	
eterogeneity: Not appli est for overall effect: Z =		(P = 0.21	1)					,,	
1.5 Physical health an	d beh	aviour							
ONG 2008 2 ubtotal (95% CI)	.167	5.833	18 18	0.78	8.782	18 18	100.0% 100.0 %	0.18 [-0.47, 0.84] 0.18 [-0.47, 0.84]	
eterogeneity: Not appli est for overall effect: Z=		(P = 0.59				10	100.07	0.10 [-0.41, 0.04]	
									-2 -1 0 1

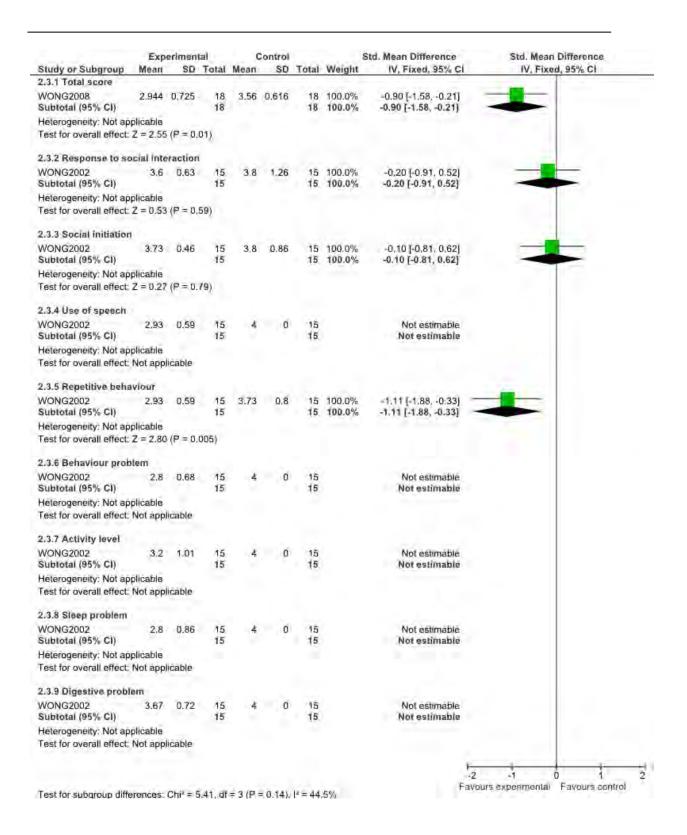
Test for subgroup differences: $Chi^2 = 1.08$, df = 4 (P = 0.90), $I^2 = 0\%$

Overall autistic behaviours (RLRS)

	F				041			Ot 1 Marco Difference	Ct. I II D'''
Study or Subgroup	Expe Mean	erimental en	Total	Mean	Control	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
2.2.1 Total score	IWEAII	30	TULAI	weam	30	TULAI	vveigni	IV, Fixeu, 9578 Ci	10, Fixed, 95% CI
WONG2002	0.1627	0.1923	15	-0.02	0.2624	14	42.8%	0.73 [-0.02, 1.49]	
WONG2008	0.1327		18	0.16	0.252	18	57.2%	-0.06 [-0.71, 0.59]	
Subtotal (95% CI)	0.143	0.511	33	0.10	0.232		100.0%	0.28 [-0.21, 0.77]	
Heterogeneity: Chi ² =	2.42 df=	1 (P = 0.1		50%		-	1001011	one of one i, on if	
Test for overall effect:			2/,1 -	3370					
2.2.2 Motor									
WONG2002	0.2487	0.5079	15	0.1	0.2941	15	45.0%	0.35 [-0.37, 1.07]	
WONG2008	0.182		18	0.18	0.68	18	55.0%	0.00 [-0.65, 0.66]	
Subtotal (95% CI)	0.102	0.433	33	0.10	0.00		100.0%	0.16 [-0.33, 0.64]	_
Heterogeneity: Chi²=	0.48 df=	1 (P = 0.4	9): I² =	0%					
Test for overall effect		•	٠,,,	0 70					
2.2.3 Social									
WONG2002	0.02867	0.3437	15	0.17	0.3971	15	45.0%	-0.37 [-1.09, 0.35]	
WONG2008	0.061	0.496	18	0.09	0.341	18	55.0%	-0.07 [-0.72, 0.59]	
Subtotal (95% CI)	0.001	0.400	33	0.00	0.041		100.0%	-0.20 [-0.69, 0.28]	
Heterogeneity: Chi ² =	0.37. df=	1 (P = 0.5	4); ² =	0%					
Test for overall effect			71.						
2.2.4 Affective									
WONG2002	0.3727	0.151	15	0.12	0.72	15	44.7%	0.47 [-0.25, 1.20]	
WONG2008	0.222	0.489	18	0.26	0.515	18	55.3%	-0.07 [-0.73, 0.58]	
Subtotal (95% CI)			33			33	100.0%	0.17 [-0.32, 0.66]	-
Heterogeneity: Chi²=	1.20, df=	1 (P = 0.2	7); 2=	17%					
Test for overall effect	Z = 0.69 (F	P = 0.49)							
2.2.5 Sensory									
WONG2002	0.157	0.281	15	-0.03	0.358	15	44.5%	0.57 [-0.17, 1.30]	+-
WONG2008	0.15	0.325	18	0.25	0.505	18	55.5%	-0.23 [-0.89, 0.43]	
Subtotal (95% CI)			33			33	100.0%	0.12 [-0.36, 0.61]	-
Heterogeneity: Chi²=	2.52, df=	1 (P = 0.1	1);	60%					
Test for overall effect	Z = 0.50 (F	P = 0.62)							
2.2.6 Language									
WONG2002	0.08667	0.3021	15	-0.07	0.3754	15	45.0%	0.45 [-0.28, 1.17]	
WONG2008	0.1	0.341	18	0	0.361	18	55.0%	0.28 [-0.38, 0.94]	- •
Subtotal (95% CI)			33			33	100.0%	0.35 [-0.13, 0.84]	-
Heterogeneity: Chi²=		•	4); l² =	0%					
Test for overall effect	Z = 1.43 (F	° = 0.15)							
									-2 -1 1 1
Test for subaroup dif	ferences: C	$chi^2 = 3.00$). df = 5	5(P = 0.	70), $ \mathbf{r} = 0$	0%			Favours control Favours expe

Test for subgroup differences: Chi² = 3.00, df = 5 (P = 0.70), I^2 = 0%

Overall autistic behaviours (CGI)



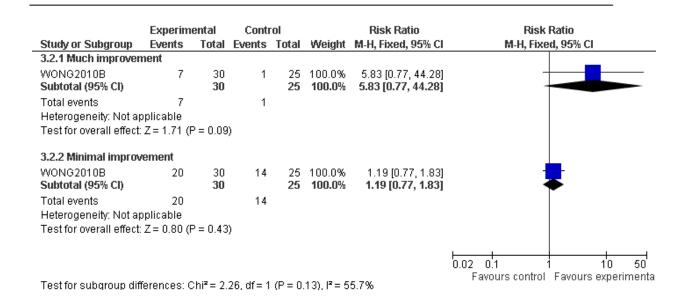
Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for overall autistic behaviours as an indirect outcome

Overall autistic behaviours (RLRS; change scores)

Autism: the management and support of children and young people on the autism spectrum

		riment			ontrol	_		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 Total score									_
WONG2010A		0.38	25	-0.22		25	47.3%	-0.43 [-0.99, 0.14]	
WONG2010B Subtotal (95% Cl)	-0.1	0.27	30 55	-0.05	0.26	25 50	52.7% 100.0 %	-0.19 [-0.72, 0.35] - 0.30 [-0.69, 0.09]	
Heterogeneity: Chi²=	0 27 Af	_ 1 /D ·		. IZ — ∩ 0	٤	30	100.078	-0.30 [-0.03, 0.03]	
neterogeneity. Crir = Test for overall effect:		,		,1 – 07	0				
restror overall ellect.	2-1.52	. (1 – 0	.10)						
3.1.2 Motor									
WONG2010A	-0.28	0.55	25	-0.08	0.46	25	47.4%	-0.39 [-0.95, 0.17]	
WONG2010B	-0.06	0.36	30	-0.11	0.32	25	52.6%	0.14 [-0.39, 0.68]	
Subtotal (95% CI)			55			50	100.0%	-0.11 [-0.49, 0.28]	-
Heterogeneity: Chi²=				; l² = 45	%				
Test for overall effect:	Z = 0.55	(P = 0	.58)						
3.1.3 Social									
WONG2010A	-0.3	0.76	25	-0.24	1	25	48.0%	-0.07 [-0.62, 0.49]	
WONG2010R	-0.11		30	-0.02		25	52.0%	-0.25 [-0.78, 0.28]	
Subtotal (95% CI)	0.11	0.00	55	0.02	0.00		100.0%	-0.16 [-0.55, 0.22]	
Heterogeneity: Chi²=	0.22, df	= 1 (P :	= 0.64)	: I² = 0%	6				
Test for overall effect:	Z = 0.83	(P = 0	.41)						
3.1.4 Affective									_
WONG2010A	-0.62			-0.35		25	47.4%	-0.39 [-0.95, 0.17]	
WONG2010B	-0.13	0.54	30 55	-0.05	0.39	25	52.6% 100.0 %	-0.17 [-0.70, 0.37] - 0.27 [-0.66, 0.11]	
Subtotal (95% CI)	ററാ ഷം	_ 1 /D.		· 12 — 0.0	,	30	100.0%	-0.27 [-0.00, 0.11]	
Heterogeneity: Chi²= Test for overall effect:				, == 0%	0				
restioi overali ellect.	∠- 1.30	(F – U	.17)						
3.1.5 Sensory									
WONG2010A	-0.35	0.65	25	-0.3	0.33	25	47.8%	-0.10 [-0.65, 0.46]	
WONG2010B	-0.04	0.39	30	0	0.39	25	52.2%	-0.10 [-0.63, 0.43]	
Subtotal (95% CI)			55			50	100.0%	-0.10 [-0.48, 0.29]	-
Heterogeneity: Chi²=		,		$ I^2 = 09 $	6				
Test for overall effect:	Z = 0.50	(P = 0	.62)						
3.1.6 Language									
WONG2010A	-0.44	0.28	25	-0.32	0.4	25	47.7%	-0.34 [-0.90, 0.22]	
WONG2010B	-0.13		30	-0.03		25	52.3%	-0.30 [-0.83, 0.24]	
Subtotal (95% CI)	5.10	0.02	55	0.00	0.00	50		-0.32 [-0.70, 0.07]	•
Heterogeneity: Chi²=	0.01, df	= 1 (P :	= 0.91)	; I² = 09	6			- · -	
Test for overall effect:									
								<u>⊢</u> -2	-1 1 1

Positive treatment response (improvement in autistic behaviours; CGI-I)



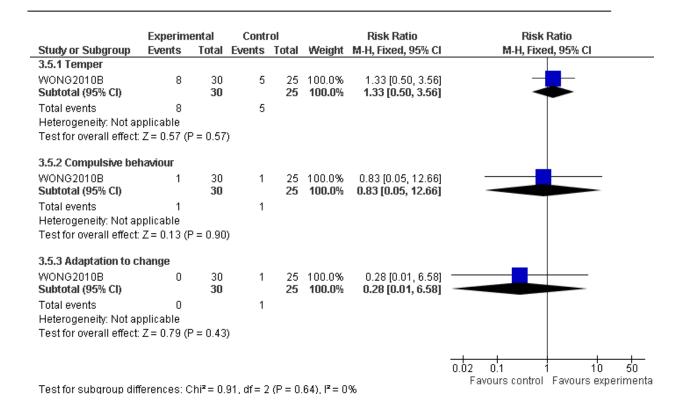
Positive treatment response for social relatedness (study-specific parent-reported 'better than before')

	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.3.1 Social response			_				_
WONG2010B Subtotal (95% CI)	4	30 30	5	25 25	100.0% 100.0 %	0.67 [0.20, 2.22] 0.67 [0.20, 2.22]	-
Total events	4		5				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.66 (F	' = U.51)				
3.3.2 Social initiation							
WONG2010B	7	30	0	25	100.0%	12.58 [0.75, 209.98]	+
Subtotal (95% CI)		30		25	100.0%	12.58 [0.75, 209.98]	
Total events	7		0				
Heterogeneity: Not ap	•						
Test for overall effect:	Z=1.76 (F	'= 0.08)				
3.3.3 Eye contact							<u>L</u>
WONG2010B	7	30	4	25	100.0%	1.46 [0.48, 4.42]	
Subtotal (95% CI)	_	30		25	100.0%	1.46 [0.48, 4.42]	
Total events	7 Aldonia		4				
Heterogeneity: Not ap Test for overall effect:	•) – n sn	\				
restion overall ellect.	2-0.07 (1	- 0.50	,				
3.3.4 Share							_
WONG2010B Subtotal (95% Cl)	0	30 30	1	25 25	100.0% 100.0 %	0.28 [0.01, 6.58] 0.28 [0.01, 6.58]	
Total events	0	30	1	23	100.070	0.20 [0.01, 0.30]	
Heterogeneity: Not ap	_		'				
Test for overall effect:	•	9 = 0.43)				
3.3.5 Curiosity							
WONG2010B	0	30	1	25	100.0%	0.28 [0.01, 6.58]	
Subtotal (95% CI)		30		25	100.0%	0.28 [0.01, 6.58]	
Total events	0		1				
Heterogeneity: Not ap	•						
Test for overall effect:	Z= 0.79 (F	° = 0.43)				
3.3.6 Patience							<u></u>
WONG2010B	1	30	0	25	100.0%	2.52 [0.11, 59.18]	
Subtotal (95% CI)		30		25	100.0%	2.52 [0.11, 59.18]	
Total events	1		0				
Heterogeneity: Not ap		1 _ 0 57					
Test for overall effect:	∠= 0.57 (F	-= 0.57	,				
							0.005 0.1 1 10 200
							0.005 0.1 1 10 200 Favours control Favours experimer
Test for subgroup diff	erences: C	hi² = 5.	50, df = 5	(P = 0.	.36), I² = 9	.1%	. arear comment

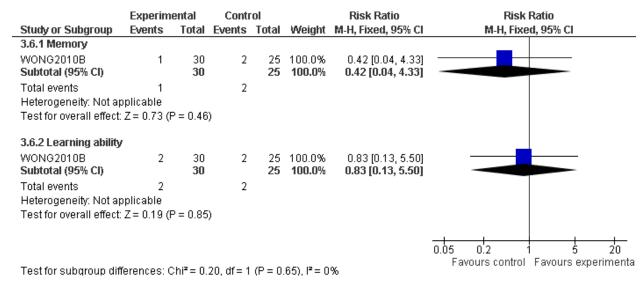
Positive treatment response for non-verbal and verbal communication (study-specific parent-reported 'better than before')

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
3.4.1 Expressive lang	guage						
WONG2010B	11	30	7	24	100.0%	1.26 [0.58, 2.75]	
Subtotal (95% CI)		30		24	100.0%	1.26 [0.58, 2.75]	-
Total events	11		7				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.57 (F	° = 0.57)				
3.4.2 Receptive lang	uage						
WONG2010B	17	30	5	25	100.0%	2.83 [1.22, 6.59]	-
Subtotal (95% CI)		30		25	100.0%	2.83 [1.22, 6.59]	-
Total events	17		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.42 (F	P = 0.02)				
3.4.3 Pointing							
WONG2010B	1	30	0	25	100.0%	2.52 [0.11, 59.18]	
Subtotal (95% CI)		30		25	100.0%	2.52 [0.11, 59.18]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.57 (F	P = 0.57)				
3.4.4 Imitation							
WONG2010B	1	30	0	25	100.0%	2.52 [0.11, 59.18]	
Subtotal (95% CI)		30		25	100.0%	2.52 [0.11, 59.18]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.57 (F	P = 0.57)				
							0.02 0.1 1 10 50
							Favours control Favours experimer

Positive treatment response for stereotypy interest and behaviour (study-specific parent-reported 'better than before')



Positive treatment response for cognition (study-specific parent-reported 'better than before')



Positive treatment response for motor abnormalities (study-specific parent-reported 'better than before')

	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.7.1 Motor skill							
WONG2010B	5	30	0	25	100.0%	9.23 [0.53, 159.14]	
Subtotal (95% CI)		30		25	100.0%	9.23 [0.53, 159.14]	
Total events	5		0				
Heterogeneity: Not as	oplicable						
Test for overall effect:	Z = 1.53 (F	9 = 0.13)				
3.7.2 Coordination							
WONG2010B	8	30	2	25	100.0%	3.33 [0.78, 14.29]	
Subtotal (95% CI)		30		25	100.0%	3.33 [0.78, 14.29]	
Total events	8		2				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 1.62 (F	9 = 0.11)				
3.7.3 Drooling							
WONG2010B	2	30	1	25	100.0%	1.67 [0.16, 17.32]	
Subtotal (95% CI)		30		25	100.0%	1.67 [0.16, 17.32]	
Total events	2		1				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z= 0.43 (F	9 = 0.67)				
							0.01 0.1 1 10 10
Test for subgroup diff							Favours control Favours experime

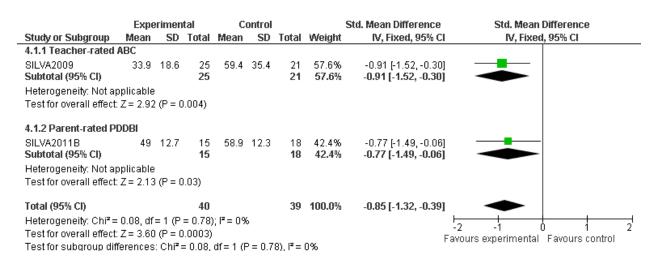
Positive treatment response for other parent-reported changes (study-specific parent-reported 'better than before')

	Ехрегіт		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.8.1 Appetite							
WONG2010B	3	30	1	25	100.0%	2.50 [0.28, 22.56]	
Subtotal (95% CI)		30		25	100.0%	2.50 [0.28, 22.56]	
Total events	3		1				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.82 (F	P = 0.41)				
3.8.2 Attention span							
WONG2010B	9	30	0	25	100.0%	15.94 [0.97, 260.91]	
Subtotal (95% CI)		30		25	100.0%	15.94 [0.97, 260.91]	
Total events	9		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.94 (F	P = 0.05)				
3.8.3 Sleeping patter	n						
WONG2010B	7	30	3	25	100.0%	1.94 [0.56, 6.75]	+
Subtotal (95% CI)		30		25	100.0%	1.94 [0.56, 6.75]	◆
Total events	7		3				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.05 (F	P = 0.29)				
3.8.4 "Crafty"							
WONG2010B	2	30	1	25	100.0%	1.67 [0.16, 17.32]	
Subtotal (95% CI)		30		25	100.0%	1.67 [0.16, 17.32]	
Total events	2		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.43 (F	P = 0.67)				
							0.005 0.1 1 10 200
Taet for cubaroup diff		N . : 9 4	00 46 0	/D 0	50) IZ 0	01	Favours control Favours experimen

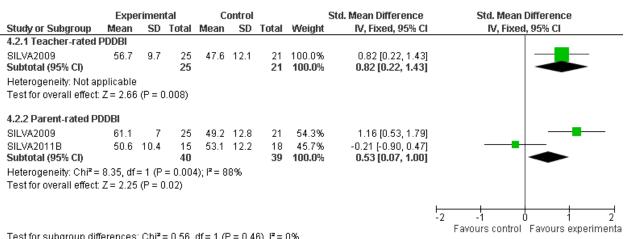
Test for subgroup differences: $Chi^2 = 1.96$, df = 3 (P = 0.58), $I^2 = 0\%$

Qigong massage training versus waitlist for overall autistic behaviours as an indirect outcome

Overall autistic behaviours

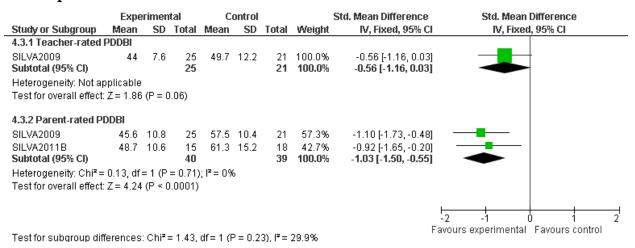


Social, language, and communication abilities



Test for subgroup differences: $Chi^2 = 0.56$, df = 1 (P = 0.46), $I^2 = 0\%$

Maladaptive behaviour



1.7.2 Hormones for overall autistic behaviours as a direct or indirect outcome

Secretin versus placebo for overall autistic behaviours as a direct or indirect outcome

Positive treatment response (decrease of >4.07 points CARS or parent-rated CGI 'much/very much improved')

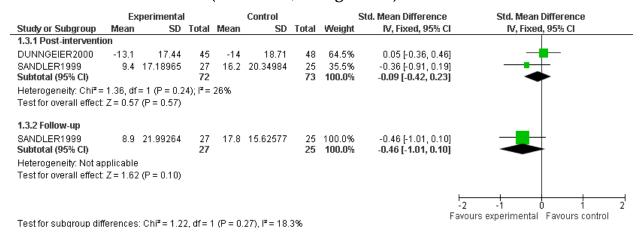
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 Post-treatmen	t						
CONIGLIO2001 Subtotal (95% CI)	11	28 28	7	29 29	100.0% 100.0 %	1.63 [0.74, 3.60] 1.63 [0.74, 3.60]	
Total events	11		7				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 1.20 (F	P = 0.23)				
1.1.2 Follow-up							
CONIGLIO2001	10	28	8	29	52.0%	1.29 [0.60, 2.80]	-
SANDLER1999	9	27	7	25	48.0%	1.19 [0.52, 2.71]	-
Subtotal (95% CI)		55		54	100.0%	1.24 [0.71, 2.19]	-
Total events	19		15				
Heterogeneity: Chi ² :	= 0.02, df = 1	1 (P = 0)	.88); I ^z = I	0%			
Test for overall effect	Z = 0.76 (F	9 = 0.45)				
							0.1 0.2 0.5 1 2 5 10
							Favours control Favours experimenta

Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I^2 = 0%

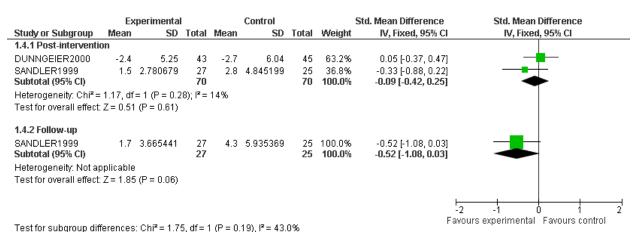
Overall autistic behaviours (CARS; endpoint or change scores)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
DUNNGEIER2000	-1.2	2.06	47	-1.5	2.77	48	69.6%	0.12 [-0.28, 0.52]	_ 	
MOLLOY2002	39.2	4.3	19	38.3	5.2	23	30.4%	0.18 [-0.43, 0.79]		
Total (95% CI)			66			71	100.0%	0.14 [-0.20, 0.48]	•	
Heterogeneity: Chi²= Test for overall effect:		,); I ^z = 0%	6			F	-2 -1 0 1 avours experimental Favours co	ntrol 2

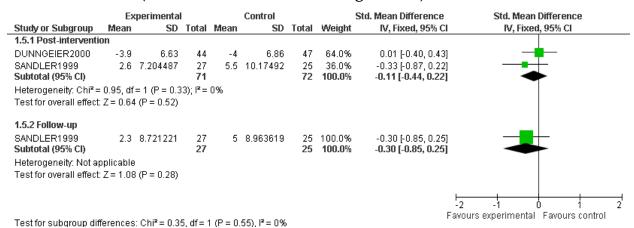
Overall autistic behaviours (ABC Total; change score)



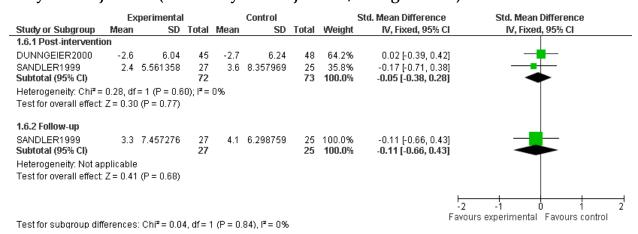
Sensory function (ABC sensory; change scores)



Social relatedness (ABC social relatedness; change scores)



Body and object use (ABC body and object use; change scores)

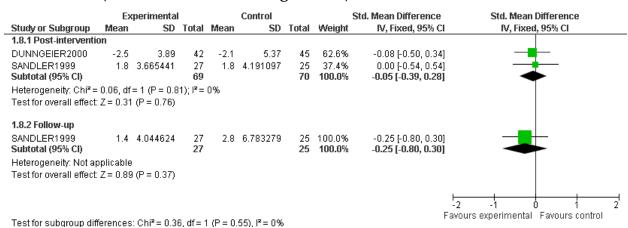


Language (ABC language; change scores)

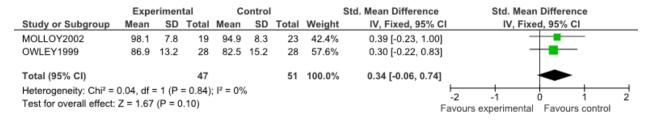
	Ex	perimental	l		Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.7.1 Post-interventi	on								
DUNNGEIER2000	-0.9	3.89	42	-1.8	6.48	42	62.0%	0.17 [-0.26, 0.60]	-
SANDLER1999	1.1	4.802991	27	2.6	5.208589	25	38.0%	-0.30 [-0.84, 0.25]	
Subtotal (95% CI)			69			67	100.0%	-0.01 [-0.35, 0.33]	•
Heterogeneity: Chi²=	1.70, df	= 1 (P = 0.1	9); l² =	41%					
Test for overall effect	Z = 0.05	(P = 0.96)							
1.7.2 Follow-up									
SANDLER1999	0.1	4.802991	27	1.6	4.481809	25	100.0%	-0.32 [-0.87, 0.23]	
Subtotal (95% CI)			27			25	100.0%	-0.32 [-0.87, 0.23]	-
Heterogeneity: Not a	oplicable	1							
Test for overall effect	Z=1.14	(P = 0.26)							
									+ - + + - + + +
									-2 -1 1 1

Test for subgroup differences: $Chi^2 = 0.89$, df = 1 (P = 0.35), $I^2 = 0\%$

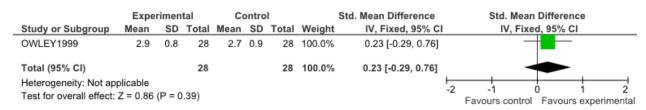
Socialization (ABC socialization; change scores)



Overall autistic behaviours (GARS)



Overall autistic behaviours (CGI)

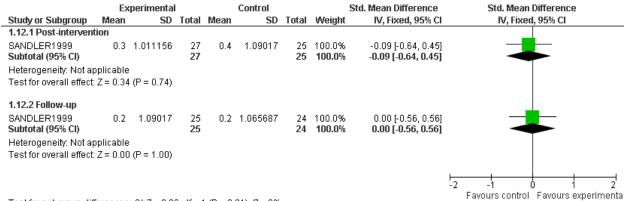


Response to social interaction (CGI; change scores)

	Ex	perimenta	ıl		Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.11.1 Post-intervent	tion								
SANDLER1999	0.1	1.39034	27	0.1	1.2113	25	100.0%	0.00 [-0.54, 0.54]	 _
Subtotal (95% CI)			27			25	100.0%	0.00 [-0.54, 0.54]	-
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 0.00	(P = 1.00))						
1.11.2 Follow-up									
SANDLER1999	-0.2	1.69582	25	0.3	1.184096	24	100.0%	-0.34 [-0.90, 0.23]	
Subtotal (95% CI)			25			24	100.0%	-0.34 [-0.90, 0.23]	
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 1.18	6 (P = 0.24))						
									-2 -1 0 1 2
Test for subgroup diff	ferences	: Chi 3 = 0 1	70 df=	1 (P = 1	0.40) (2 = 0.9	X			Favours control Favours experiment

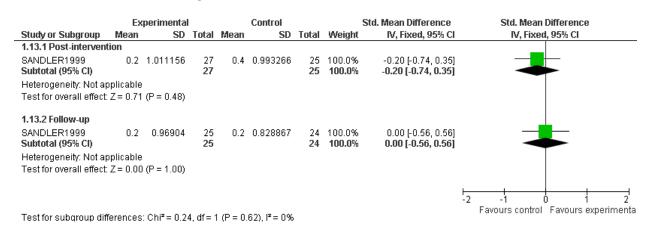
Test for subgroup differences: $Chi^2 = 0.70$, dt = 1 (P = 0.40), $i^2 = 0\%$

Social initiation (CGI; change scores)



Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I^2 = 0%

Use of speech (CGI; change scores)



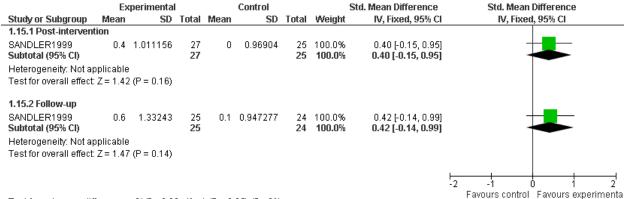
Autism: the management and support of children and young people on the autism spectrum

Types of repetitive behaviour (CGI; change scores)

	Ex	kperimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.14.1 Post-intervent	tion								
SANDLER1999 Subtotal (95% CI)	0.1	1.011156	27 27	0.3	1.2113	25 25	100.0% 100.0 %	-0.18 [-0.72, 0.37] - 0.18 [-0.72, 0.37]	-
Heterogeneity: Not ap	oplicable)							
Test for overall effect:	Z= 0.64	4 (P = 0.52)							
1.14.2 Follow-up									
SANDLER1999 Subtotal (95% CI)	-0.1	1.2113	25 25	0.2	1.065687	24 24	100.0% 100.0 %	-0.26 [-0.82, 0.30] - 0.26 [-0.82, 0.30]	-
Heterogeneity: Not as	oplicable)							
Test for overall effect:	Z = 0.90	(P = 0.37)							
									-2 -1 0 1
Tact for cubaroup diff	¥	. Obiz = 0.0	4 df = 1	1 /0 = 0	0.4\ 18 = 0.00				Favours control Favours experime

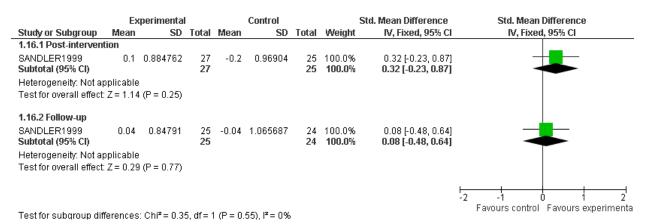
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$

Behaviour problems (CGI; change scores)



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I^2 = 0%

Activity level (CGI; change scores)



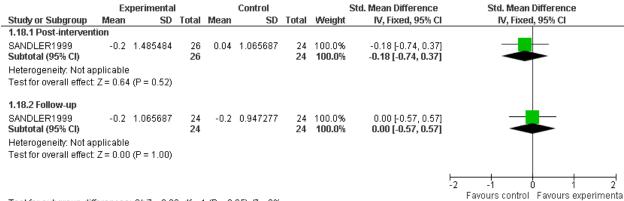
Autism: the management and support of children and young people on the autism spectrum

Sleep problems (CGI; change scores)

	Ex	perimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.17.1 Post-intervent	tion								
SANDLER1999 Subtotal (95% CI)	-0.1	1.33243	25 25	-0.3	1.184096	24 24	100.0% 100.0 %	0.16 [-0.41, 0.72] 0.16 [-0.41, 0.72]	-
Heterogeneity: Not as	pplicable								
Test for overall effect	Z= 0.54	(P = 0.59)							
1.17.2 Follow-up									
SANDLER1999 Subtotal (95% CI)	-0.5	1.420916	24 24	-0.2	1.184096	24 24	100.0% 100.0 %	-0.23 [-0.79, 0.34] - 0.23 [-0.79, 0.34]	
Heterogeneity: Not as	pplicable								
Test for overall effect									
									-2 -1 0 1 Favours control Favours experime
Toot for outpareous dif	×	O 1:2 0 0:	0 46 7	(0 0	20 17 000				ravours control ravours expendin

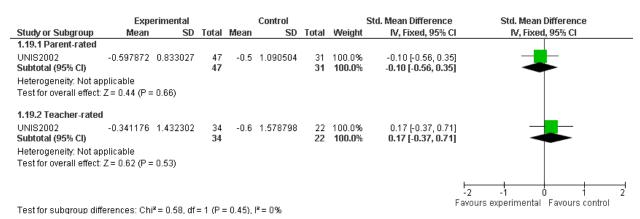
Test for subgroup differences: $Chi^2 = 0.88$, df = 1 (P = 0.35), $I^2 = 0\%$

Digestive problems (CGI; change scores)

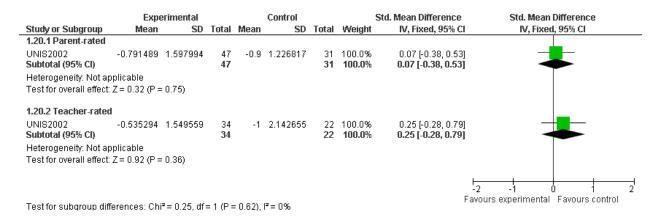


Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), l² = 0%

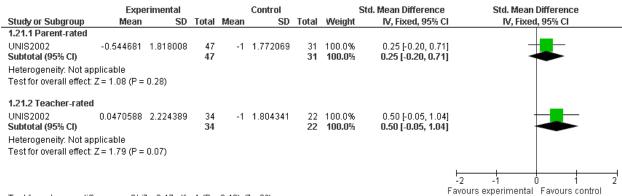
Overall autistic behaviours (SOS total change score; porcine+synthetic groups combined)



Social (SOS change score; porcine+synthetic groups combined)

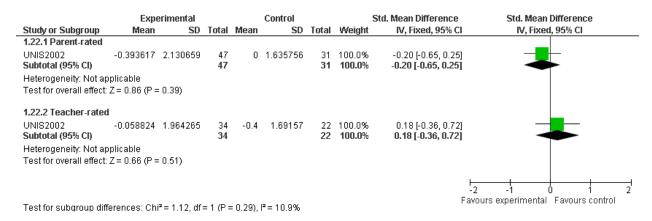


Communication (SOS change score; porcine+synthetic groups combined)



Test for subgroup differences: $Chi^2 = 0.47$, df = 1 (P = 0.49), $I^2 = 0\%$

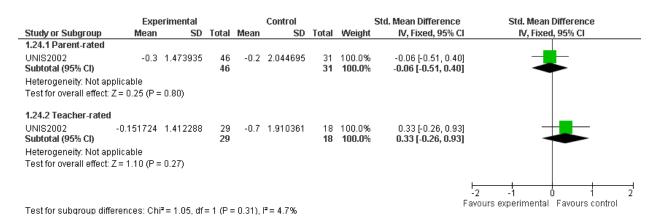
Repetitive behaviour (SOS change score; porcine+synthetic groups combined)



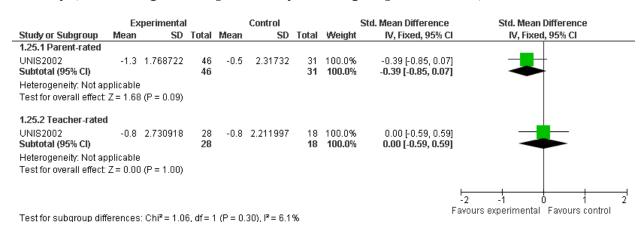
Digestive (SOS change score; porcine+synthetic groups combined)

	Ex	kperimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.23.1 Parent-rated									
UNI82002	-0.3	1.171035	47	-0.4	1.226817	31	100.0%	0.08 [-0.37, 0.54]	
Subtotal (95% CI)			47			31	100.0%	0.08 [-0.37, 0.54]	-
Heterogeneity: Not a	pplicable)							
Test for overall effect	t: Z = 0.36	6 (P = 0.72)							
1.23.2 Teacher-rate	d								
JNI82002	-0.45	1.083939	20	-1	2.618361	15	100.0%	0.28 [-0.39, 0.96]	
Subtotal (95% CI)			20			15	100.0%	0.28 [-0.39, 0.96]	
Heterogeneity: Not a	pplicable)							
Test for overall effect	t: Z = 0.83	3 (P = 0.41)							
								-2	-1 0 1
	_							Favou	rs experimental Favours control
Fest for subgroup di	πerences	s: Chi*= 0.2-	4. af = 1	1 (P = 0.	.63), 1*= 0%				

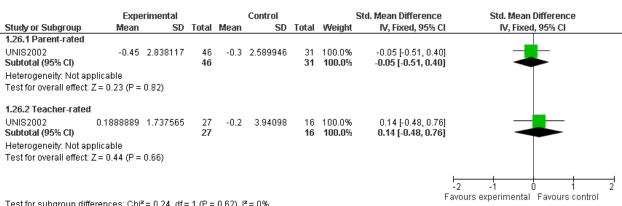
Mood (SOS change score; porcine+synthetic groups combined)



Sensory (SOS change score; porcine+synthetic groups combined)

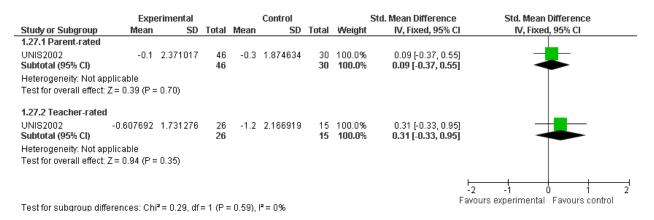


Hyperactivity (SOS change score; porcine+synthetic groups combined)

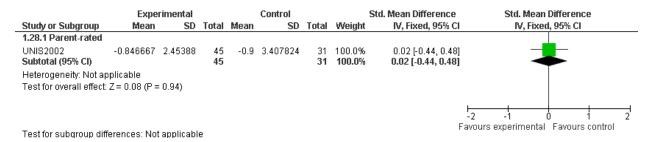


Test for subgroup differences: $Chi^2 = 0.24$, df = 1 (P = 0.62), $I^2 = 0\%$

Lethargy (SOS change score; porcine+synthetic groups combined)



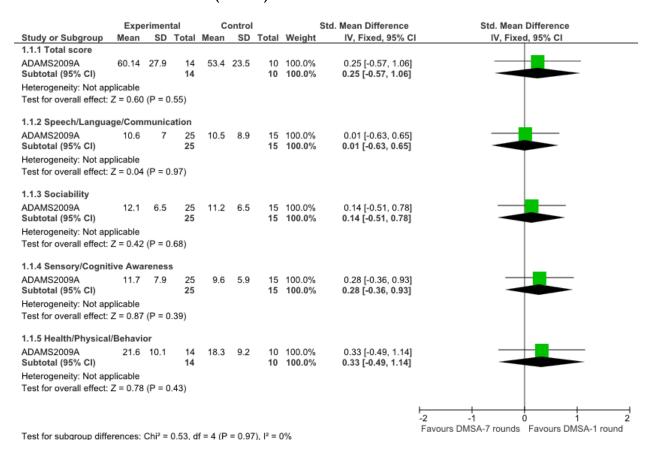
Sleep (SOS change score; porcine+synthetic groups combined)



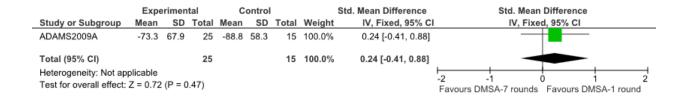
1.7.3 Medical procedures for overall autistic behaviours as a direct or indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for overall autistic behaviours as a direct outcome

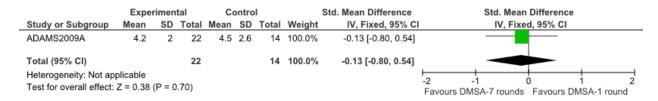
Overall autistic behaviours (ATEC)



Overall autistic behaviours (PDDBI)

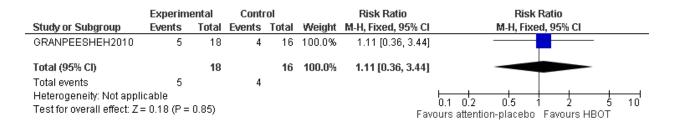


Overall autistic behaviours (SAS)

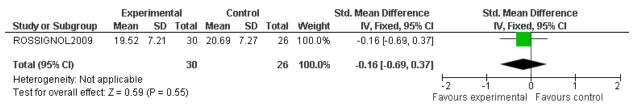


HBOT versus placebo for overall autistic behaviours as a direct or indirect outcome

Positive treatment response (improvement in ADOS diagnostic classification based on total score)



Overall autistic behaviours (ADOS total)



Overall autistic behaviours (parent-rated ATEC)

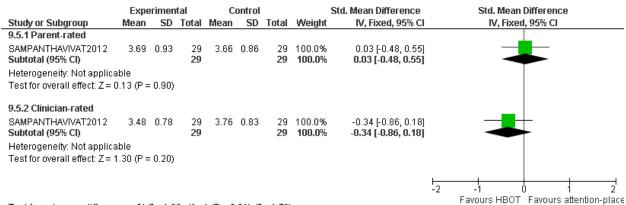
	Exp	eriment	al	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.3.1 Total score									
ROSSIGNOL2009	65.9	16.4	30	70.1	21.9	26	48.9%	-0.22 [-0.74, 0.31]	
SAMPANTHAVIVAT2012	58.31	21.94	29	55.86	24.93	29	51.1%		
Subtotal (95% CI)			59			55	100.0%	-0.05 [-0.42, 0.32]	-
Heterogeneity: Chi ² = 0.72));	0%					
Test for overall effect: Z = 0	0.28 (P =	0.78)							
9.3.2 Speech/Language/0	commun	ication							
ROSSIGNOL2009	15.5	5.1	30	15.4	6.6	26	49.1%	0.02 [-0.51, 0.54]	
SAMPANTHAVIVAT2012	13.93	6.15		12.72	6.76	29	50.9%	0.18 [-0.33, 0.70]	- -
Subtotal (95% CI)			59				100.0%	0.10 [-0.27, 0.47]	-
Heterogeneity: Chi ² = 0.20	i, df = 1 (P = 0.66	5); I² = 0	0%					
Test for overall effect: $Z = 0$	0.54 (P =	0.59)							
0.2.2 Conjobility									
9.3.3 Sociability							40.00	0.001.075.000	_
ROSSIGNOL2009	14.5 13.45	6.5 6.44	30	16	6.8	26 29	48.9% 51.1%	-0.22 [-0.75, 0.30]	<u> </u>
SAMPANTHAVIVAT2012 Subtotal (95% CI)	13.45	0.44	59 59	12.24	6.84		100.0%	0.18 [-0.34, 0.70] - 0.02 [-0.39, 0.35]	
Heterogeneity: Chi ² = 1.14	df = 1 (P = 0.29		1306		55	100.078	-0.02 [-0.00, 0.00]	$\overline{}$
Test for overall effect: Z = (7,1 -	1370					
	J. J. J.	0.00,							
9.3.4 Sensory/Cognitive A									_
ROSSIGNOL2009	15.1	3.9	30	18.5	6.2	26	47.6%	-0.66 [-1.20, -0.12]	 _
SAMPANTHAVIVAT2012	14.83	7.12	29	13.9	7.03	29	52.4%	0.13 [-0.39, 0.64]	
Subtotal (95% CI)			59			55	100.0%	-0.25 [-0.62, 0.13]	
Heterogeneity: $Chi^2 = 4.28$ Test for overall effect: $Z = 1$			i); i*= i	7%					
restroi overali ellect. Z =	1.28 (1" =	0.20)							
9.3.5 Health/Physical/Beh	avior								
ROSSIGNOL2009	20.8	8.7	30	20.2	7.3	26	49.0%	0.07 [-0.45, 0.60]	
SAMPANTHAVIVAT2012	16.76	8.24	29	17	9.43	29	51.0%	-0.03 [-0.54, 0.49]	
Subtotal (95% CI)			59			55	100.0%	0.02 [-0.35, 0.39]	-
Heterogeneity: Chi ² = 0.07			θ); $\mathbf{I}^{\mathbf{z}} = 0$	0%					
Test for overall effect: Z = 0	D.12 (P =	0.91)							
									-2 -1 0 1
Test for subaroup differen	nas: Chi	²= 1.87	df = A	P = 0.7	76) IZ=	N96			Favours HBOT Favours attention-

Overall autistic behaviours (clinician-rated ATEC)

	Eyn	erimen	tal	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.4.1 Total score								,,	
SAMPANTHAVIVAT2012 Subtotal (95% CI)	52.38	19.11	29 29	52.93	18.93	29 29	100.0% 100.0 %	-0.03 [-0.54, 0.49] - 0.03 [-0.54, 0.49]	-
Heterogeneity: Not applic	able								
Test for overall effect: Z=	0.11 (P =	0.91)							
9.4.2 Speech/Language/	Commun	ication							
SAMPANTHAVIVAT2012	13.66	7.25	29	13.93	6.97	29	100.0%	-0.04 [-0.55, 0.48]	 _
Subtotal (95% CI)			29			29	100.0%	-0.04 [-0.55, 0.48]	-
Heterogeneity: Not applic									
Test for overall effect: Z=	0.14 (P =	: 0.89)							
9.4.3 Sociability									
SAMPANTHAVIVAT2012	14.86	6.52		13.31	4.58	29	100.0%	0.27 [-0.25, 0.79]	
Subtotal (95% CI)			29			29	100.0%	0.27 [-0.25, 0.79]	
Heterogeneity: Not applic									
Test for overall effect: Z=	1.03 (P =	: 0.30)							
9.4.4 Sensory/Cognitive	Awarene	SS							
SAMPANTHAVIVAT2012	13.93	5.55		14.31	4.86	29	100.0%	-0.07 [-0.59, 0.44]	
Subtotal (95% CI)			29			29	100.0%	-0.07 [-0.59, 0.44]	
Heterogeneity: Not applic Test for overall effect: Z=		. 0. 70\							
restion overall effect. Z =	0.27 (F =	- 0.70)							
9.4.5 Health/Physical/Bel	naviour								_
SAMPANTHAVIVAT2012	10.79	5.35		12.07	6.93	29	100.0%	-0.20 [-0.72, 0.31]	
Subtotal (95% CI)	-1-1-		29			29	100.0%	-0.20 [-0.72, 0.31]	
Heterogeneity: Not applic Test for overall effect: Z =		- 0.445							
restror overall ellect. Z=	0.77 (P =	0.44)							
									-2 -1 0 1
									Favours HBOT Favours attention
Foot for outbaroup difforo	aaaa: Obi	2 - 4 76	AF 4	40 - 0.3	201 12	0.0%			, around the of Taround attentio

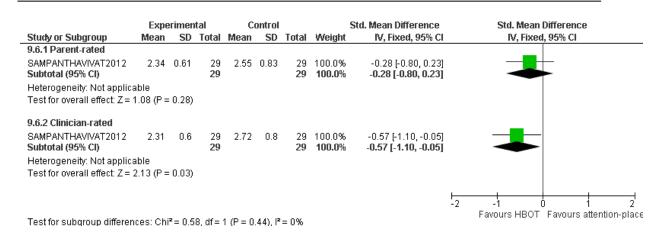
Test for subgroup differences: $Chi^2 = 1.75$, df = 4 (P = 0.78), $I^2 = 0\%$

Global severity (CGI-S)



Test for subgroup differences: $Chi^2 = 1.02$, df = 1 (P = 0.31), $I^2 = 1.7\%$

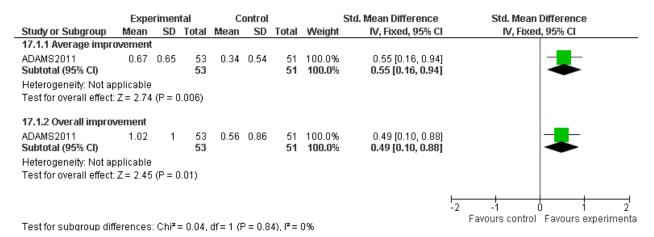
Global improvement (CGI-I)



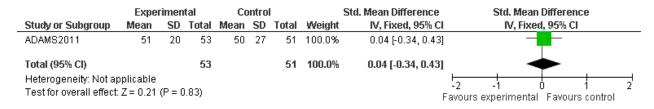
1.7.4 Nutritional interventions for overall autistic behaviours as a direct or indirect outcome

Multivitamin/mineral supplement versus placebo for overall autistic behaviours as a direct outcome

Overall autistic behaviours (PGI-R)



Overall autistic behaviours (ATEC)



Overall autistic behaviours (SAS)

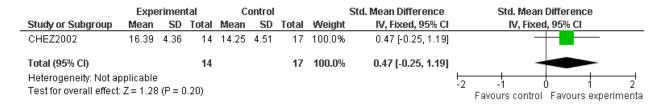
	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ADAMS2011	5.1	2.2	53	5.2	2.6	51	100.0%	-0.04 [-0.43, 0.34]	-
Total (95% CI)			53			51	100.0%	-0.04 [-0.43, 0.34]	•
Heterogeneity: Not ap Test for overall effect).83)					F	-2 -1 0 1 2 avours experimental Favours control

Overall autistic behaviours (PDDBI)

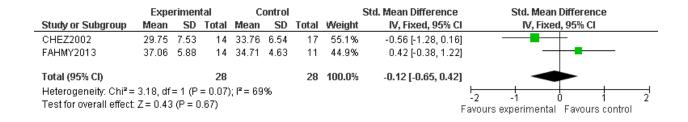
	Expe	rimen	tal	Co	ontro	ı		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ADAMS2011	-78	52	53	-79	68	51	100.0%	0.02 [-0.37, 0.40]	-
Total (95% CI)			53			51	100.0%	0.02 [-0.37, 0.40]	•
Heterogeneity: Not a Test for overall effect).93)					F	-2 -1 0 1 2 avours experimental Favours control

L-carnosine or L-carnitine supplement versus placebo for overall autistic behaviours as a direct outcome

Global improvement (PGI-I)



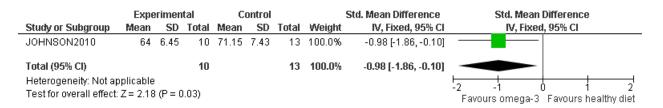
Overall autistic behaviours (CARS)



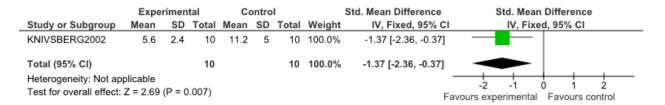
Overall autistic behaviours (GARS)

	Exp	eriment	tal	C	ontrol			Std. Mean Difference	Std. Mean Diff	егепсе
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95	5% CI
CHEZ2002	44.35	14.93	14	49.88	16.8	17	100.0%	-0.34 [-1.05, 0.38]	-	-
Total (95% CI)			14			17	100.0%	-0.34 [-1.05, 0.38]		
Heterogeneity: Not ap Test for overall effect			35)					I · Fa	I I I I I I I I I I I I I I I I I I I	1 2 vours control

Omega-3 fatty acids versus placebo for overall autistic behaviours as an indirect outcome

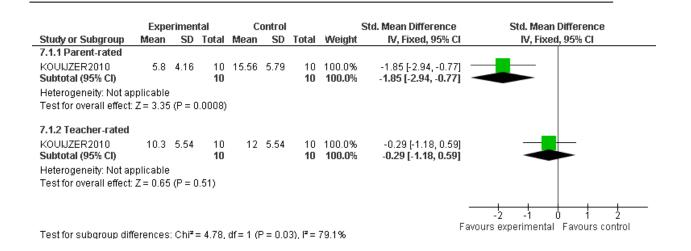


Gluten-free and casein-free diet versus treatment-as-usual for overall autistic behaviours as a direct outcome

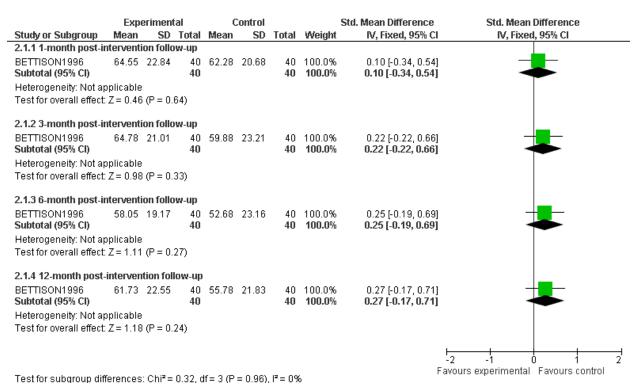


1.7.5 Sensory interventions for overall autistic behaviours as a direct or indirect outcome

Neurofeedback versus treatment-as-usual for overall autistic behaviours as a direct outcome



Auditory integration training versus attention-placebo (structured listening) for overall autistic behaviours as an indirect outcome

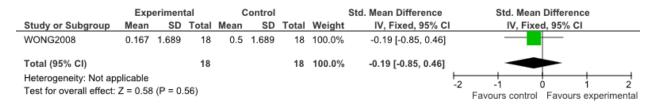


1.8 BIOMEDICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

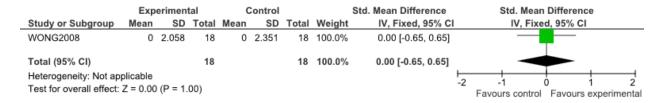
1.8.1 Complementary therapies for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Electro-acupuncture and conventional educational programme versus conventional educational programme only for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Communication (ADOS change score)



Social interaction (ADOS change score)



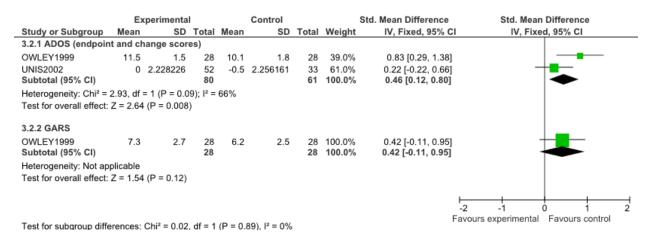
1.8.2 Hormones for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Secretin versus placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

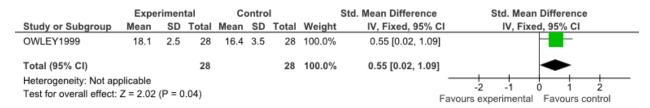
Communication

	Ex	perimenta	I		Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 ADOS (endpoin	t and ch	ange scor	es)						
OWLEY1999	6.5	1.7	28	6.3	2.2	28	41.1%	0.10 [-0.42, 0.62]	-
UNIS2002 Subtotal (95% CI)	-0.2	1.548616	52 80	0.2	1.833131	33 61	58.9% 100.0%		-
Heterogeneity: Chi ² =	0.94, df =	= 1 (P = 0.3	3); I ² =	0%					
Test for overall effect:	Z = 0.58	(P = 0.56)							
3.1.2 GARS									
OWLEY1999 Subtotal (95% CI)	9.2	3	28 28	8	3.3	28 28	100.0% 100.0%		
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.39	(P = 0.16)							
									-2 -1 0 1
									avours experimental Favours control

Social interaction



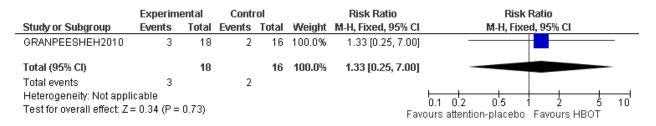
Communication and Social Interaction (ADOS; change score)



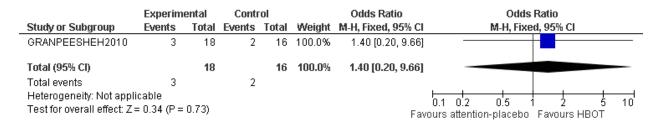
1.8.3 Medical procedures for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Hyperbaric oxygen treatment (HBOT) versus attention-placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

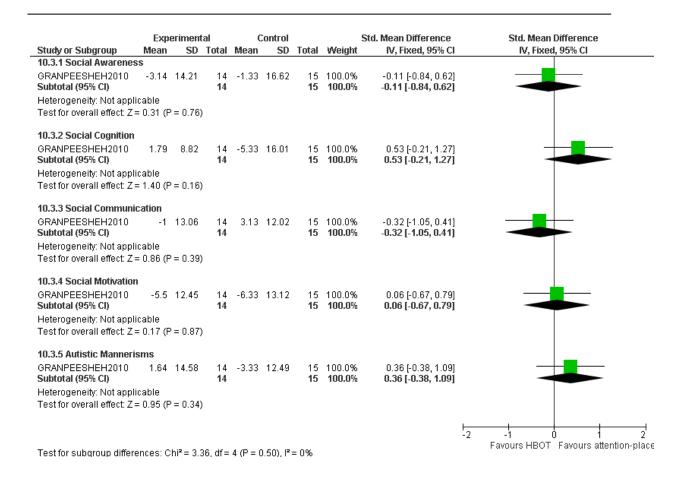
Positive treatment response (improvement in ADOS diagnostic classification based on Communication domain)



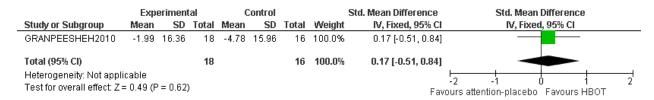
Positive treatment response (improvement in ADOS diagnostic classification based on Socialization domain)



Social impairment (SRS change score)

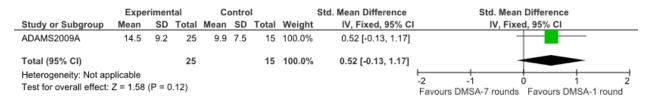


Appropriate vocalization (behavioural observation change score)

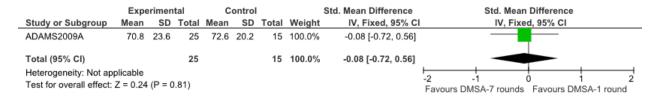


Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Social Pragmatic Problems (PDDBI)



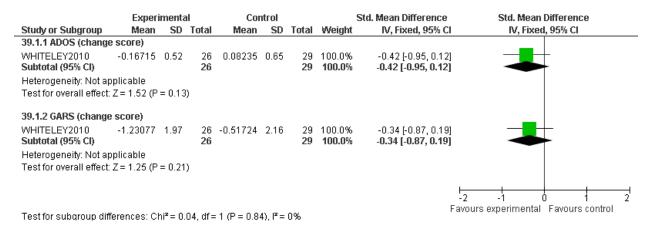
Social Approach Behaviours (PDDBI)



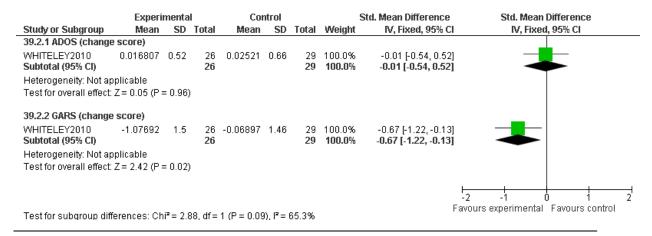
1.8.4 Nutritional interventions for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Gluten-free and casein-free diet versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

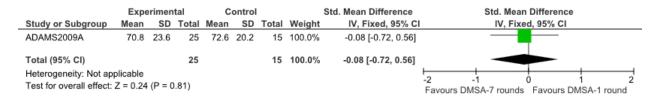
Communication (direct outcome)



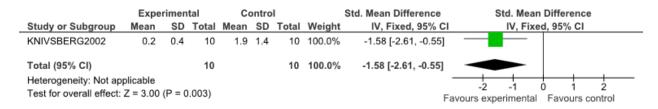
Social Interaction (direct outcome)



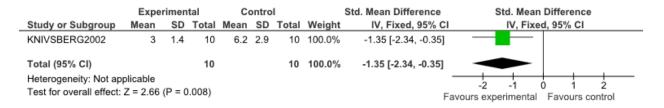
Communication and interaction (DIPAB; indirect outcome)



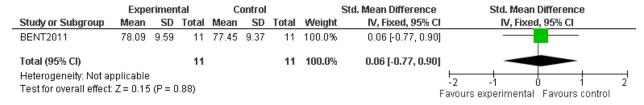
Resistance to communication and interaction (DIPAB; indirect outcome)



Social isolation (DIPAB; indirect outcome)



Omega-3 fatty acids versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



Omega-3 fatty acids versus healthy diet control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Frequency of positive vocalizations (behavioural observation)

	Exp	eriment	tal	C	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
JOHNSON2010	16	11.02	10	13.75	10.14	13	100.0%	0.21 [-0.62, 1.03]	
Total (95% CI)			10			13	100.0%	0.21 [-0.62, 1.03]	
Heterogeneity: Not ap Test for overall effect			63)						-2 -1 0 1 2 Favours healthy diet Favours omega-3

Frequency of social initiations (behavioural observation)

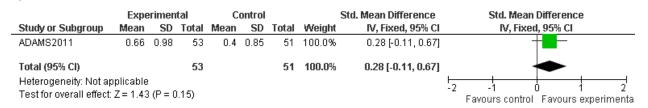
	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
JOHNSON2010	5.6	5.72	10	3.52	3.52	13	100.0%	0.44 [-0.40, 1.27]	
Total (95% CI)			10			13	100.0%	0.44 [-0.40, 1.27]	
Heterogeneity: Not ap Test for overall effect:	•).31)						-2 -1 0 1 2 Favours healthy diet Favours omega-3

Multivitamin/mineral supplement versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Sociability improvement (PGI-R)

	Exper	imen	tal	C	ontrol			Std. Mean Difference		Std. Mean D	ifferenc	e
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed,	95% CI	
ADAMS2011	0.77	1	53	0.63	0.92	51	100.0%	0.14 [-0.24, 0.53]		-	_	
Total (95% CI)			53			51	100.0%	0.14 [-0.24, 0.53]		—	>	
Heterogeneity: Not ap Test for overall effect:	•	(P = 0	1.46)						-2	-1 0 Favours control	Favours	1 2 experimenta

Eye contact improvement (PGI-R)



L-carnosine supplement versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Communication (GARS)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CHEZ2002	18.14	6.27	14	16.88	6.48	17	100.0%	0.19 [-0.52, 0.90]	
Total (95% CI)			14			17	100.0%	0.19 [-0.52, 0.90]	
Heterogeneity: Not ap Test for overall effect:).60)					F	-2 -1 0 1 2 avours experimental Favours control

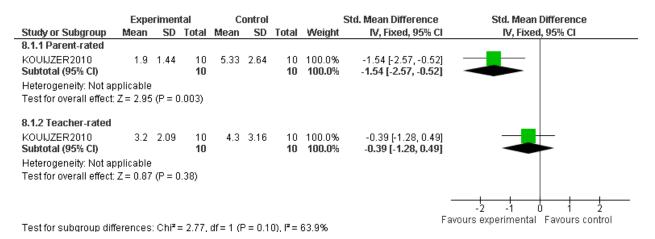
Social interaction (GARS)

	Ехре	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CHEZ2002	13.36	6.58	14	17.18	7.76	17	100.0%	-0.51 [-1.23, 0.21]	-
Total (95% CI)			14			17	100.0%	-0.51 [-1.23, 0.21]	
Heterogeneity: Not a Test for overall effect			0.16)					F	-2 -1 0 1 2 avours experimental Favours control

1.8.5 Sensory interventions for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Neurofeedback versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

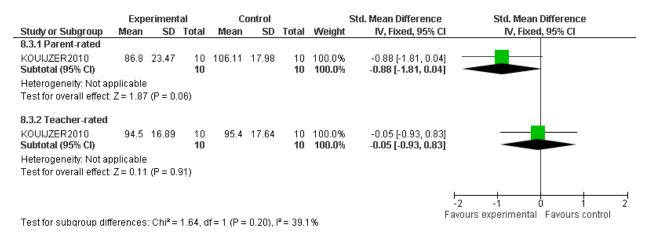
Reciprocal social interaction (SCQ)



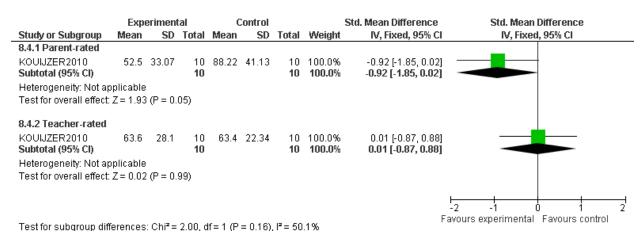
Communication (SCQ)

	Expe	erimen	tal	C	ontrol		9	itd. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.2.1 Parent-rated									
KOUIJZER2010	2.5	2.12	10	5.22	2.43	10	100.0%	-1.14 [-2.10, -0.18]	
Subtotal (95% CI)			10			10	100.0%	-1.14 [-2.10, -0.18]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.33	P = 0	.02)						
8.2.2 Teacher-rated									
KOUIJZER2010	4.2	2.29	10	4.6	1.77	10	100.0%	-0.19 [-1.07, 0.69]	
Subtotal (95% CI)			10			10	100.0%	-0.19 [-1.07, 0.69]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.42	P = 0	.68)						
								_	-2 -1 0 1 2
Test for subaroup diff								Favou	ırs experimental Favours control

Communication (CCC-2)



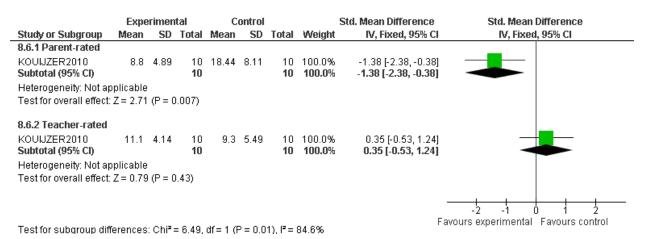
Social impairment (SRS)



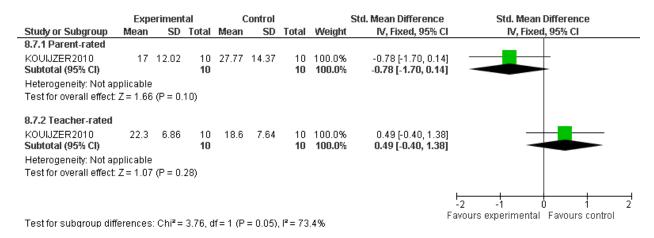
Social Awareness (SRS)

	Experimental			С	ontrol			Std. Mean Difference	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
8.5.1 Parent-rated												
KOUIJZER2010	8.9	4	10	12.11	5.44	10	100.0%	-0.64 [-1.55, 0.26]				
Subtotal (95% CI)			10			10	100.0%	-0.64 [-1.55, 0.26]				
Heterogeneity: Not app	olicable											
Test for overall effect: 2	Z = 1.40	(P = 0).16)									
8.5.2 Teacher-rated												
KOUIJZER2010	8.7	3.62	10	7.9	3.24	10	100.0%	0.22 [-0.66, 1.10]				
Subtotal (95% CI)			10			10	100.0%	0.22 [-0.66, 1.10]				
Heterogeneity: Not app	olicable											
Test for overall effect: 2	Z = 0.50	(P = 0)	0.62)									
								ŀ	-2 -1 1 2			
									vours experimental Favours control			
Test for subgroup diffe	rences	: Chi²:	= 1.81,	df = 1 (F	o = 0.1	8), I²=	44.9%	1 0	Tarour on the control			

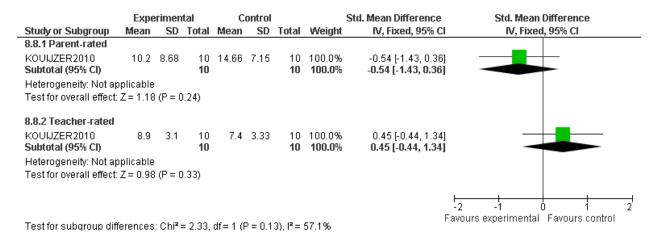
Social Cognition (SRS)



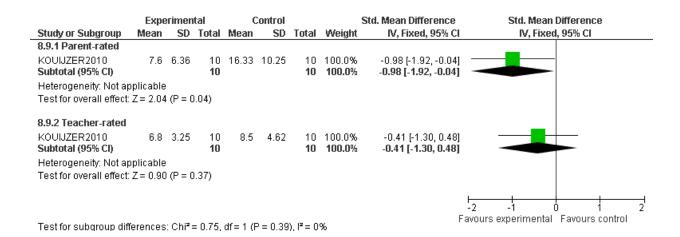
Social Communication (SRS)



Social Motivation (SRS)



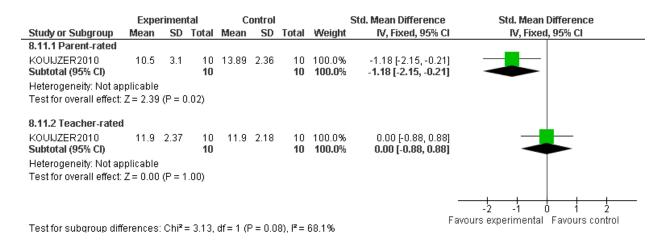
Autistic Mannerisms (SRS)



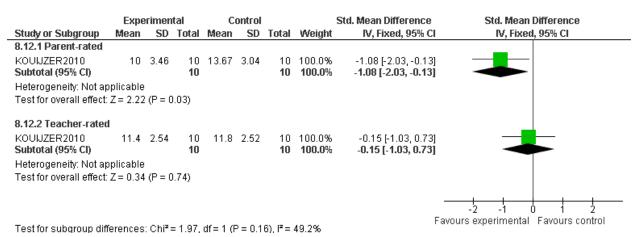
Social relations (CCC-2)

	Experimental		tal	C	ontrol		5	itd. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
8.10.1 Parent-rated											
KOUIJZER2010 Subtotal (95% CI)	12.9	3.31	10 10	14.22	3.49	10 10	100.0% 100.0 %	-0.37 [-1.26, 0.51] - 0.37 [-1.26, 0.51]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.82	(P = 0)	.41)								
8.10.2 Teacher-rated											
KOUIJZER2010 Subtotal (95% CI)	13.7	1.7	10 10	13.7	2.79	10 10	100.0% 100.0 %	0.00 [-0.88, 0.88] 0.00 [-0.88, 0.88]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.00	(P = 1	.00)								
								!	-2 -1 0 1		
Test for subgroup diff		· Obiz-	- 0.24	df _ 1 /F	-05	C) 12 - 1	nov	Fa	vours experimental Favours control		

Interests (CCC-2)



Inappropriate initialization (CCC-2)

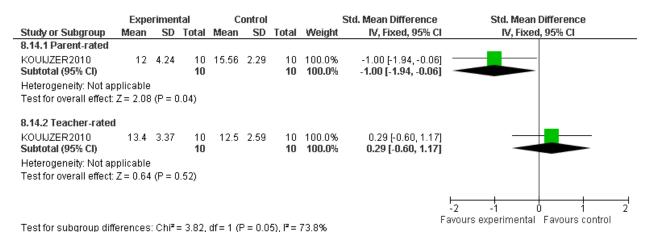


Stereotyped conversation (CCC-2)

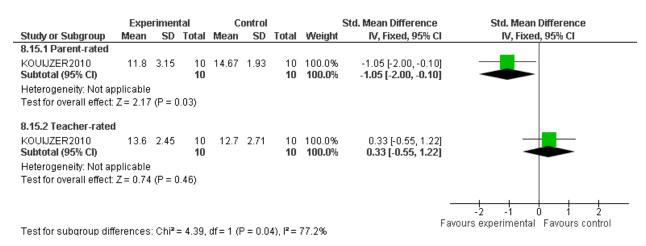
Experimental			tal	C	ontrol			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
8.13.1 Parent-rated											
KOUIJZER2010	11.2	3.76	10	13.33	3.57	10	100.0%	-0.56 [-1.45, 0.34]			
Subtotal (95% CI)			10			10	100.0%	-0.56 [-1.45, 0.34]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.22	P = 0).22)								
8.13.2 Teacher-rated											
KOUIJZER2010	12.9	3.21	10	11.9	3.03	10	100.0%	0.31 [-0.58, 1.19]			
Subtotal (95% CI)			10			10	100.0%	0.31 [-0.58, 1.19]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.68	(P = 0	0.50)								
								<u>⊢</u> -2	-1 0 1 :		
Taet for eubaroun diffe	oronooo	· Chiz	- 1 01	df = 1 /0	0 = 0.4	OV 13 —	Favo	urs experimental Favours control			

Test for subgroup differences: Chi² = 1.81, df = 1 (P = 0.18), I^2 = 44.6%

Context use (CCC-2)

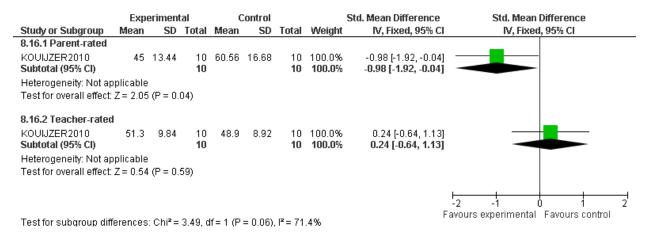


Non-verbal communication (CCC-2)



Autism: the management and support of children and young people on the autism spectrum

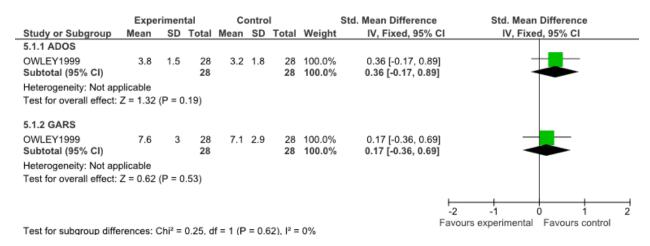
Pragmatics (CCC-2)



1.9 BIOMEDICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

1.9.1 Hormones for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

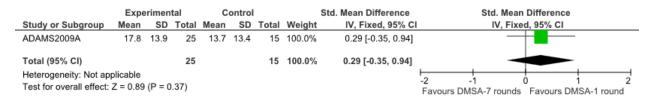
Secretin versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



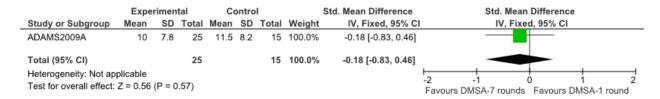
1.9.2 Medical procedures for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Sensory/Perceptual Approach Behaviours (PDDBI)

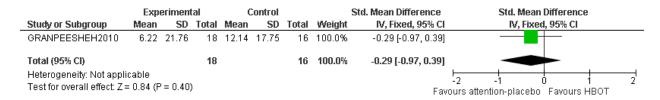


Ritualisms/Resistance to Change (PDDBI)

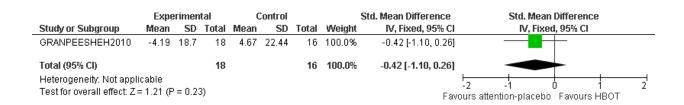


HBOT versus attention-placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Vocal stereotypy (behavioural observation; change score)

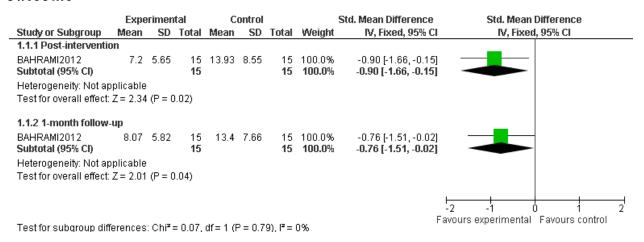


Physical stereotypy (behavioural observation; change score)



1.9.3 Motor intervention for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

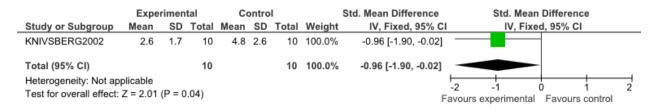
Kata exercise training versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome



1.9.4 Nutritional interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Gluten-free and casein-free diet versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

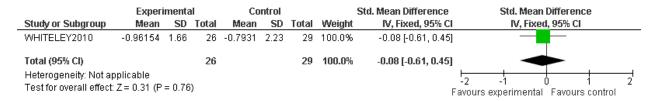
Unusual or bizarre behaviour (DIPAB)



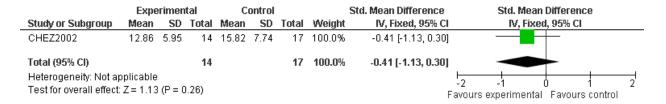
Repetitive Behaviours (change score; ADOS)

	Experimental			Co	ntrol			Std. Mean Difference	Std. Me	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fix	ked, 95% CI		
WHITELEY2010	-0.14706	0.46	26	0.03431	0.61	29	100.0%	-0.33 [-0.86, 0.20]] —	+		
Total (95% CI)			26			29	100.0%	-0.33 [-0.86, 0.20]		•		
Heterogeneity: Not ap Test for overall effect:	•	= 0.23)						-2 -1 Favours experimen	0 1 tal Favours co	2 ontrol	

Stereotyped behaviour (change score; GARS)

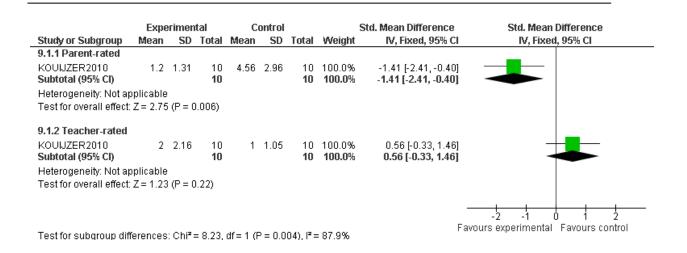


L-carnosine supplement versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



1.9.5 Sensory intervention for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Neurofeedback versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

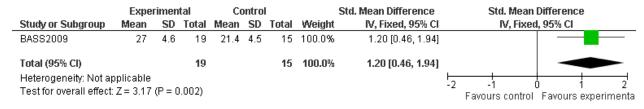


1.10PSYCHOSOCIAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

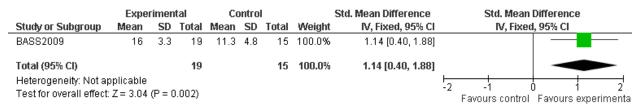
1.10.1 Animal-based intervention for behaviour that challenges as an indirect outcome

Horseback riding versus waitlist control for behaviour that challenges as an indirect outcome

Inattention/distractability (Sensory Profile)



Sedentary (Sensory Profile)

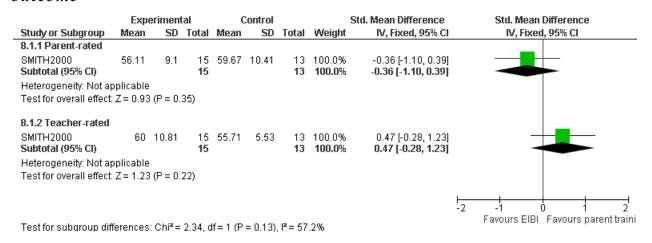


1.10.2Behavioural interventions for behaviour that challenges as a direct or indirect outcome

Behavioural and medical intervention versus medical intervention only for behaviour that challenges as a direct outcome

Study or Subgroup	Std. Mean Difference	SE	Experimental Total			Std. Mean Difference IV, Fixed, 95% C	
CARR2006	-1.64648386	0.50542511	10	11	100.0%	-1.65 [-2.64, -0.66	
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	•		10	11	100.0%	-1.65 [-2.64, -0.66	1 -2 -1 0 1 2 Favours experimental Favours control

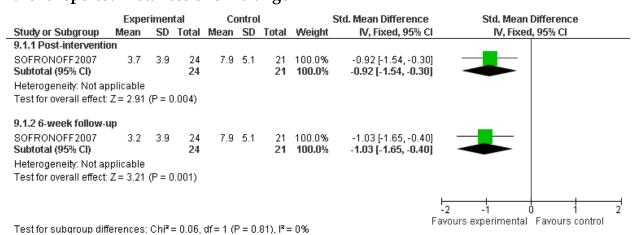
EIBI versus parent training for behaviour that challenges as an indirect outcome



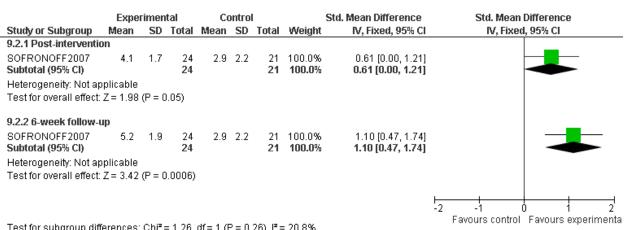
1.10.3 Cognitive-behavioural interventions for behaviour that challenges as a direct or indirect outcome

CBT versus waitlist control for behaviour that challenges as a direct outcome

Parent-reported instances of child anger

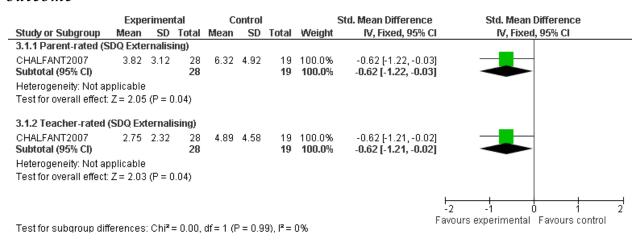


Parent confidence in child managing own anger



Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.8%

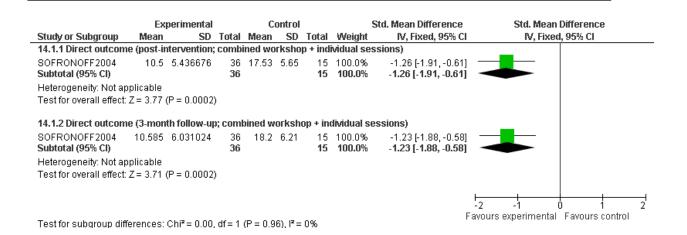
CBT versus waitlist control for behaviour that challenges as an indirect outcome

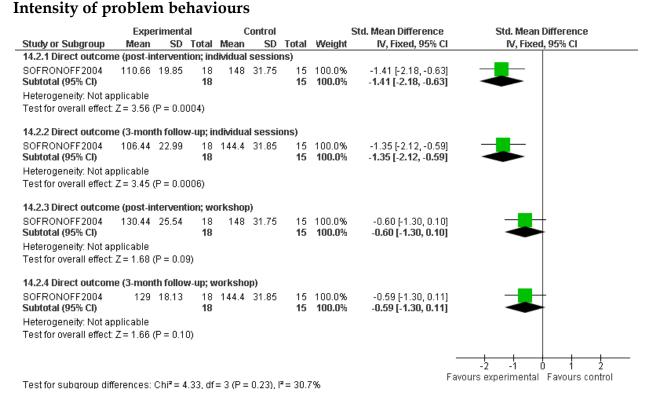


1.10.4 Parent training for behaviour that challenges as a direct or indirect outcome

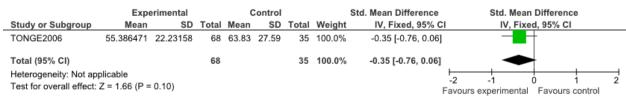
Parent training versus treatment-as-usual for behaviour that challenges as a direct or indirect outcome

Frequency of problem behaviours



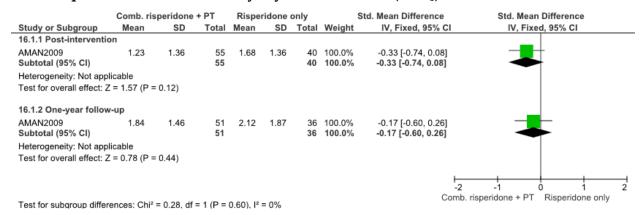


Problem behaviour (indirect outcome; DBC-TBPS; 6-month follow-up; PEC+PEBM combined)

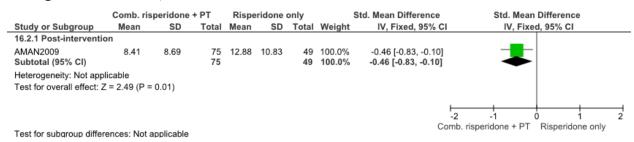


Combined parent training and antipsychotic versus antipsychotic-only for behaviour that challenges as a direct outcome

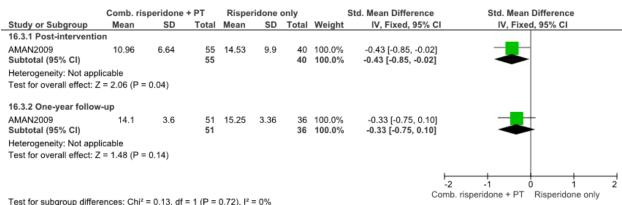
Noncompliant behaviour in everyday circumstances (HSQ)



Noncompliant behaviour in everyday circumstances (Noncompliance index - Daily Living Skills [VABS])



Irritability (ABC)



Lethargy/Social withdrawal (ABC)

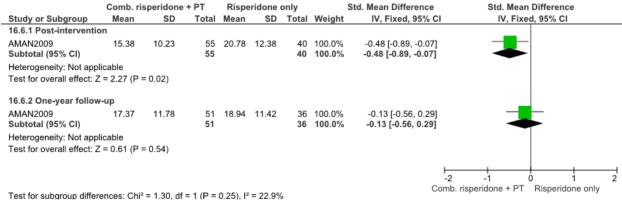
	Comb. ris	peridone	+ PT	Rispe	ridone	only	5	Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	SD Total		SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
16.4.1 Post-intervention	on										
AMAN2009	4.26	5.17	55	6.44	7.16	40	100.0%	-0.36 [-0.77, 0.06]			
Subtotal (95% CI)			55			40	100.0%	-0.36 [-0.77, 0.06]	→		
Heterogeneity: Not app	licable										
Test for overall effect: 2		0.09)									
16.4.2 One-year follov	v-up								_		
AMAN2009	4.65	5.21	51	7.39	6.83	36	100.0%	-0.46 [-0.89, -0.03]	— —		
Subtotal (95% CI)			51			36	100.0%	-0.46 [-0.89, -0.03]	•		
leterogeneity: Not app	olicable										
Test for overall effect: 2	Z = 2.08 (P =	0.04)									
								<u> </u>	- 		
								-2	-1 0 1		
Test for subgroup differ	rences: Chi²	= 0.11. df	= 1 (P =	0.74). I ²	= 0%			Comb. ri	speridone + PT Risperidone on		

Stereotypic behaviour (ABC)

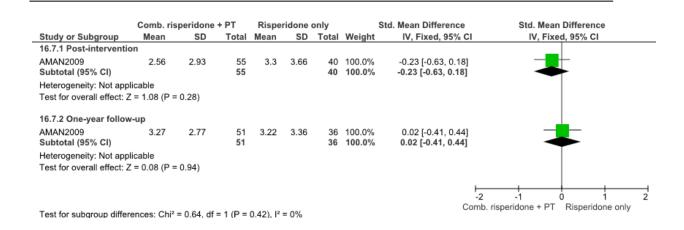
	Comb. ris	peridone	+ PT	Rispe	ridone	only		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
16.5.1 Post-interventi	on								
AMAN2009 Subtotal (95% CI)	3.2	4.09	55 55	6.25	5.68	40 40	100.0% 100.0%	-0.63 [-1.04, -0.21] -0.63 [-1.04, -0.21]	
Heterogeneity: Not app	olicable								
Test for overall effect:		0.003)							
16.5.2 One-year follow	w-up								
AMAN2009 Subtotal (95% CI)	4.06	3.67	51 51	5.61	5.31	36 36	100.0% 100.0%	-0.35 [-0.78, 0.08] -0.35 [-0.78, 0.08]	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 1.58 (P =	0.11)							
									-2 -1 0 1
								Cor	mb. risperidone + PT Risperidone only

Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%

Hyperactivity/Noncompliance (ABC)

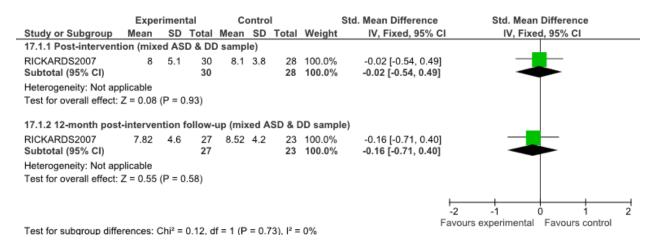


Inappropriate speech (ABC)

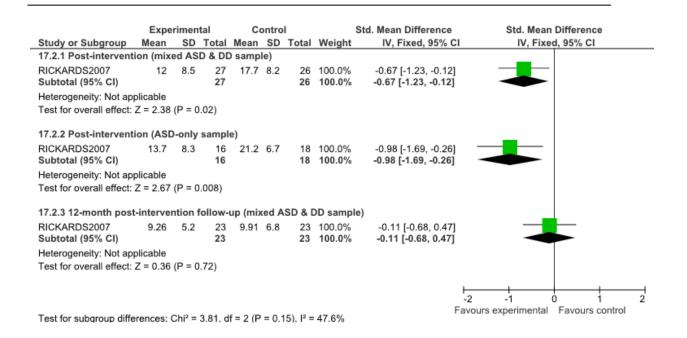


Combined parent training and early intervention centre programme versus early intervention centre programme only for behaviour that challenges as an indirect outcome

Parent-reported behaviour that challenges (BSQ)



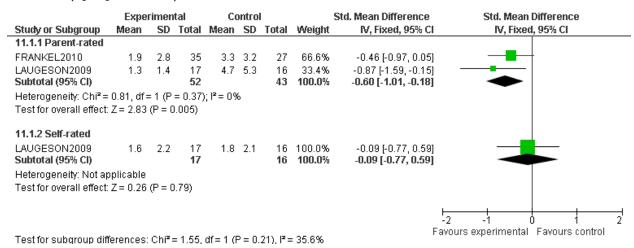
Teacher-rated behaviour that challenges (PBCL)



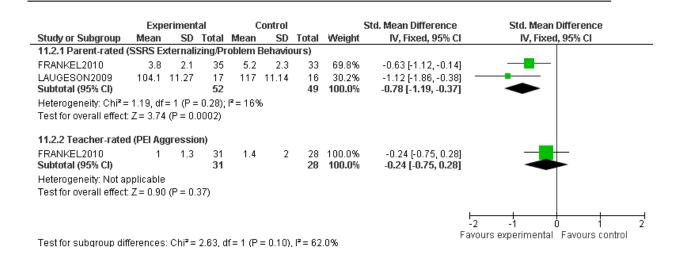
1.10.5 Social-communication interventions for behaviour that challenges as an indirect outcome

Social skills group versus treatment-as-usual for behaviour that challenges as an indirect outcome

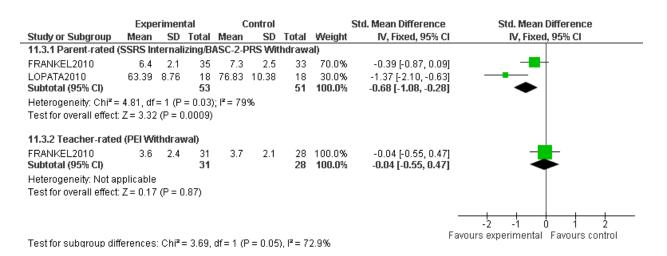
Conflict (QPQ Conflict)



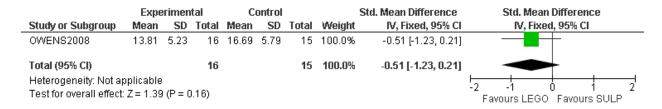
Intrusive/aggressive behaviour



Social withdrawal



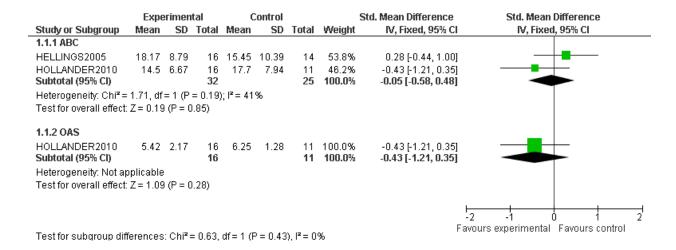
LEGO therapy versus SULP for behaviour that challenges as an indirect outcome



1.11PHARMACOLOGICAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

1.11.1 Anticonvulsants for behaviour that challenges as a direct outcome

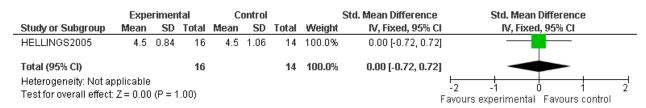
Divalproex versus placebo for behaviour that challenges as a direct outcome Irritability



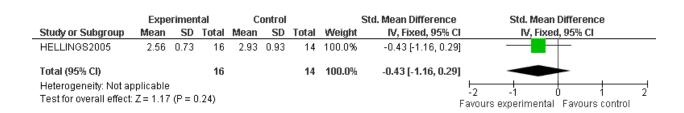
Aggression (OAS)

	Experimental Co				Control			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
HELLINGS2005	5.86	3.84	16	5.72	4.62	14	100.0%	0.03 [-0.69, 0.75]		
Total (95% CI)			16			14	100.0%	0.03 [-0.69, 0.75]		
Heterogeneity: Not ap Test for overall effect:	•).93)					F	-2 -1 0 1 2 avours experimental Favours control	1

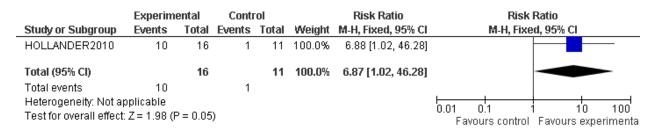
Global severity (CGI-S)



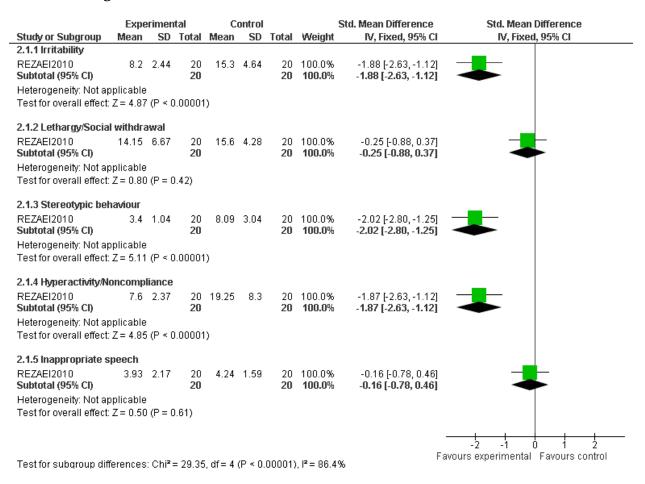
Global improvement (CGI-I)



Global improvement ('much improved/very improved' on CGI-improvement)

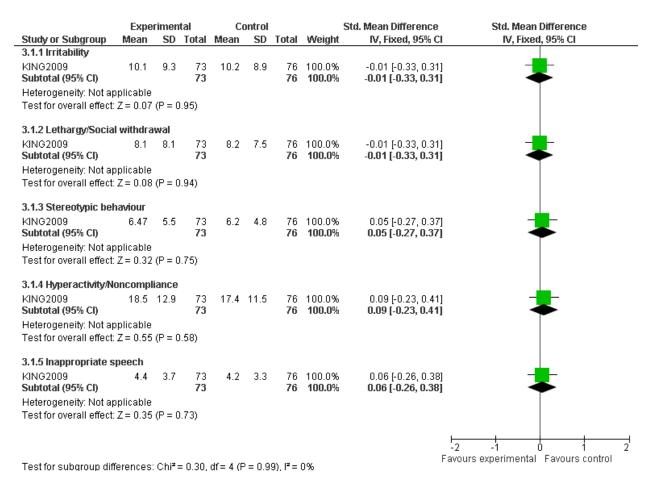


Topiramate and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



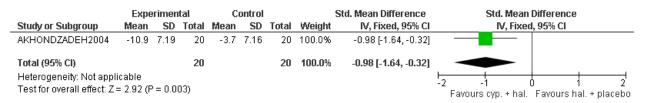
1.11.2 Antidepressants for behaviour that challenges as an indirect outcome

Citalopram versus placebo for behaviour that challenges as an indirect outcome



1.11.3 Antihistamines for behaviour that challenges as a direct outcome

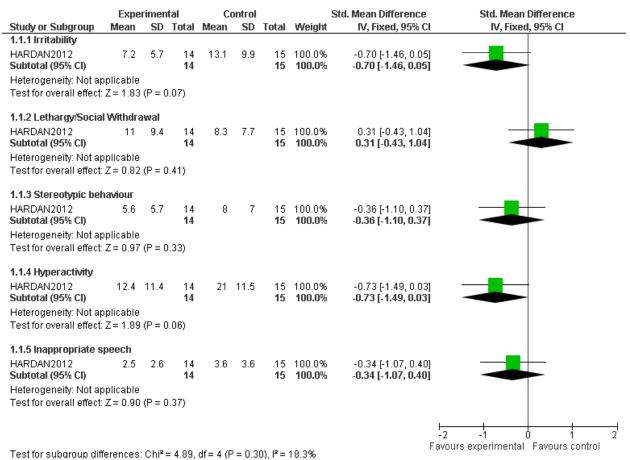
Cyproheptadine and haloperidol versus placebo and haloperidol for behaviour that challenges as a direct outcome



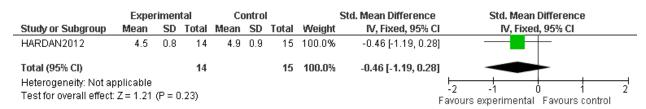
1.11.4 Antioxidants for behaviour that challenges as a direct outcome

N-acetylcysteine versus placebo for behaviour that challenges as a direct outcome

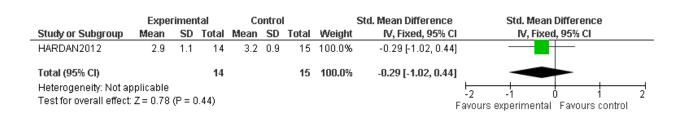
Behaviour that challenges (ABC)



Global severity (CGI-S)



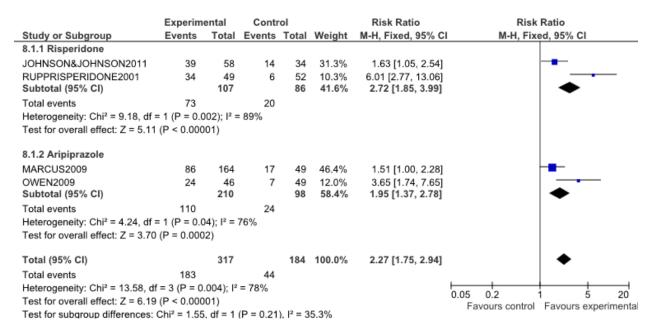
Global improvement (CGI-I)



1.11.5 Antipsychotics for behaviour that challenges as a direct or indirect outcome

Antipsychotic (risperidone or aripiprazole) versus placebo for behaviour that challenges as a direct outcome

Positive treatment response (clinician-rated: >25% improvement on ABC-Irritability with or without 'much improved/very improved' on CGI-improvement)



Positive treatment response (parent-defined target symptoms)

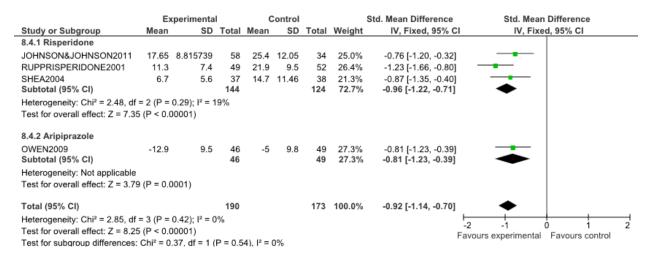
	Ехрегіт	ental	Contr	ol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
RUPPRISPERIDONE2001	31	44	9	43	100.0%	3.37 [1.83, 6.21]			_	
Total (95% CI)		44		43	100.0%	3.37 [1.83, 6.21]			•	>
Total events	31		9							
Heterogeneity: Not applicable)						0.1.0	12 05	+	
Test for overall effect: Z = 3.89	9 (P = 0.00	01)					0.1 U	avours control	Favours	0 10

111

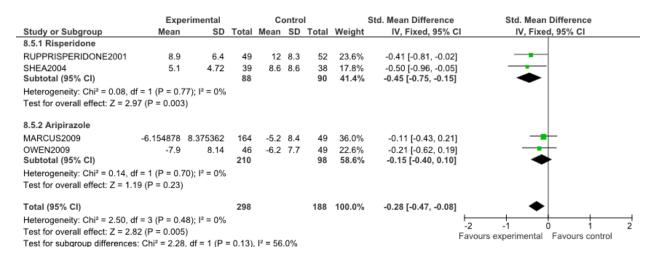
Maladaptive behaviour (VABS)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
RUPPRISPERIDONE2001	20.34	7.93	49	30.27	8.87	52	100.0%	-1.17 [-1.59, -0.75]	_		
Total (95% CI)			49			52	100.0%	-1.17 [-1.59, -0.75]	•		
Heterogeneity: Not applicable Test for overall effect: Z = 5.4		00001)					F	-2 -1 avours experimental	0 1 Favours contr	

Irritability (ABC)



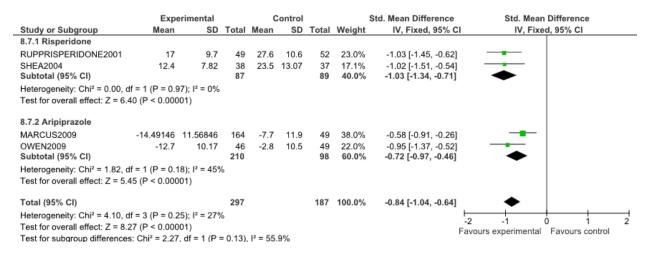
Lethargy/Social withdrawal (ABC)



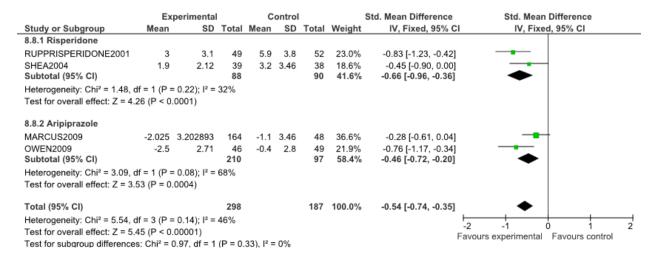
Stereotypic behaviour (ABC)

	Expe	rimental		С	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean		Total	Mean			Weight			
8.6.1 Risperidone										_
RUPPRISPERIDONE2001	5.8	4.6	49	7.3	4.8	52	24.2%	-0.32 [-0.71, 0.08]	_ _	
SHEA2004	3.7	3.66	38	5.7	6.4	38	18.1%	-0.38 [-0.83, 0.07]	· I	
Subtotal (95% CI)			87			90	42.4%	-0.34 [-0.64, -0.05]	•	
Heterogeneity: Chi2 = 0.04, df	f = 1 (P = 0.8	4); I ² = 0%								
Test for overall effect: Z = 2.2	7 (P = 0.02)									
8.6.2 Aripiprazole										
MARCUS2009	-4.392073	4 846254	164	-1.8	4.83	49	35.8%	-0.53 [-0.86, -0.21]	_ _ _	
OWEN2009	-4.8	4.07	46	-2		49	21.8%	-0.67 [-1.09, -0.26]	· I	
Subtotal (95% CI)	1.0	1.01	210	_		98	57.6%	-0.59 [-0.84, -0.33]		
Heterogeneity: Chi ² = 0.26, df	f = 1 (P = 0.6	1): I ² = 0%								
Test for overall effect: Z = 4.5										
Total (95% CI)			297			188	100.0%	-0.48 [-0.68, -0.29]	•	
Heterogeneity: Chi ² = 1.78, df	f = 3 (P = 0.6	2): I ² = 0%								_
Test for overall effect: Z = 4.9									-2 -1 0 1	
Test for subgroup differences	4	,	= 0.23).	$l^2 = 32$.0%				Favours experimental Favours control	

Hyperactivity (ABC)



Inappropriate speech (ABC)



Parent-defined target symptoms

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean	Difference	,	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% (CI	IV, Fixed	d, 95% CI		
RUPPRISPERIDONE2001	2.8	1.16	44	4.5	1.28	43	48.8%	-1.38 [-1.85, -0.91] —	-			
SHEA2004	42.6	26	39	58.6	30.33	37	51.2%	-0.56 [-1.02, -0.10]				
Total (95% CI)			83			80	100.0%	-0.96 [-1.29, -0.63]	l	•			
Heterogeneity: Chi ² = 5.96, d	f = 1 (P	= 0.01	; I ² = 8	3%					-	1 ,	<u> </u>		
Test for overall effect: Z = 5.7	74 (P < 0	.0000	I)						Favour	s experimental	Favours c	ontrol	2

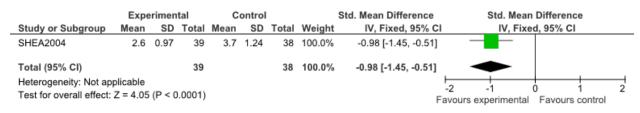
Global state: Positive treatment response (CGI)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
JOHNSON&JOHNSON2011	24	60	5	34	47.4%	2.72 [1.14, 6.47]	
SHEA2004	21	39	7	38	52.6%	2.92 [1.41, 6.06]	
Total (95% CI)		99		72	100.0%	2.83 [1.61, 4.95]	•
Total events	45		12				
Heterogeneity: Chi ² = 0.02, df =	= 1 (P = 0.9	0); I ² =	0%				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 3.63	(P = 0.000)	3)					Favours control Favours experimental

Global severity (CGI-S)

		perimental			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.11.1 Risperidone									
JOHNSON&JOHNSON2011	4.35	0.761643	58	4.6	1.04	34	40.3%	-0.28 [-0.71, 0.14]	
Subtotal (95% CI)			58			34	40.3%	-0.28 [-0.71, 0.14]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.31 (P = 0.19	3)							
8.11.2 Aripiprazole									
MARCUS2009	-1	1.141659	140	-0.6	1.28	41	59.7%	-0.34 [-0.69, 0.01]	
Subtotal (95% CI)			140			41	59.7%	-0.34 [-0.69, 0.01]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.90 (P = 0.06	6)							
Total (95% CI)			198			75	100.0%	-0.32 [-0.59, -0.05]	•
Heterogeneity: Chi ² = 0.04, df =	1 (P = 0)	$(.84); I^2 = 09$	%						1-2 -1 1 2
Test for overall effect: $Z = 2.30$ (P = 0.02	2)						,	2 , 0 , 2
Test for subgroup differences:	•		P = 0.8	4), I² = 0)%			r	Favours experimental Favours control

Global improvement (CGI-I)



114

Low dose antipsychotic (risperidone or aripiprazole) versus placebo for behaviour that challenges as a direct outcome

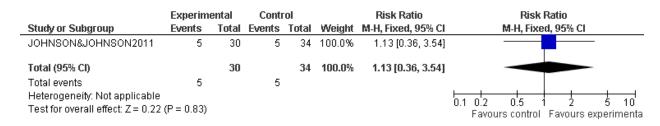
Positive treatment response (clinician-rated: >25% improvement on ABC-Irritability with or without 'much improved/very improved' on CGI-improvement)

	Ехрегіте	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
9.1.1 Risperidone (0.125-0.179	5mg/day)						
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	15	29 29	14	34 34	42.4% 42.4%		-
Total events	15		14				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.84$	(P = 0.40)						
9.1.2 Aripiprazole (5mg/day)							
MARCUS2009	29	52	17	49	57.6%		-
Subtotal (95% CI)		52		49	57.6%	1.61 [1.02, 2.53]	-
Total events	29		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.05	(P = 0.04)						
Total (95% CI)		81		83	100.0%	1.46 [1.03, 2.06]	•
Total events	44		31				
Heterogeneity: Chi ^z = 0.48, df=	1 (P = 0.4	9); $I^2 = 0$	0%				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 2.14	(P = 0.03)						Favours control Favours experimenta
Test for subgroup differences:	$Chi^2 = 0.48$	3, df = 1	(P = 0.49)	3), I² = 0)%		1 avours control 1 avours experimenta

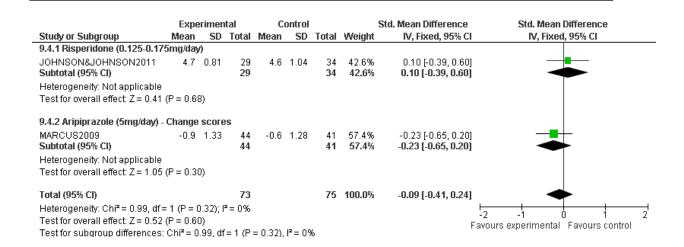
Behaviour that challenges (ABC)

		eriment			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup 9.2.1 Irritability	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
JOHNSON&JOHNSON2011 Subtotal (95% CI)	19.7	9.24	29 29	25.4	12.05	34 34	100.0% 100.0 %	-0.52 [-1.02, -0.01] - 0.52 [-1.02, -0.01]	.
Heterogeneity: Not applicable Test for overall effect: Z = 2.02	(P = 0.04	4)							
9.2.2 Lethargy/Social withdra	wal (cha	nge sc	оге)						
MARCUS2009 Subtotal (95% CI) Heterogeneity: Not applicable	-5.8	8.65	52 52	-5.2	8.4	49 49	100.0% 100.0 %	-0.07 [-0.46, 0.32] - 0.07 [-0.46, 0.32]	*
Test for overall effect: Z = 0.35	(P = 0.73)	3)							
9.2.3 Stereotypic behaviour (d	_							0.554.0.05 0.45	_
MARCUS2009 Subtotal (95% CI)	-4.5	4.9	52 52	-1.8	4.83	49 49	100.0% 100.0 %	-0.55 [-0.95, -0.15] - 0.55 [-0.95, -0.15]	•
Heterogeneity: Not applicable Test for overall effect: Z = 2.71	(P = 0.00	07)							
9.2.4 Hyperactivity (change so	соге)								_
MARCUS2009 Subtotal (95% CI)	-14	11.54	52 52	-7.7	11.9	49 49	100.0% 100.0 %	-0.53 [-0.93, -0.14] - 0.53 [-0.93, -0.14]	-
Heterogeneity: Not applicable Test for overall effect: Z = 2.63	(P = 0.00	08)							
9.2.5 Inappropriate speech (c	hange s	соге)							_
MARCUS2009 Subtotal (95% CI)	-2	3.61	52 52	-1.1	3.46	48 48	100.0% 100.0 %	-0.25 [-0.65, 0.14] - 0.25 [-0.65, 0.14]	
Heterogeneity: Not applicable Test for overall effect: Z = 1.26	(P = 0.21	1)	JZ			40	100.0%	-0.25 [-0.05, 0.14]	
								⊢	
								-2 Favoi	-1 0 1 urs experimental Favours contro
Test for subgroup differences:	Chi² = 4	.39, df=	4 (P =	0.36), I	² = 8.9%	6		1 avot	are experimental Tarears contro

Global state: Positive treatment response (CGI)

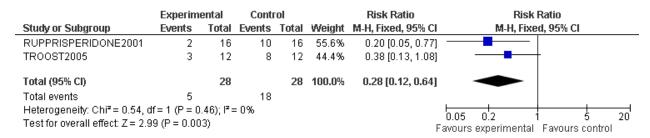


Global severity (CGI-S)

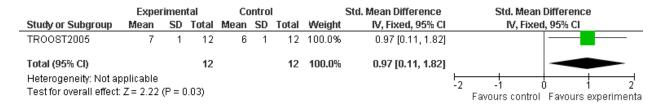


Continued risperidone versus switch to placebo for behaviour that challenges as a direct outcome

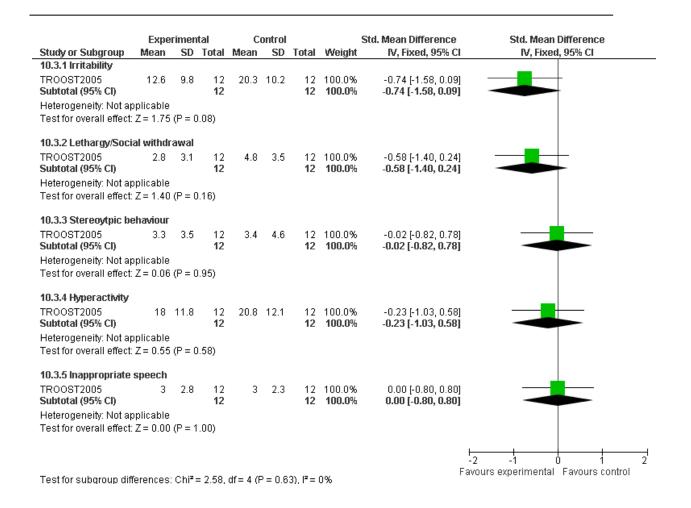
Relapse rate after discontinuation



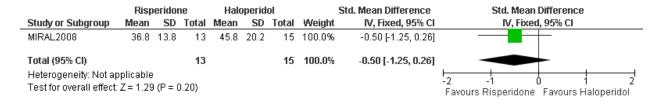
Time to relapse after discontinuation (in weeks)



Behaviour that challenges (ABC)



Risperidone versus haloperidol for behaviour that challenges as an indirect outcome



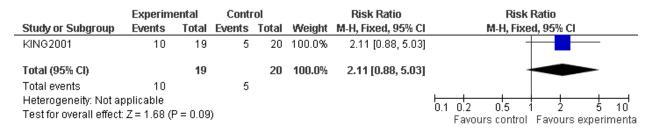
1.11.6 Antivirals for behaviour that challenges as a direct outcome

Amantadine hydrochloride versus placebo for behaviour that challenges as a direct outcome

Positive parent-rated treatment response (>25% improvement on ABC-Irritability and/or hyperactivity)

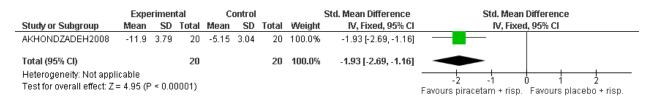
	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2001	9	19	7	19	100.0%	1.29 [0.60, 2.74]	
Total (95% CI)		19		19	100.0%	1.29 [0.60, 2.74]	
Total events	9		7				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 0.65 (F	° = 0.51)				Favours control Favours experimenta

Positive investigator-rated treatment response ('much improved/very improved' on CGI-improvement)



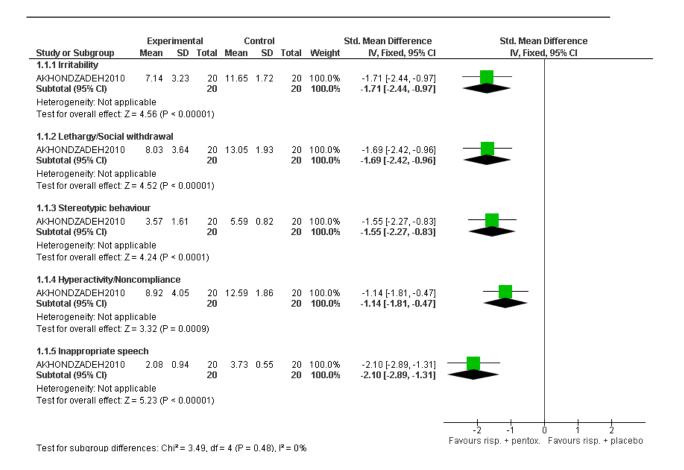
1.11.7Cognitive enhancers for behaviour that challenges as a direct outcome

Piracetam and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



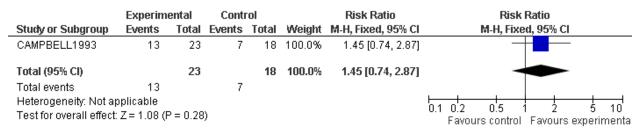
1.11.8 Methylxanthines for behaviour that challenges as a direct outcome

Pentoxifylline and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



1.11.9Opioid antagonists for behaviour that challenges as a direct outcome

Naltrexone versus placebo for behaviour that challenges as a direct outcome



1.11.10 Selective noradrenaline reuptake inhibitors (SNRIs) for behaviour that challenges as an indirect outcome

Atomoxetine versus placebo for behaviour that challenges as an indirect outcome

	Expe	eriment			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.1.1 Irritability									
ELILILLY2009	14.5	9.36	43	15.4	9.8		100.0%	-0.09 [-0.51, 0.32]	_
Subtotal (95% CI)			43			46	100.0%	-0.09 [-0.51, 0.32]	-
Heterogeneity: Not ap									
Test for overall effect:	Z = 0.44	(P = 0.6	66)						
10.1.2 Lethargy/Soci	al withdr	awal							
ELILILLY2009	11.1	9.34	43	11.5	8.17	46	100.0%	-0.05 [-0.46, 0.37]	-
Subtotal (95% CI)			43			46	100.0%	-0.05 [-0.46, 0.37]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.21	(P = 0.8)	33)						
10.1.3 Stereotypic be	haviour								
ELILILLY2009	3.6	4.01	43	3.6	4.12	46	100.0%	0.00 [-0.42, 0.42]	_
Subtotal (95% CI)			43			46	100.0%	0.00 [-0.42, 0.42]	•
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.00	(P = 1.0	00)						
10.1.4 Hyperactivity/	Noncom	pliance							
ELILILLY2009	22.5	11.05	43	24.6	10.33	45	100.0%	-0.19 [-0.61, 0.22]	—
Subtotal (95% CI)			43			45	100.0%	-0.19 [-0.61, 0.22]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.91	(P = 0.3)	36)						
10.1.5 Inappropriate	speech								
ELILILLY2009	3.8	2.92	43	4.5	3.26	46	100.0%	-0.22 [-0.64, 0.19]	-
Subtotal (95% CI)			43			46	100.0%	-0.22 [-0.64, 0.19]	◆
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.05	(P = 0.2)	29)						
		-							
								-2	-1 0 1
								_	rs experimental Favours control

1.12BIOMEDICAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

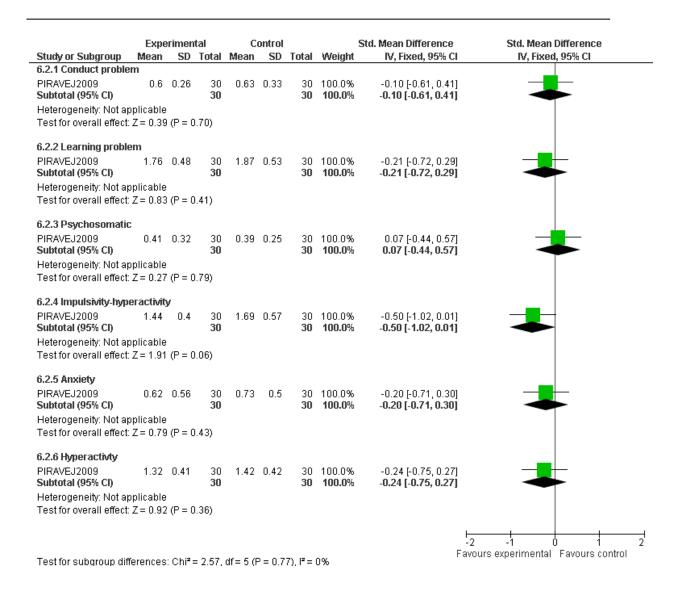
1.12.1 Complementary therapies for behaviour that challenges as a direct or indirect outcome

Thai massage and sensory integration therapy versus sensory integration therapy only for behaviour that challenges as a direct outcome

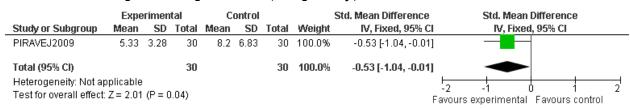
Teacher-rated behaviour that challenges (CTRS)

		rimen			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
6.1.1 Conduct proble	m								
PIRAVEJ2009	0.64	0.35	30	0.71	0.26	30	100.0%	-0.22 [-0.73, 0.28]	— <u>—</u> —
Subtotal (95% CI)			30			30	100.0%	-0.22 [-0.73, 0.28]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.87	(P = 0)	.39)						
6.1.2 Hyperactivity									_
PIRAVEJ2009	1.24	0.5	30	1.49	0.37	30	100.0%	-0.56 [-1.08, -0.04]	_
Subtotal (95% CI)			30			30	100.0%	-0.56 [-1.08, -0.04]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.13	(P = 0)	.03)						
6.1.3 Inattention-pass	sivity								_
PIRAVEJ2009	1.18	0.51	30	1.34	0.36	30	100.0%	-0.36 [-0.87, 0.15]	
Subtotal (95% CI)			30			30	100.0%	-0.36 [-0.87, 0.15]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.37	(P = 0)	.17)						
6.1.4 Hyperactivity in	dex								
PIRAVEJ2009	1.1	0.49	30	1.28	0.4	30	100.0%	-0.40 [-0.91, 0.11]	
Subtotal (95% CI)			30			30	100.0%	-0.40 [-0.91, 0.11]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.52	(P = 0)	.13)						
								<u> -2</u>	-
								_	rs experimental Favours control

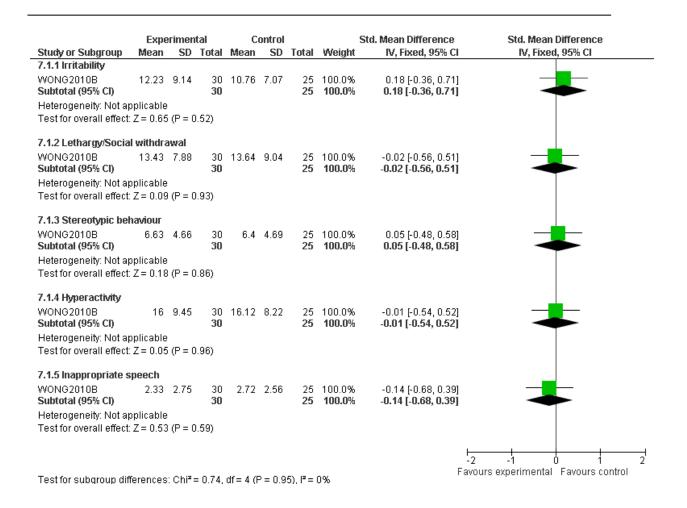
Parent-rated behaviour that challenges (CPRS)



Parent-rated sleep-related problems (sleep diary)



Electro-acupuncture versus sham electro-acupuncture for behaviour that challenges as an indirect outcome



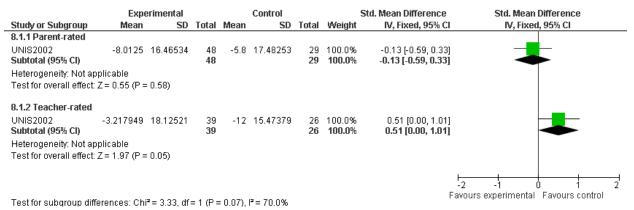
Electro-acupuncture and conventional educational programme versus conventional educational programme only for behaviour that challenges as an indirect outcome

	Exp	erimenta			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
3.1.1 Total score									-
VONG2008 Subtotal (95% CI)	15.556	22.356	18 18	9.5	17.47		100.0% 100.0%	0.30 [-0.36, 0.95] 0.30 [-0.36, 0.95]	-
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.38)						
3.1.2 Irritability									_
NONG2008 Subtotal (95% CI)	4.389	7.261	18 18	1.61	5.466		100.0% 100.0%	0.42 [-0.24, 1.08] 0.42 [-0.24, 1.08]	
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.21)						
3.1.3 Lethargy/Social	withdrav	wal							
NONG2008 Subtotal (95% CI)	3.056	6.991	18 18	1.44	6.474		100.0% 100.0%	0.23 [-0.42, 0.89] 0.23 [-0.42, 0.89]	
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.48)						
3.1.4 Stereotypic beha	aviour								
VONG2008 Subtotal (95% CI)	2.306	3.035	18 18	1.44	2.854	18 18	100.0% 100.0%	0.29 [-0.37, 0.94] 0.29 [-0.37, 0.94]	
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.39)						
3.1.5 Hyperactivity									
VONG2008 Subtotal (95% CI)	4.639	7.467	18 18	5.11	7.395		100.0% 100.0%	-0.06 [-0.72, 0.59] -0.06 [-0.72, 0.59]	
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.85)						
3.1.6 Inappropriate sp	eech								
VONG2008 Subtotal (95% CI)	1.168	1.654	18 18	-0.11	2.541		100.0% 100.0%	0.58 [-0.09, 1.25] 0.58 [-0.09, 1.25]	
Heterogeneity: Not app Fest for overall effect: 2		(P = 0.09)						
									-2 -1 0

1.12.2 Hormones for behaviour that challenges as an indirect outcome

Secretin versus placebo for behaviour that challenges as an indirect outcome

Behaviour that challenges (ABC total change score; porcine+synthetic groups combined)

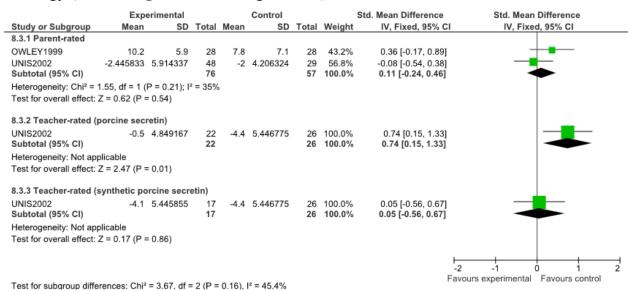


Irritability (ABC; endpoint and change scores)

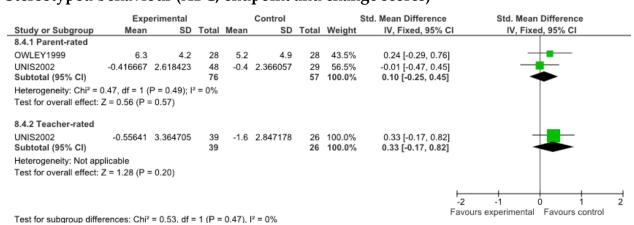
	Exp	erimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.2.1 Parent-rated									
OWLEY1999	10.1	10.2	28	10.9	8.1	28	43.7%	-0.09 [-0.61, 0.44]	
UNIS2002	-2.133333	5.002897	48	-1.5	5.126457	29	56.3%	-0.12 [-0.59, 0.34]	
Subtotal (95% CI)			76			57	100.0%	-0.11 [-0.45, 0.24]	-
Heterogeneity: Chi2 =	0.01, df = 1 ($P = 0.91$); I^2	2 = 0%						
Test for overall effect:	Z = 0.61 (P =	0.54)							
8.2.2 Teacher-rated									
UNIS2002	-0.215385	6.192379	39	-1.5	6.808469	26	100.0%	0.20 [-0.30, 0.69]	-
Subtotal (95% CI)			39			26	100.0%	0.20 [-0.30, 0.69]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.78 (P =	0.44)							
									-2 -1 0 1
T	01.12	0.07.16	4 (5)	0.00	2 00/			F	avours experimental Favours control

Test for subgroup differences: Chi² = 0.97, df = 1 (P = 0.33), I² = 0%

Lethargy (ABC; endpoint and change scores)



Stereotyped behaviour (ABC; endpoint and change scores)

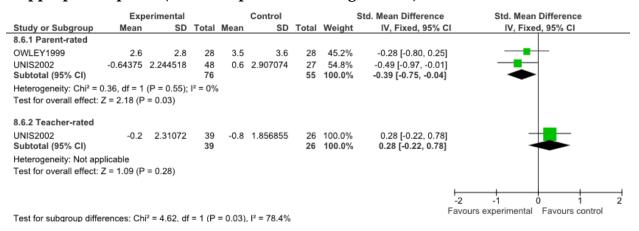


Hyperactivity (ABC; endpoint and change scores)

	Experimental				Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
8.5.1 Parent-rated									
OWLEY1999	18.5	10.6	28	18.6	11.4	28	43.6%	-0.01 [-0.53, 0.51]	
UNIS2002	-2.272917	5.490126	48	-2.2	8.2812	29	56.4%	-0.01 [-0.47, 0.45]	
Subtotal (95% CI)			76			57	100.0%	-0.01 [-0.36, 0.34]	•
Heterogeneity: Chi2 = 0	0.00, df = 1 (P = 1.00); I	2 = 0%						
Test for overall effect:	Z = 0.06 (P =	= 0.95)							
8.5.2 Teacher-rated									
UNIS2002	-0.120513	7.148993	39	-3.7	5.818146	26	100.0%	0.53 [0.03, 1.04]	 _
Subtotal (95% CI)			39			26	100.0%	0.53 [0.03, 1.04]	-
Heterogeneity: Not app	plicable								
Test for overall effect:	Z = 2.06 (P =	= 0.04)							
									
									2
Test for subgroup diffe	erences: Chi²	= 3.01. df =	1 (P =	0.08).	² = 66.7%				Favours experimental Favours control

Test for subgroup differences: $Chi^2 = 3.01$, df = 1 (P = 0.08), $I^2 = 66.7$ %

Inappropriate speech (ABC; endpoint and change scores)



1.12.3 Medical procedures for behaviour that challenges as a direct or indirect outcome

HBOT versus attention-placebo for behaviour that challenges as a direct or indirect outcome

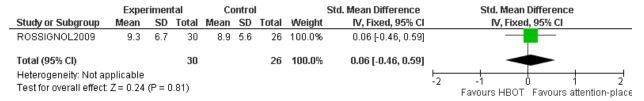
Behaviour that challenges

	Expe	erimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
8.1.1 Direct outcome (A	ABC total)								
ROSSIGNOL2009	46.4	24.7	30	45.5	17.3	26	63.1%	0.04 [-0.48, 0.57]		
Subtotal (95% CI)			30			26	63.1%	0.04 [-0.48, 0.57]		
Heterogeneity: Not appl	licable									
Test for overall effect: Z	= 0.15 (P	9 = 0.88	3)							
8.1.2 Indirect outcome	(behavio	ural ol	bserva	tion-Ch	allengi	ing bel	aviour ch	ange score)		
GRANPEESHEH2010	-2.71	8.54	18	1.11	4.32	16	36.9%	-0.54 [-1.23, 0.15]		
Subtotal (95% CI)			18			16	36.9%	-0.54 [-1.23, 0.15]		
Heterogeneity: Not appl	licable									
Test for overall effect: Z	= 1.54 (P	9 = 0.12	2)							
Total (95% CI)			48			42	100.0%	-0.17 [-0.59, 0.24]		
Heterogeneity: Chi ² = 1.	74, df = 1	(P = 0).19); l²	= 43%					<u> </u>	
Test for overall effect: Z		•							-2	-1 U 1
Test for subgroup differ	,		,	= 1 (P =	0.19)	$I^2 = 4.2$	6%			Favours HBOT Favours attention-pl

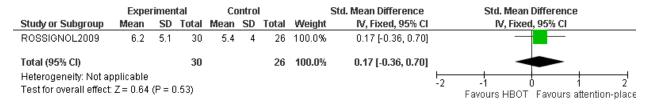
Irritability (ABC; direct outcome)

	Expe	rimen	tal	Co	ontro	ı		Std. Mean Difference		Std. Mean	Difference)	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI		
ROSSIGNOL2009	10.5	7.4	30	11.3	6.4	26	100.0%	-0.11 [-0.64, 0.41]			_		
Total (95% CI)			30			26	100.0%	-0.11 [-0.64, 0.41]		-	_		
Heterogeneity: Not ap									-2 -	 	 	 	<u> </u>
Test for overall effect:	Z = 0.42	(P = 0)	1.67)						Favo	ours HBOT	Favours	attentior	n-place

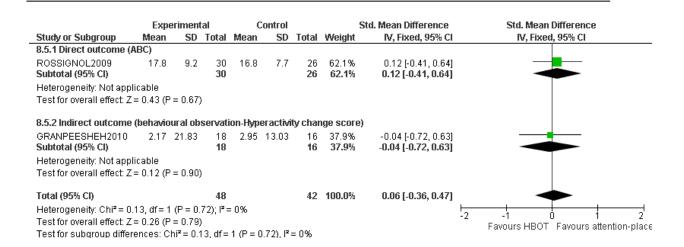
Lethargy/Social withdrawal (ABC; direct outcome)



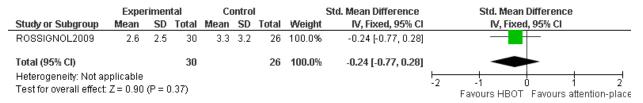
Stereotypy (ABC; direct outcome)



Hyperactivity

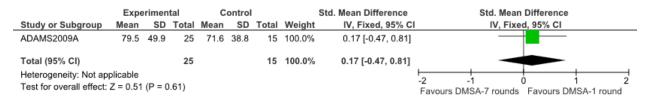


Inappropriate speech (ABC; direct outcome)

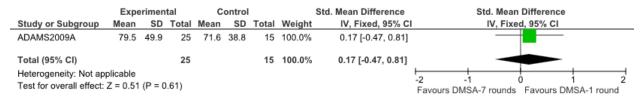


Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for behaviour that challenges as an indirect outcome

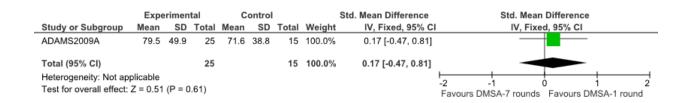
Maladaptive Behaviours Composite (PDDBI)



Arousal Regulation Problems (PDDBI)



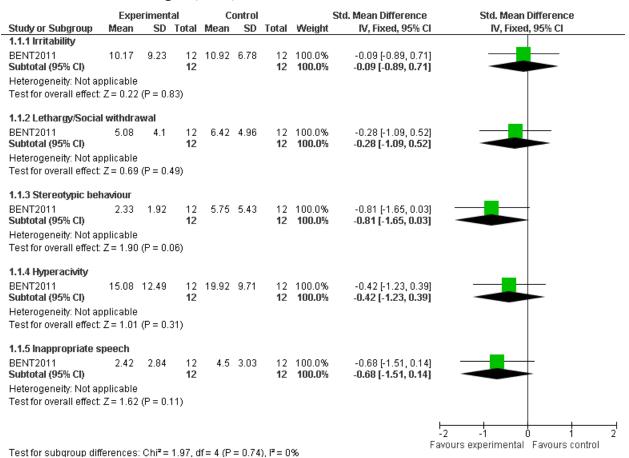
Aggressiveness (PDDBI)



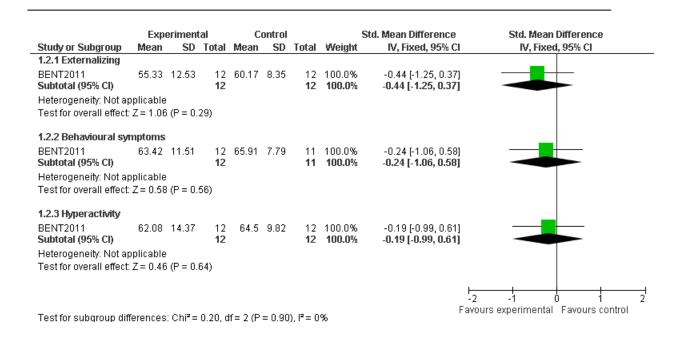
1.12.4 Nutritional interventions for behaviour that challenges as a direct or indirect outcome

Omega-3 fatty acids versus placebo for behaviour that challenges as a direct outcome

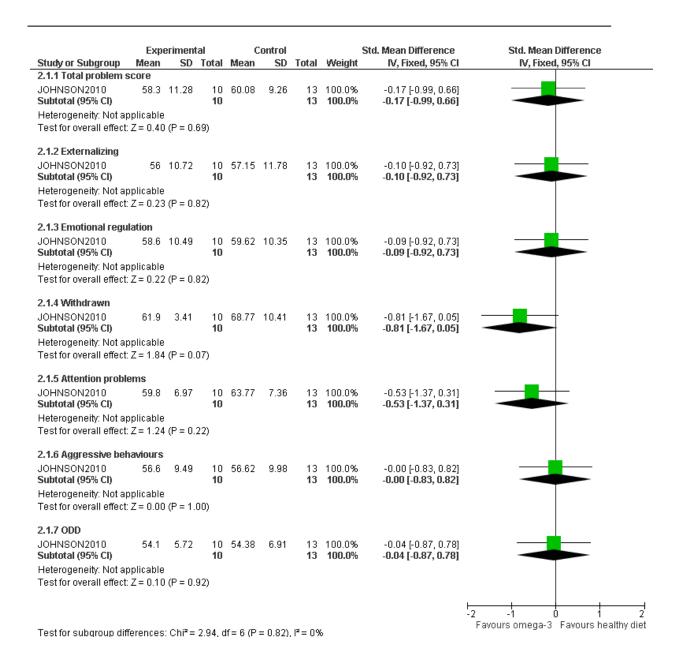
Behaviour that challenges (ABC)



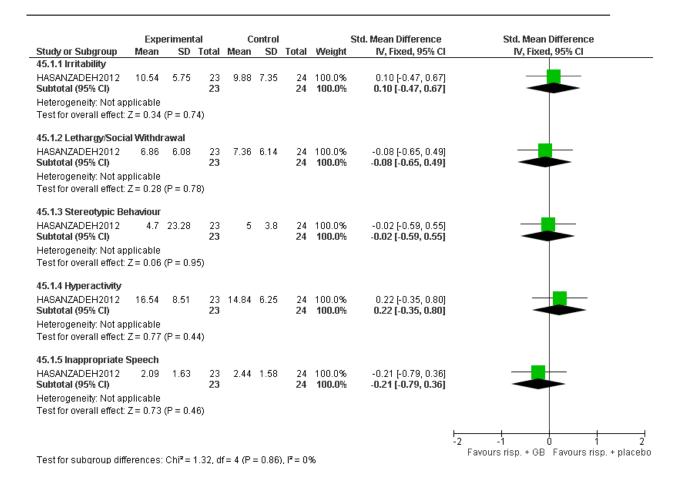
Behaviour that challenges (BASC)



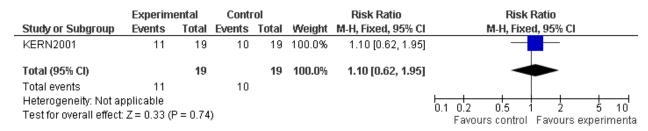
Omega-3 fatty acids versus healthy diet control for behaviour that challenges as a direct outcome



Ginkgo biloba and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome

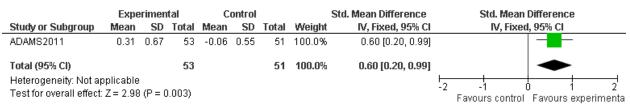


Dimethylglycine supplement versus placebo for behaviour that challenges as a direct outcome



Multivitamin/mineral supplement versus placebo for behaviour that challenges as an indirect outcome

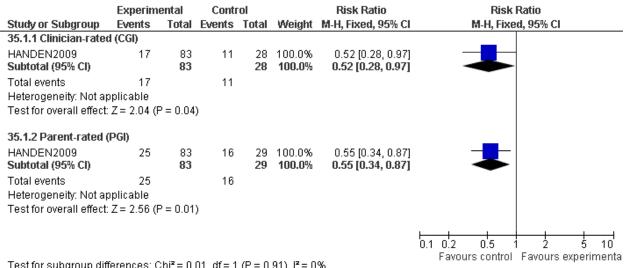
Hyperactivity improvement (PGI-R)



Tantrumming improvement (PGI-R)

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ADAMS2011	0.4	1.08	53	-0.1	0.8	51	100.0%	0.52 [0.13, 0.91]	-
Total (95% CI)			53			51	100.0%	0.52 [0.13, 0.91]	•
Heterogeneity: Not ap Test for overall effect:).009)						-2 -1 0 1 2 Favours control Favours experimenta

Immunoglobulin (dosages combined) versus placebo for behaviour that challenges as an indirect outcome



Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$

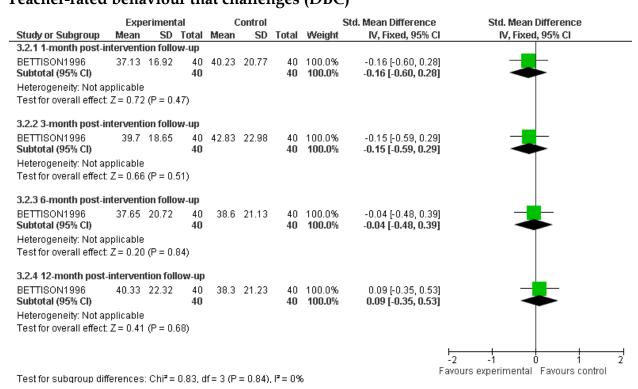
1.12.5 Sensory interventions for behaviour that challenges as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for behaviour that challenges as an indirect outcome

Parent-rated behaviour that challenges (DBC)

		eriment			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 1-month post-ir	ntervent	ion follo	w-up						<u>L</u>
BETTISON1996	54.93	25.28	40	53.53	21.23	40	100.0%	0.06 [-0.38, 0.50]	— —
Subtotal (95% CI)			40			40	100.0%	0.06 [-0.38, 0.50]	-
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 0.27	P = 0.7	'9)						
3.1.2 3-month post-ir	ntervent	ion follo	w.iin						
BETTISON1996		23.46	40	49.8	18.38	40	100.0%	0.20 [-0.24, 0.64]	
Subtotal (95% CI)	04.00	20.40	40	40.0	10.00	40	100.0%	0.20 [-0.24, 0.64]	•
Heterogeneity: Not ap	policable	!							
Test for overall effect:			(7)						
3.1.3 6-month post-ir	ntervent	ion follo	w-up						<u></u>
BETTISON1996	53.83	25.86	40	47.93	19.29	40	100.0%	0.26 [-0.18, 0.70]	
Subtotal (95% CI)			40			40	100.0%	0.26 [-0.18, 0.70]	
Heterogeneity: Not ap									
Test for overall effect:	Z = 1.14	I(P = 0.2)	(5)						
3.1.4 12-month post-	interver	tion foll	ow-up						
BETTISON1996	52.88	24.93	40	47.2	21.71	40	100.0%	0.24 [-0.20, 0.68]	+
Subtotal (95% CI)			40			40	100.0%	0.24 [-0.20, 0.68]	*
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	•		(8)						
									-2 -1 0 1 2
								F	avours experimental Favours control
Test for subgroup diff	erences	: Chi²=1	D.48. c	lf = 3 (P	= 0.92).	$1^2 = 0\%$	5		•

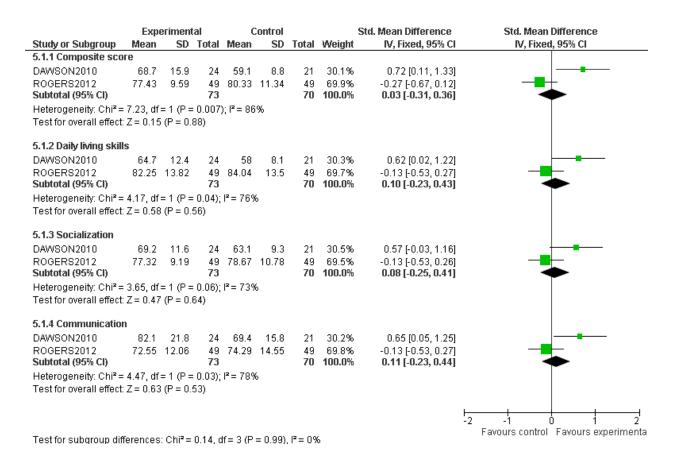
Teacher-rated behaviour that challenges (DBC)



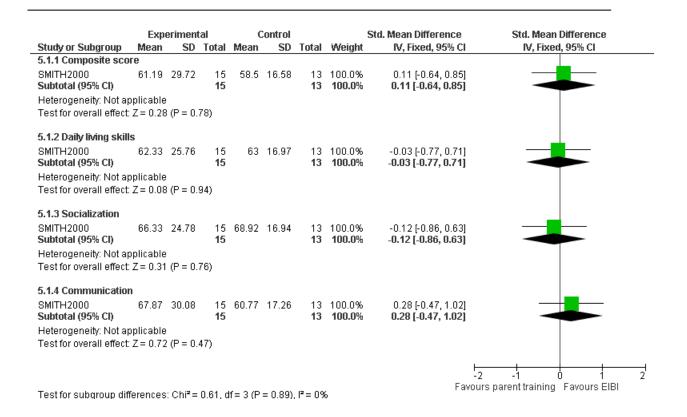
1.13PSYCHOSOCIAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

1.13.1 Behavioural interventions for adaptive behaviour as a direct or indirect outcome

EIBI or EBI (ESDM or P-ESDM) versus treatment-as-usual for adaptive behaviour as a direct or indirect outcome

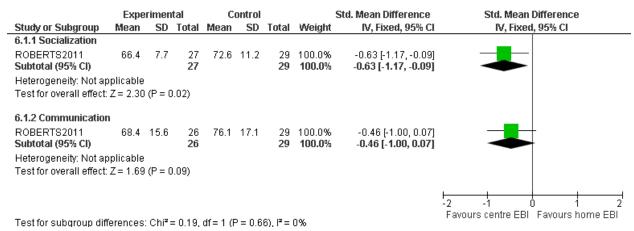


EIBI versus parent training for adaptive behaviour as a direct outcome

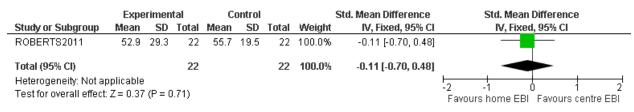


Home-based EBI versus centre-based EBI for adaptive behaviour as a direct outcome

Adaptive behaviour (VABS)



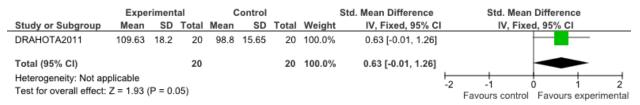
Adaptive functioning and psychopathology (DBC total)



137

1.13.2Cognitive-behavioural interventions for adaptive behaviour as an indirect outcome

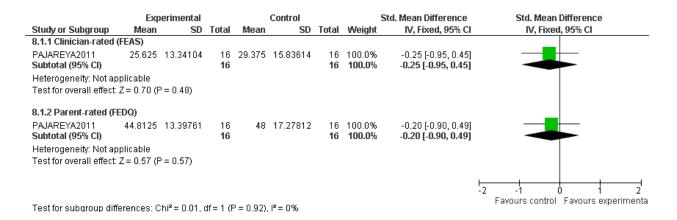
CBT versus waitlist for adaptive behaviour as an indirect outcome



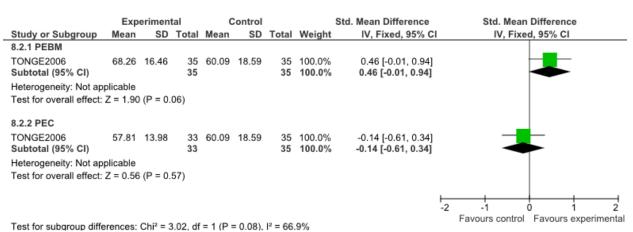
1.13.3 Parent training for adaptive behaviour as a direct or indirect outcome

Parent training versus treatment-as-usual for adaptive behaviour as a direct or indirect outcome

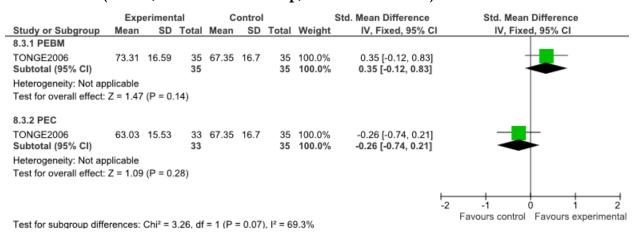
Functional emotional development (direct outcome)



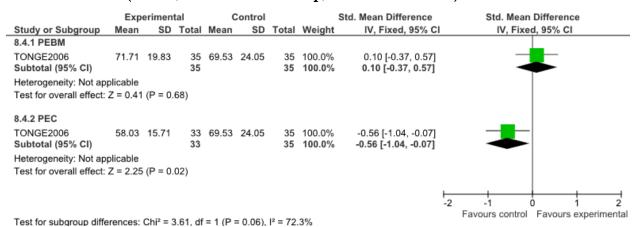
Daily living skills (VABS; 6-month follow-up; indirect outcome)



Socialization (VABS; 6-month follow-up; indirect outcome)

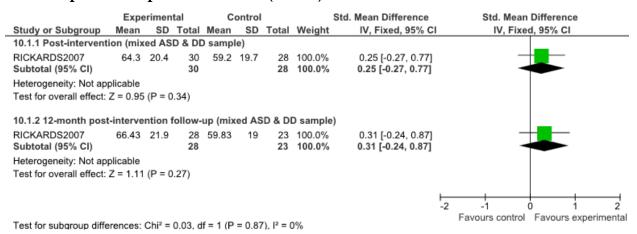


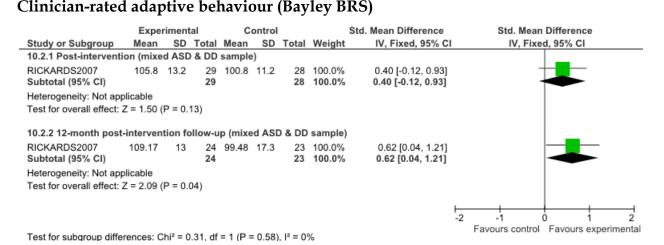
Communication (VABS; 6-month follow-up; indirect outcome)



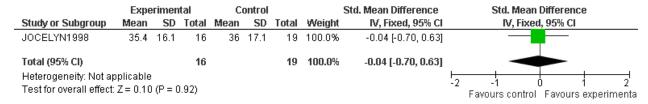
Combined parent training and early intervention centre programme versus early intervention centre programme only for adaptive behaviour as a direct outcome

Parent-reported adaptive behaviour (VABS)





Parent and day-care staff training versus standard day-care for adaptive behaviour as an indirect outcome

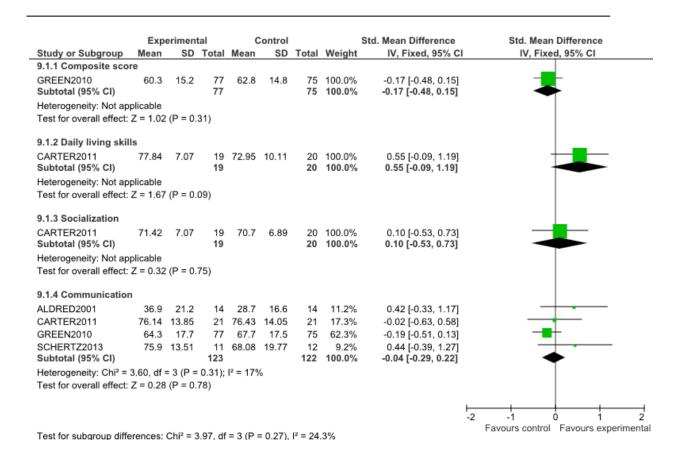


Combined parent training and antipsychotic versus antipsychotic-only for adaptive behaviour as an indirect outcome

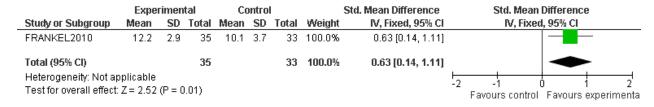
		speridone -			ridone			td. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.1.1 Composite score	е								
MAN2009	57.87	19.03	75	47.84	15.81	-	100.0%	0.56 [0.19, 0.93]	
Subtotal (95% CI)			75			49	100.0%	0.56 [0.19, 0.93]	-
leterogeneity: Not appli									
est for overall effect: Z	= 2.99 (P =	0.003)							
2.1.2 Daily living skills	S								_
MAN2009	55.65	21.86	75	45.34	20.48	49	100.0%	0.48 [0.12, 0.85]	— — — — — — — — — — — — — — — — — — —
Subtotal (95% CI)			75			49	100.0%	0.48 [0.12, 0.85]	•
leterogeneity: Not appli	cable								
est for overall effect: Z	= 2.58 (P =	0.010)							
2.1.3 Socialization									
MAN2009	67.42	18.48	75	56.59	17.38	49	100.0%	0.60 [0.23, 0.96]	-
Subtotal (95% CI)			75			49	100.0%	0.60 [0.23, 0.96]	•
leterogeneity: Not appli	cable								
est for overall effect: Z	= 3.18 (P =	0.001)							
2.1.4 Communication									
MAN2009	63.9	22.65	75	53.57	20.23	49	100.0%	0.47 [0.11, 0.84]	_
Subtotal (95% CI)			75			49	100.0%	0.47 [0.11, 0.84]	•
leterogeneity: Not appli	cable								
est for overall effect: Z	= 2.54 (P =	0.01)							
									<u> </u>
									-2 -1 0 1

1.13.4 Social-communication interventions for adaptive behaviour as an indirect outcome

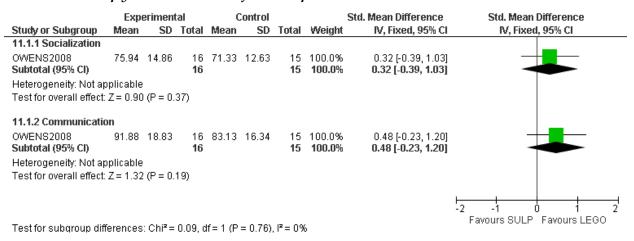
Caregiver-mediated social communication intervention versus treatment-asusual for adaptive behaviour as an indirect outcome



Social skills group versus treatment-as-usual for adaptive behaviour as an indirect outcome



LEGO® therapy versus SULP for adaptive behaviour as an indirect outcome

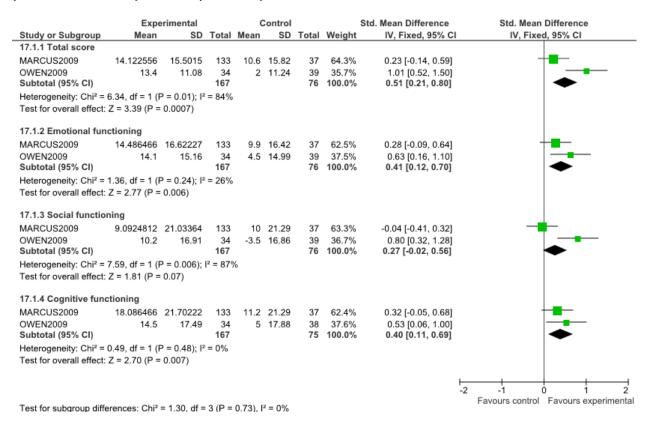


142

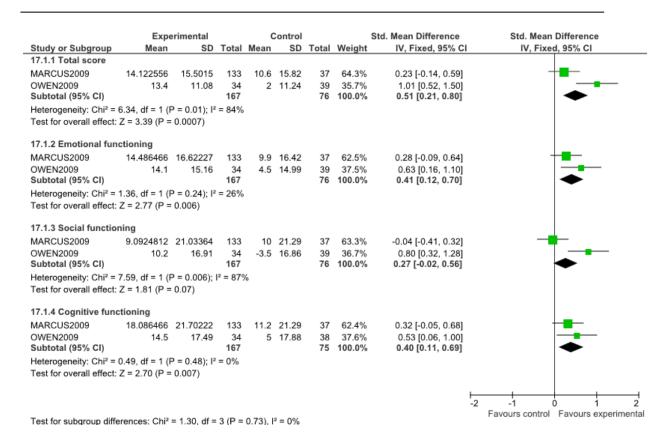
1.14PHARMACOLOGICAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

1.14.1 Antipsychotics for adaptive behaviour as an indirect outcome

Aripiprazole versus placebo for adaptive behaviour as an indirect outcome



Low dose aripiprazole versus placebo for adaptive behaviour as an indirect outcome



1.15BIOMEDICAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

1.15.1 Complementary therapies for adaptive behaviour as an indirect outcome

Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for adaptive behaviour as an indirect outcome

Adaptive behaviour (WeeFIM; change scores)

	Ехре	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.1.1 Total score									
WONG2010A		4.96	25		4.02	25	44.4%	1.06 [0.47, 1.66]	_
WONG2010B	1.03	3.85	30	-0.08	6.7	25	55.6%	0.21 [-0.33, 0.74]	-
Subtotal (95% CI)			55			50	100.0%	0.59 [0.19, 0.98]	-
Heterogeneity: Chi²=					'%				
Test for overall effect:	Z = 2.90) (P = 0	1.004)						
9.1.2 Self-care									
WONG2010A	5	3.92	25	15	2.59	25	44.6%	1.04 [0.44, 1.63]	
WONG2010A	_	3.29	30	-0.36		25	55.4%	0.18 [-0.35, 0.71]	
Subtotal (95% CI)	0.5	3.23	55	-0.50	3.33	50	100.0%	0.56 [0.17, 0.96]	•
Heterogeneity: Chi²=	4 43 df	= 1 (P		· I² = 77	96	-	1001011	5155 [5111, 5155]	
Test for overall effect:				, 1 – 77	7.0				
9.1.3 Mobility							40.10	0.001.000.000	_
WONG2010A		1.73	25		2.05	25	48.1%	0.20 [-0.35, 0.76]	
WONG2010B	-0.17	0.75	30	0.4	2.36	25 50	51.9%	-0.33 [-0.87, 0.20]	
Subtotal (95% CI)			55			50	100.0%	-0.08 [-0.46, 0.31]	_
Heterogeneity: Chi²=				; I* = 46	1%				
Test for overall effect:	∠= 0.39	(F = U	1.70)						
9.1.4 Cognition									
WONG2010A	1.28	1.37	25	0.42	1.16	25	46.7%	0.67 [0.10, 1.24]	
WONG2010B		1.29	30		1.92	25	53.3%	0.31 [-0.22, 0.85]	
Subtotal (95% CI)			55			50	100.0%	0.48 [0.09, 0.87]	•
Heterogeneity: Chi²=	0.79, df	= 1 (P	= 0.38)	; I² = 09	6			•	
Test for overall effect:		•							
0.45.0									
9.1.5 Comprehension		0.53		0.40	0.05	0.5	400.000	0.54.1.0.00.4.05	
WONG2010B Subtotal (95% Cl)	0.53	0.57	30 30	0.16	0.85	25 25	100.0% 100.0 %	0.51 [-0.03, 1.05] 0.51 [-0.03, 1.05]	
	ما مام منامد		30			23	100.070	0.51[-0.05, 1.05]	
Heterogeneity: Not ap			0.00						
Test for overall effect:	∠= 1.86) (P = U	(00.						
9.1.6 Expression									
WONG2010B	0.3	0.84	30	0.16	0.75	25	100.0%	0.17 [-0.36, 0.70]	———
Subtotal (95% CI)			30			25	100.0%	0.17 [-0.36, 0.70]	◆
Heterogeneity: Not ap	plicable							· •	
Test for overall effect:	Z = 0.64	P = 0	1.53)						
1 4 7 Coolal interacti	nn.								
9.1.7 Social interaction		0.52	20	0.0	0.50	25	100.00	0.0010.22.0.00	
WONG2010B Subtotal (95% Cl)	0.07	0.52	30 30	0.2	0.58	25 25	100.0% 100.0 %	-0.23 [-0.77, 0.30] - 0.23 [-0.77, 0.30]	
, ,	- لطحمناه،		30			23	100.0%	-0.23 [-0.77, 0.30]	
Heterogeneity: Not ap Test for overall effect:			1301						
reation overall ellect.	0.00	, (i – u)						
9.1.8 Problem solving	3								
WONG2010B	-0.13	0.35	30	0	0.71		100.0%	-0.24 [-0.77, 0.30]	
Subtotal (95% CI)			30			25	100.0%	-0.24 [-0.77, 0.30]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.87	' (P = 0	1.39)						
0 1 0 Memory									
9.1.9 Memory	0.00	0.40	20	0.04	0.54	25	100.00	0431040007	
WONG2010B Subtotal (95% Cl)	0.03	0.49	30 30	-0.04	0.54	25 25	100.0% 100.0 %	0.13 [-0.40, 0.67] 0.13 [-0.40, 0.67]	
, ,	nlicabla		30			23	100.070	0. 13 [-0.40, 0.07]	
			162)						
Heterogeneity: Not ap	Z = 0.00	, (r = u	1.02)						
									I
Heterogeneity, Not ap Test for overall effect:									<u> </u>
									-2 -1 0 1 Favours control Favours experi

Adaptive behaviour (PEDI)

	Exper				ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.2.1 Self-care (functi									
WONG2010B Subtotal (95% CI)	60.33 1	10.17	30 30	62.56	9.75	25 25	100.0% 100.0%	-0.22 [-0.75, 0.31] - 0.22 [-0.75, 0.31]	
Heterogeneity: Not app	oliooblo		JU			23	100.070	-0.22 [-0.75, 0.51]	
Test for overall effect: 2		P – 0 .	12)						
Tool for overall eller.	0.01 (, - 0.	/						
9.2.2 Self-care (indep	endence)							
WONG2010B	29.7	8.23		33.12	7.11		100.0%	-0.44 [-0.97, 0.10]	_
Subtotal (95% CI)			30			25	100.0%	-0.44 [-0.97, 0.10]	
Heterogeneity: Not app									
Test for overall effect: 2	Z = 1.59 (P = 0.1	11)						
9.2.3 Mobility (function	nal skill)								
WONG2010B	,	1.43	30	57.68	1.77	25	100.0%	-0.11 [-0.64, 0.42]	 _
Subtotal (95% CI)			30			25	100.0%	-0.11 [-0.64, 0.42]	◆
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.41 (P = 0.0	38)						
0.2.4 Mahilib. /indones									
9.2.4 Mobility (indeper	,	242	20	22.00	4.07	25	400.000	0401070 000	
WONG2010B Subtotal (95% CI)	33.3	2.12	30 30	33.68	1.87	25 25	100.0% 100.0 %	-0.19 [-0.72, 0.35] - 0.19 [-0.72, 0.35]	
Heterogeneity: Not app	nlicable		50			2.5	100.07	-0.15 [-0.12, 0.05]	
Test for overall effect: 2		P = 0.4	49)						
	•		,						
9.2.5 Social function (<u></u>
WONG2010B	29.43 1	16.26		28.76	14.14		100.0%	0.04 [-0.49, 0.57]	
Subtotal (95% CI)	-11 1-1 -		30			25	100.0%	0.04 [-0.49, 0.57]	
Heterogeneity: Not app Test for overall effect: 2		n – n i	171						
restitut overall ellect. 2	0.10 (,r – u.	57)						
9.2.6 Social function (independ	dence))						
WONG2010B	12.3	6.56	30	13.2	5.92	25	100.0%	-0.14 [-0.67, 0.39]	
Subtotal (95% CI)			30			25	100.0%	-0.14 [-0.67, 0.39]	
Heterogeneity: Not app									
Test for overall effect: 2	Z = 0.52 (P = 0.0	30)						
									-2 -1 0 1
Test for subgroup diffe									Favours control Favours experime

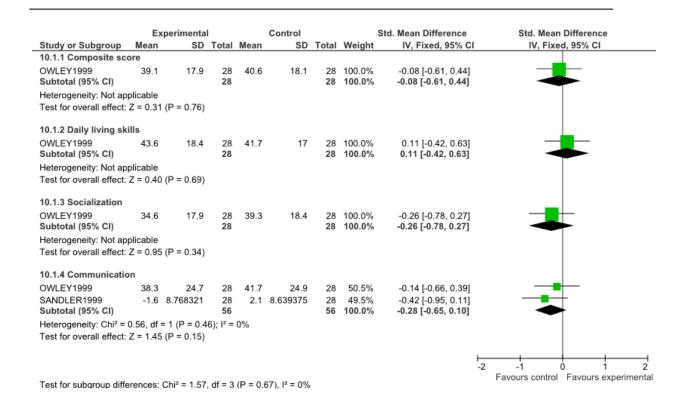
Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only for adaptive behaviour as an indirect outcome

Study or Subgroup	Mean	erimenta SD		Mean	Control	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
10.1.1 Total score			. Jean	vaii	30	. o.ui	giit	,, 00/0 01	, - 1200, 0070 01
NONG2002		5.606	15	- 1	1.354	13	36.2%	1.61 [0.74, 2.48]	
WONG2002 WONG2008			18			18	63.8%		
	1.2/0	8.532	33	3.5	7.312		100.0%	-0.27 [-0.93, 0.38]	
Subtotal (95% CI)						31	100.076	0.41 [-0.11, 0.93]	
Heterogeneity: Chi ² = 1		,		'); 2 = 9	91%				
Test for overall effect: Z	Z = 1.53	(P = 0.13	3)						
10.1.2 Self-care									
WONG2002	4.933	6.147	15	0.54	1.854	13	41.3%	0.91 [0.12, 1.70]	
WONG2008		6.366	18		5.531	18	58.7%	-0.37 [-1.03, 0.29]	
Subtotal (95% CI)	0.5	0.300	33	2.75	0.001		100.0%	0.16 [-0.35, 0.67]	
, ,	07 46 -	1 /D = 0	-	- 020/		0.	100.070	0.10[-0.00, 0.07]	
Heterogeneity: Chi² = 5 Fest for overall effect: 2			, ,	= 83%					
10.1.3 Mobility									
WONG2002	11.867	8.417	15	1	1.78	13	35.5%	1.68 [0.80, 2.56]	
WONG2002 WONG2008		2.674	18		2.576	18	64.5%	-0.11 [-0.77, 0.54]	
	0.306	2.074	33	0.61	2.576		100.0%		
Subtotal (95% CI)		4.75		. 10		31	100.076	0.52 [-0.00, 1.05]	
Heterogeneity: Chi ² = 1		4		$ I^2 = 90$)%				
Test for overall effect: 2	Z = 1.95	(P = 0.0	5)						
10.1.4 Cognition									
WONG2002	8.533	6.534	15	1.46	2.025	13	37.9%	1.38 [0.54, 2.22]	
WONG2008	0.472		18		4.321	18	62.1%	0.16 [-0.50, 0.81]	
Subtotal (95% CI)	J Z	3.70	33	3.17			100.0%	0.62 [0.10, 1.14]	
Heterogeneity: Chi ² = 5	: na at -	1 /D = 0		= 900/		٠.		2.22 [2.14, 11.4]	
Test for overall effect: Z			,,,	- 60%					
10.1 F Comprehension									
10.1.5 Comprehension		4 007	40	0.40	4 004	40	400.00/	0.47.1.4.0.0.403	
WONG2008	-0.28	1.007	18	0.42	1.801		100.0%	-0.47 [-1.13, 0.19]	
			40			40		0.47 [4.42 0.40]	
Subtotal (95% CI)			18			18	100.0%	-0.47 [-1.13, 0.19]	-
Heterogeneity: Not app						18	100.0%	-0.47 [-1.13, 0.19]	
, ,		(P = 0.17				18	100.0%	-0.47 [-1.13, 0.19]	
Heterogeneity: Not app		(P = 0.17				18	100.0%	-0.47 [-1.13, 0.19]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression	Z = 1.39	•	7)	-0.36	0.637				
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008	Z = 1.39	(P = 0.17		-0.36	0.637	18	100.0%	0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI)	Z = 1.39 (•	7)	-0.36	0.637	18			
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 olicable	1.085	7) 18 18	-0.36	0.637	18	100.0%	0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 olicable	1.085	7) 18 18	-0.36	0.637	18	100.0%	0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction	Z = 1.39 0 olicable Z = 1.17	1.085 (P = 0.24	7) 18 18			18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Test for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 10.1.7 Social interaction	Z = 1.39 0 olicable Z = 1.17	1.085	7) 18 18 14)	-0.36	0.637	18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction	Z = 1.39 0 olicable Z = 1.17	1.085 (P = 0.24	7) 18 18			18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI)	Z = 1.39 0 olicable Z = 1.17 on 0.222	1.085 (P = 0.24	7) 18 18 14)			18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 oblicable Z = 1.17 (on 0.222 oblicable	1.085 (P = 0.24 1.114	18 18 18 11 18			18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Test for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 10.1.7 Social interaction	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114	18 18 19 18			18 18	100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression NONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction NONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23	18 18 19 18 18 18	-0.28	1.32	18 18 18	100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114	7) 18 18 14) 18 18 3)	-0.28		18 18 18	100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI)	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23	18 18 19 18 18 18	-0.28	1.32	18 18 18	100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving	Z = 1.39 (0 oblicable Z = 1.17 (con	1.085 (P = 0.24 1.114 (P = 0.23	18 18 18 11 18 18 18 18	-0.28	1.32	18 18 18	100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2	Z = 1.39 (0 oblicable Z = 1.17 (con	1.085 (P = 0.24 1.114 (P = 0.23	18 18 18 11 18 18 18 18	-0.28	1.32	18 18 18	100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Fest for overall effect: 2 10.1.9 Memory WONG2008	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23	7) 18 18 19 18 18 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.9 Memory WONG2008 Subtotal (95% CI)	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solvin WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solvin WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.9 Memory WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solving WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.9 Memory WONG2008 Subtotal (95% CI)	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 IO.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 IO.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 IO.1.8 Problem solvin WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 IO.1.8 Problem solvin WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 IO.1.9 Memory WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	
Heterogeneity: Not app Fest for overall effect: 2 10.1.6 Expression WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.7 Social interaction WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.8 Problem solvin WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.9 Memory WONG2008 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: 2 10.1.9 Memory WONG2008 Subtotal (95% CI) Heterogeneity: Not app	Z = 1.39 (0 oblicable Z = 1.17 (on	1.085 (P = 0.24 1.114 (P = 0.23 0.85 (P = 0.32	7) 18 18 19 18 18 18 18 18 18 18	-0.28	1.32	18 18 18 18	100.0% 100.0% 100.0% 100.0% 100.0%	0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.40 [-0.26, 1.06] 0.33 [-0.32, 0.99] 0.33 [-0.32, 0.99]	

1.15.2 Hormones for adaptive behaviour as an indirect outcome

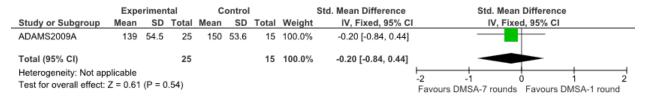
Secretin versus placebo for adaptive behaviour as an indirect outcome

Autism: the management and support of children and young people on the autism spectrum



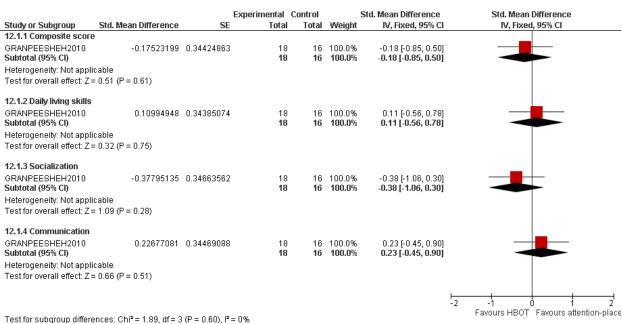
1.15.3 Medical procedures for adaptive behaviour as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for adaptive behaviour as an indirect outcome



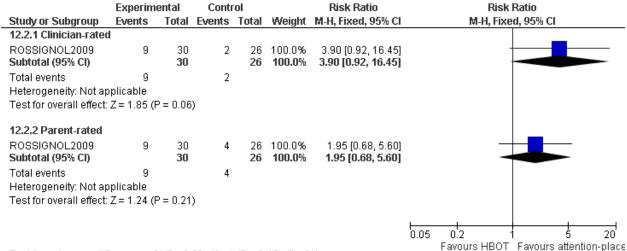
HBOT versus attention-placebo for adaptive behaviour as an indirect outcome

Adaptive behaviours (VABS; change scores)



1est 101 subgroup differences. C111 = 1.05, d1 = 3 (F = 0.00), 1 = 0 %

Positive treatment response ('much improved/very improved' on CGI/PGIimprovement for overall functioning)



Test for subgroup differences: $Chi^2 = 0.58$, df = 1 (P = 0.45), $I^2 = 0\%$

1.15.4 Nutritional interventions for adaptive behaviour as an indirect outcome

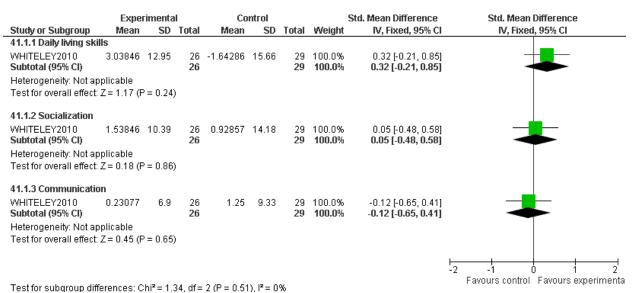
Omega-3 fatty acids versus placebo for adaptive behaviour as an indirect outcome

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	l, 95% CI	
BENT2011	29.25	8.47	12	31	8.64	12	100.0%	-0.20 [-1.00, 0.60]			
Total (95% CI)			12			12	100.0%	-0.20 [-1.00, 0.60]	~		
Heterogeneity: Not ap Test for overall effect			0.63)					F	-2 -1 (avours experimental	H 1 Favours cor	2 ntrol

Omega-3 fatty acids versus healthy diet control for adaptive behaviour as an indirect outcome

	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
JOHNSON2010	28.5	4.95	10	23.84	8.06	13	100.0%	0.65 [-0.20, 1.50]	
Total (95% CI)			10			13	100.0%	0.65 [-0.20, 1.50]	
Heterogeneity: Not ap Test for overall effect:).13)						-2 -1 0 1 2 Favours healthy diet Favours omega-3

Gluten-free and casein-free diet versus treatment-as-usual for adaptive behaviour as an indirect outcome

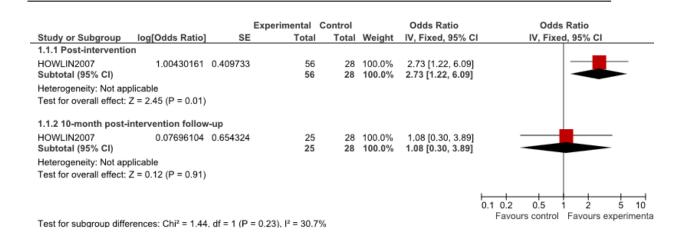


1.16PSYCHOSOCIAL INTERVENTIONS AIMED AT SPEECH AND LANGUAGE

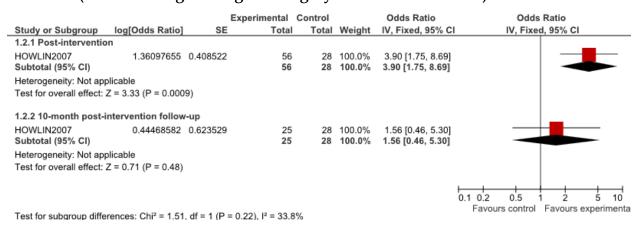
1.16.1 AAC interventions for speech and language as a direct outcome

PECS training for teachers versus treatment-as-usual for speech and language as a direct outcome

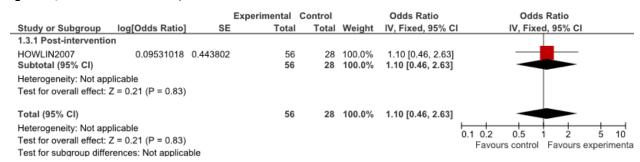
Spontaneous child communicative initiations (odds of being in a higher initiation category)



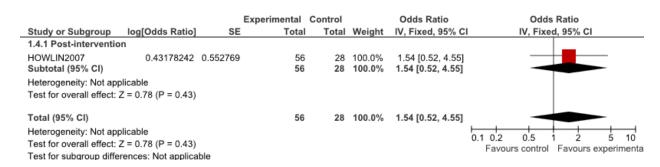
PECS use (odds of being in a higher category for rate of PECS use)



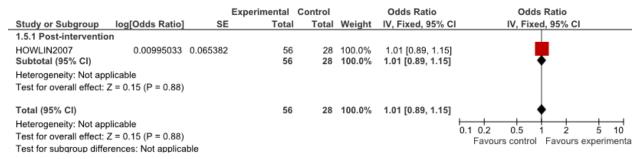
Speech/vocalisation use (odds of being in a higher category for rate of speech/vocalisation use)



Receptive language (odds of being in a higher category on BPVS)

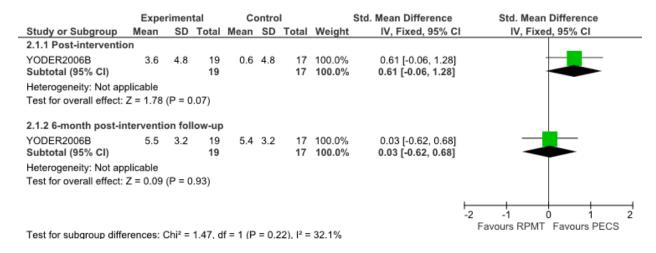


Expressive language (odds of being in a higher category on EOWPVT)

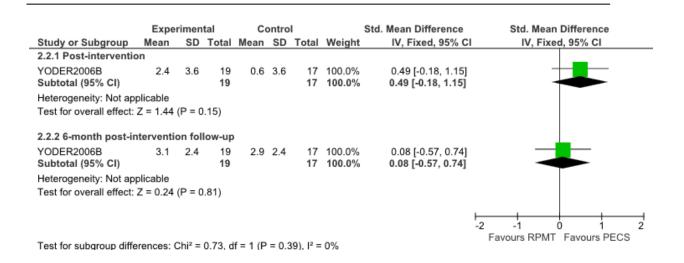


PECS versus RPMT for speech and language as a direct outcome

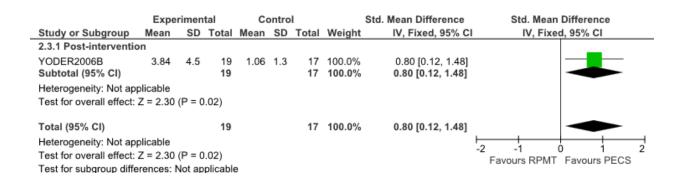
Frequency of nonimitative spoken acts



Number of different nonimitative words



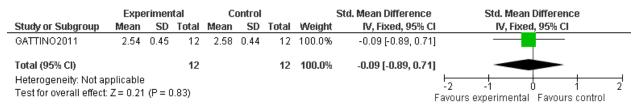
Number of picture exchanges (EScs-Abridged)



1.16.2 Arts-based interventions for speech and language as a direct outcome

Music therapy versus treatment-as-usual for speech and language as a direct outcome

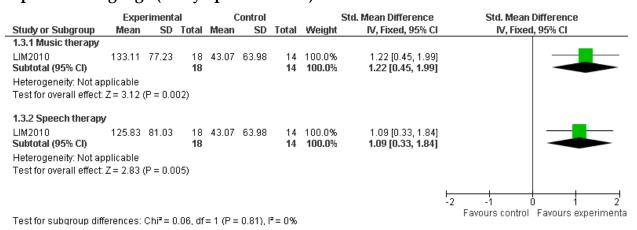
Verbal communication (CARS-BR)



Non-verbal communication (CARS-BR)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
GATTINO2011	2.5	0.37	12	2.33	0.54	12	100.0%	0.35 [-0.45, 1.16]	
Total (95% CI)			12			12	100.0%	0.35 [-0.45, 1.16]	
Heterogeneity: Not a Test for overall effect	•).39)					F	-2 -1 0 1 2 avours experimental Favours control

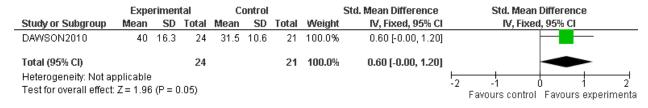
Expressive language (study-specific VPES)



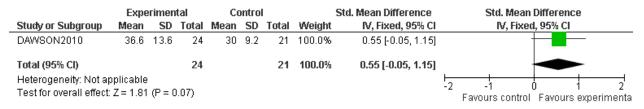
1.16.3 Behavioural interventions for speech and language as an indirect outcome

EIBI (ESDM) versus treatment-as-usual for speech and language as an indirect outcome

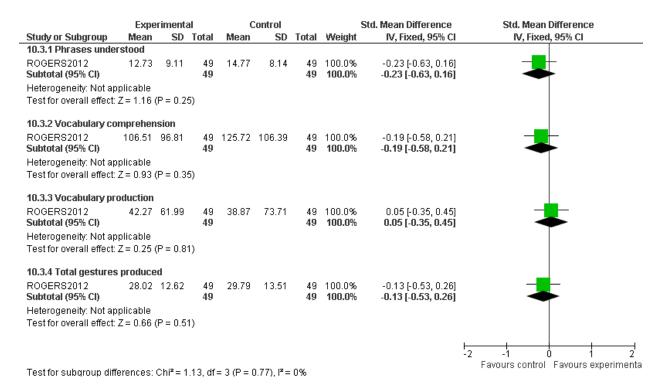
Receptive language (MSEL)



Expressive language (MSEL)

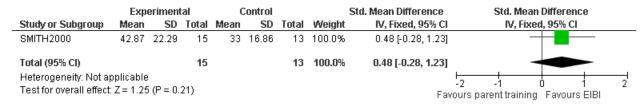


EBI (P-ESDM) versus treatment-as-usual for speech and language as an indirect outcome

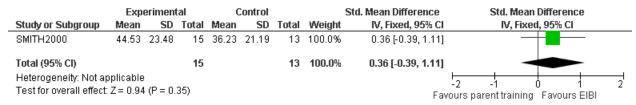


EIBI versus parent training for speech and language as an indirect outcome

Receptive language (Reynell Developmental Language Scale-Comprehension)



Expressive language (Reynell Developmental Language Scale-Expressive)

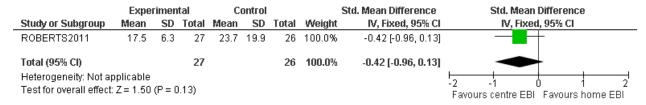


Receptive + Expressive language (Reynell Developmental Language Scale-Comprehension+Expression)

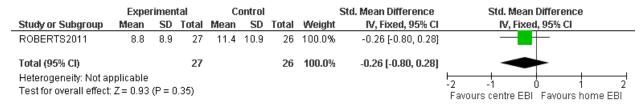
	Exp	erimen	tal	0	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
SMITH2000	87.4	46.21	15	61.33	31.88	13	100.0%	0.63 [-0.13, 1.39]	_
Total (95% CI)			15			13	100.0%	0.63 [-0.13, 1.39]	
Heterogeneity: Not a	•		4.43					-2	-1 0 1
Test for overall effect	Z=1.61	(P=0.	.11)					Favours	parent training Favours EIBI

Home-based EBI versus centre-based EBI for speech and language as an indirect outcome

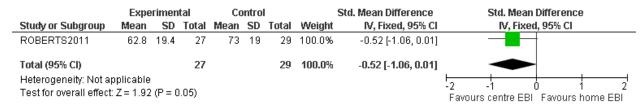
Receptive language (Reynell Developmental Language Scale-Comprehension)



Expressive language (Reynell Developmental Language Scale-Expressive)



Everyday language functioning (Pragmatics Profile)



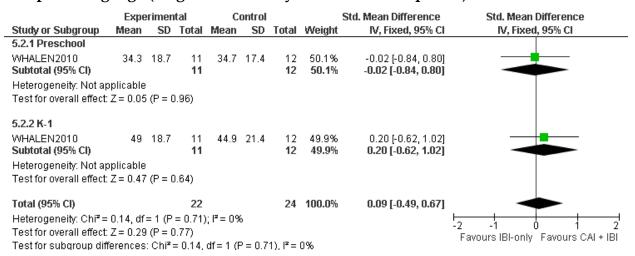
1.16.4Educational interventions for speech and language as a direct or indirect outcome

Combined TeachTown and IBI versus IBI-only for speech and language as a direct outcome

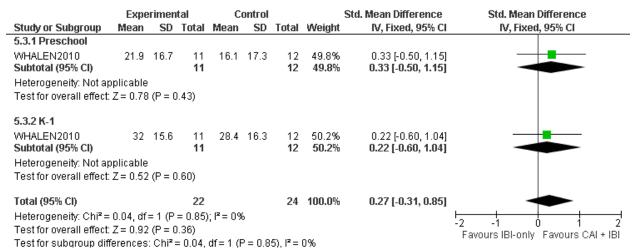
Receptive language (PPVT-III)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.1.1 Preschool									
WHALEN2010	23.4	21.7	11	14.9	19.6	12	49.7%	0.40 [-0.43, 1.22]	
Subtotal (95% CI)			11			12	49.7%	0.40 [-0.43, 1.22]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.94	(P = 0	1.35)						
5.1.2 K-1									
WHALEN2010	36.1	26.3	11	29.8	18.7	12	50.3%	0.27 [-0.55, 1.09]	- •
Subtotal (95% CI)			11			12	50.3%	0.27 [-0.55, 1.09]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.64	(P = 0	1.52)						
Total (95% CI)			22			24	100.0%	0.33 [-0.25, 0.92]	-
Heterogeneity: Chi ² =	0.05, df	= 1 (P	= 0.83)	$ I^2 = 09 $	6				
Test for overall effect:									-2 -1 0 1
Test for subgroup diff		•		df = 1 / F	P = N 8	3)	N%		Favours IBI-only Favours CAI + II

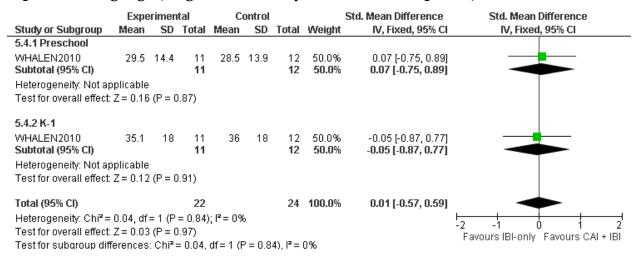
Receptive language (Brigance Inventory of Child Development)



Expressive language (EVT)



Expressive language (Brigance Inventory of Child Development)

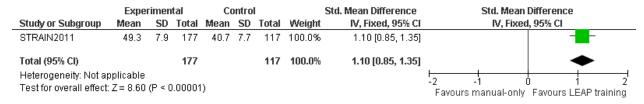


LEAP training versus manual-only control for speech and language as an indirect outcome

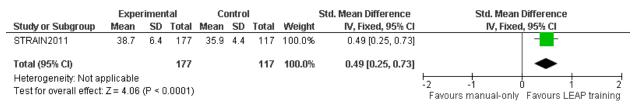
Total language score (PLS-4)

	Expe	rimen	tal	Co	ntro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
STRAIN2011	51.3	8.1	177	43.8	7.7	117	100.0%	0.94 [0.70, 1.19]	-
Total (95% CI)			177			117	100.0%	0.94 [0.70, 1.19]	
Heterogeneity: Not ap Test for overall effect:			.00001)					-2 -1 0 1 2 Favours manual-only Favours LEAP training

Receptive language (MSEL; language age in months)



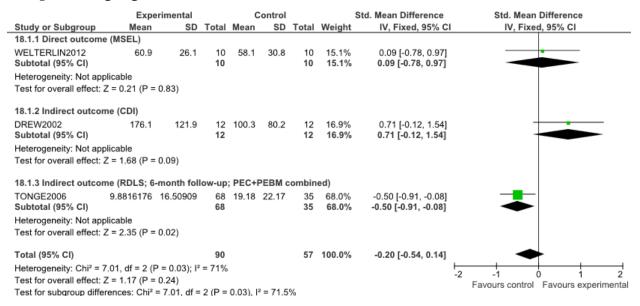
Expressive language (MSEL; language age in months)



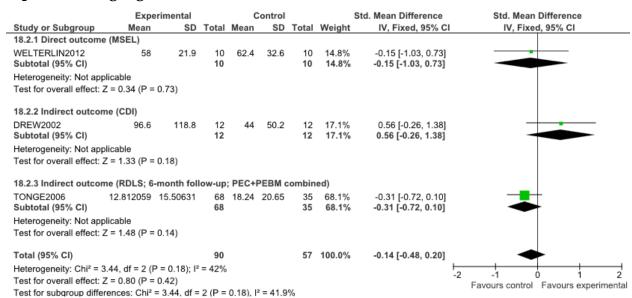
1.16.5 Parent training for speech and language as a direct or indirect outcome

Parent training versus treatment-as-usual for speech and language as a direct or indirect outcome

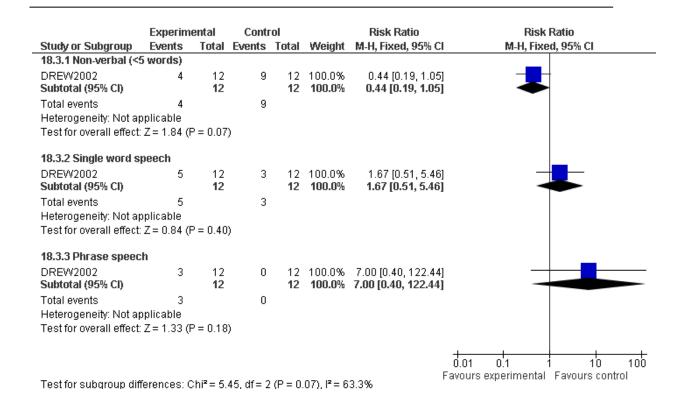
Receptive language



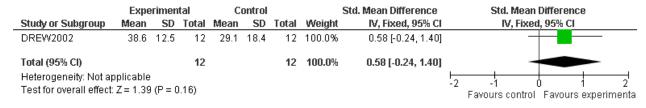
Expressive language



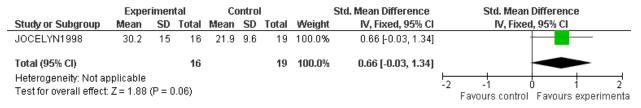
Overall language rating (ADI-R; indirect outcome)



Total gestures produced (CDI; indirect outcome)



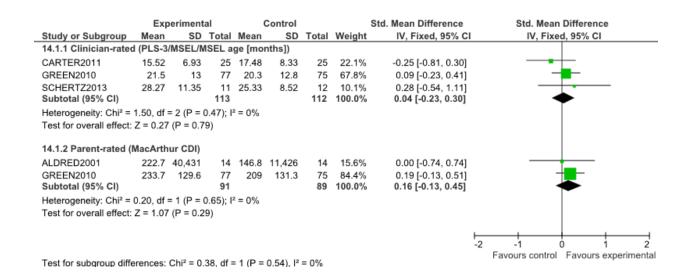
Parent and day-care staff training versus standard day-care for speech and language as an indirect outcome



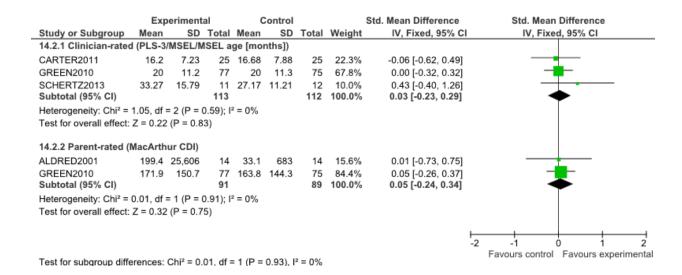
1.16.6 Social-communication interventions for speech and language as an indirect outcome

Caregiver-mediated social communication intervention versus treatment-asusual for speech and language as an indirect outcome

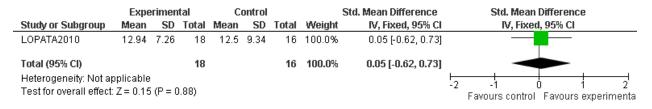
Receptive language



Expressive language

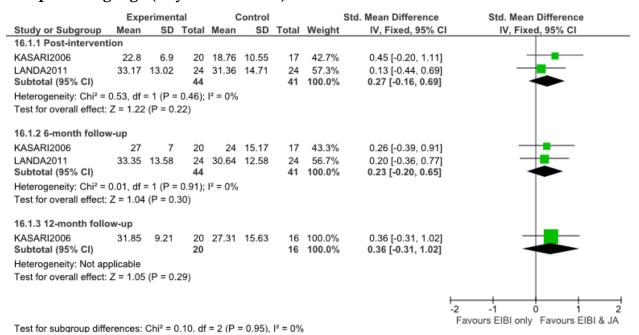


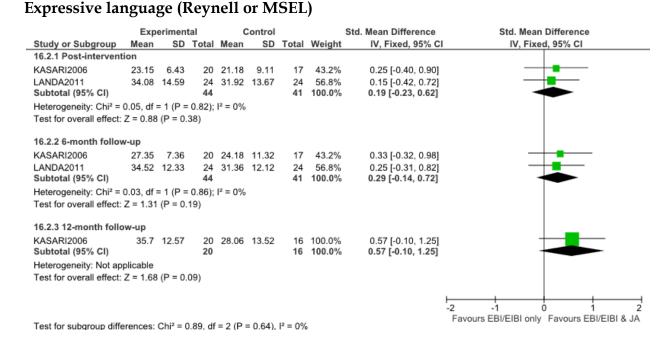
Social skills group versus treatment-as-usual for speech and language as an indirect outcome



Joint attention training and EBI/EIBI versus EBI/EIBI only for speech and language as an indirect outcome

Receptive language (Reynell or MSEL)



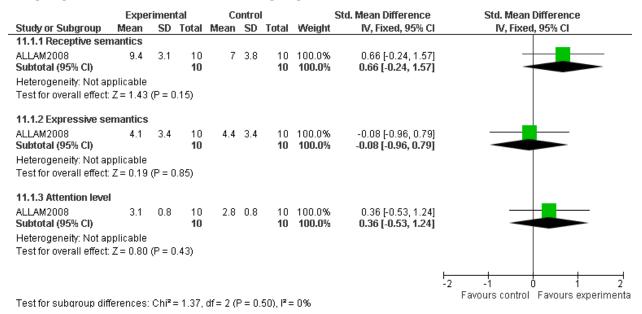


1.17BIOMEDICAL INTERVENTIONS AIMED AT SPEECH AND LANGUAGE

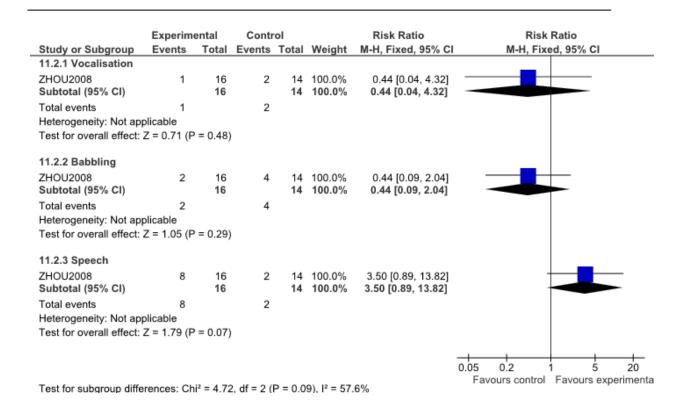
1.17.1 Complementary therapies for speech and language as a direct or indirect outcome

Acupuncture/acupressure and language therapy versus language therapy only for speech and language as a direct outcome

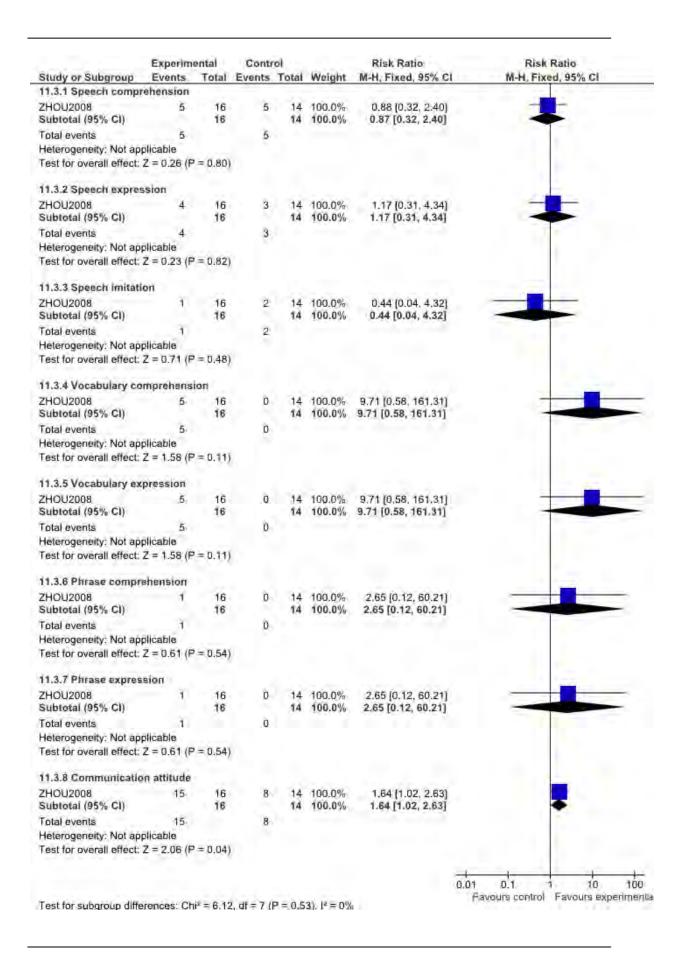
Language and attention (Arabic Language Test)



Positive treatment response (improvement in basic developmental assessment)



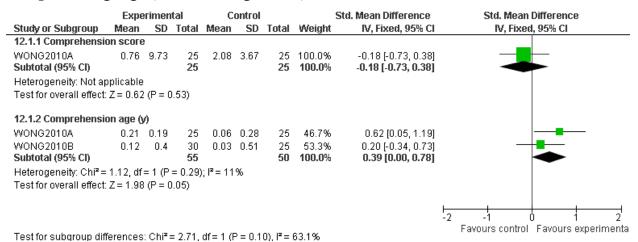
Positive treatment response (number of participants improved on CRRC signsignificance relations scale)



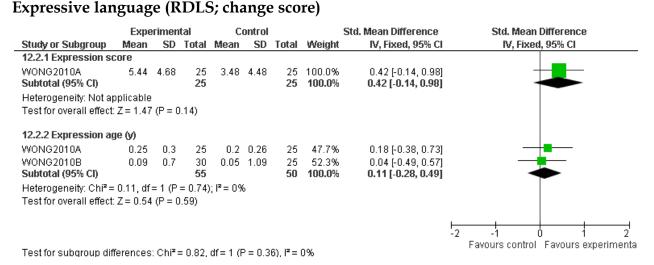
165

Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for speech and language as an indirect outcome

Receptive language (RDLS; change score)



Evenuesiya languaga (DDI Si shanga sagua



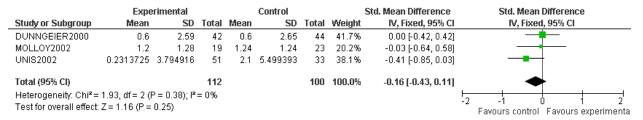
1.17.2 Hormones for speech and language as an indirect outcome

Secretin versus placebo for speech and language as an indirect outcome

Receptive Language (PLS-3/MSEL/PPVT-III or MSEL)

	Favou	Favours control Control						Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
DUNNGEIER2000	1.5	3.98	44	0.6	2.68	45	47.8%	0.26 [-0.15, 0.68]		
MOLLOY2002	19	10.1	19	20.3	10.9	23	22.5%	-0.12 [-0.73, 0.49]		-
OWLEY1999	29.1	21.8	28	40.1	31.6	28	29.7%	-0.40 [-0.93, 0.13]		-
Total (95% CI)			91			96	100.0%	-0.02 [-0.31, 0.27]		•
Heterogeneity: Chi ² =			, ,	² = 48%	6				-2	-1 0 1 2
Test for overall effect:	Z = 0.14	(P = 0.	89)						-	Favours control Favours experimental

Expressive language (PLS-3 change score/MLU behavioural observation/EOWPVT-R change score)



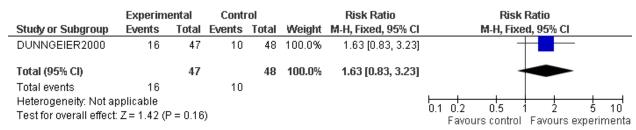
Receptive and expressive language (PLS-3 total; change score)

	Ехре	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
DUNNGEIER2000	2.4	5.12	41	1.1	3.98	44	100.0%	0.28 [-0.15, 0.71]	+
Total (95% CI)			41			44	100.0%	0.28 [-0.15, 0.71]	-
Heterogeneity: Not ap Test for overall effect:).20)						-2 -1 0 1 2 Favours control Favours experimenta

Vocabulary (type-token ratio behavioural observation or CDI vocabulary)

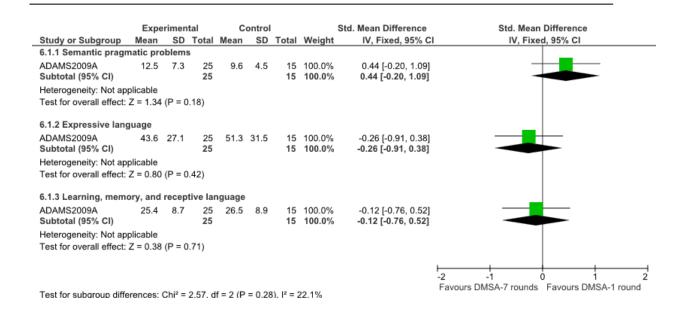
	Favou	rs control			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
MOLLOY2002	0.36	0.39	19	0.3	0.32	23	37.1%	0.17 [-0.44, 0.78]	
UNIS2002	14.351163	52.09288	43	23.4	36.68927	30	62.9%	-0.19 [-0.66, 0.27]	-
Total (95% CI)			62			53	100.0%	-0.06 [-0.43, 0.31]	•
Heterogeneity: Chi²= Test for overall effect:			= 0%						-2 -1 0 1 2 Favours control Favours experimenta

Positive treatment response (>=4 points improvement on PLS-3)

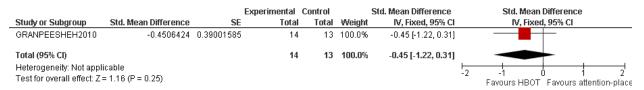


1.17.3 Medical procedures for speech and language as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for speech and language as an indirect outcome



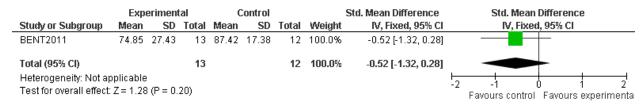
HBOT versus attention-placebo for speech and language as an indirect outcome



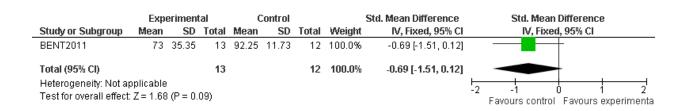
1.17.4 Nutritional interventions for speech and language as an indirect outcome

Omega-3 fatty acids versus placebo for speech and language as an indirect outcome

Receptive language (PPVT)

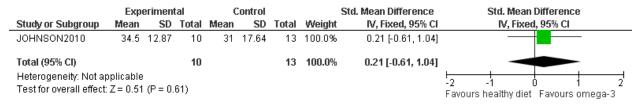


Expressive language (EVT)

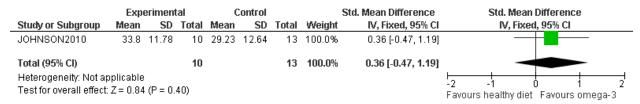


Omega-3 fatty acids versus healthy diet control for speech and language as an indirect outcome

Receptive language (MSEL)

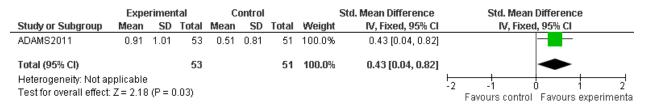


Expressive language (MSEL)

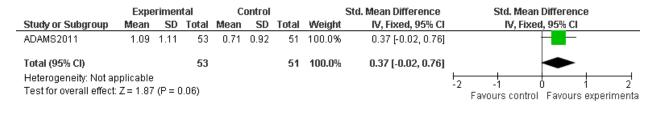


Multivitamin/ mineral supplement versus placebo for speech and language as an indirect outcome

Receptive language improvement (PGI-R)

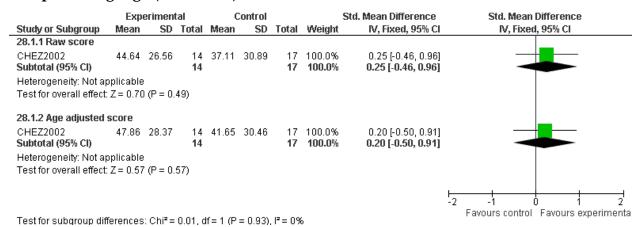


Expressive language improvement (PGI-R)

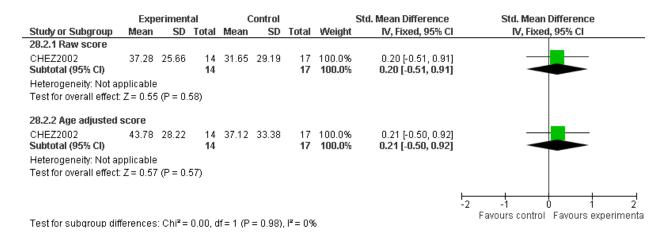


L-carnosine supplement versus placebo for speech and language as an indirect outcome

Receptive language (ROWPVT)

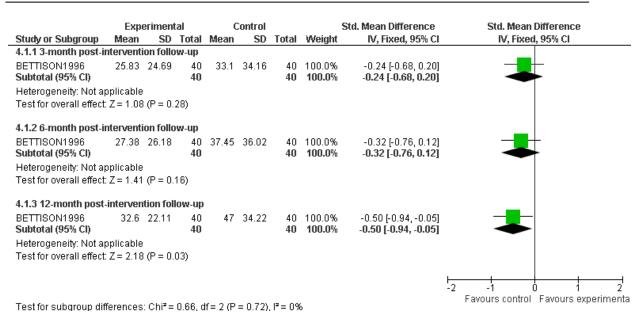


Expressive language (EOWPVT)



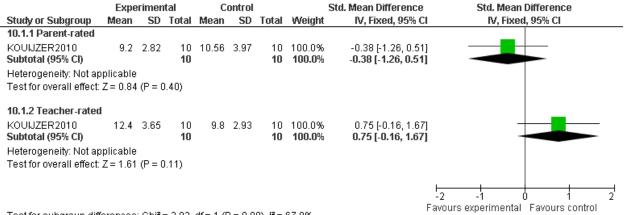
1.17.5 Sensory interventions for speech and language as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for speech and language as an indirect outcome



Neurofeedback versus treatment-as-usual for speech and language as an indirect outcome

Speech production (CCC-2)



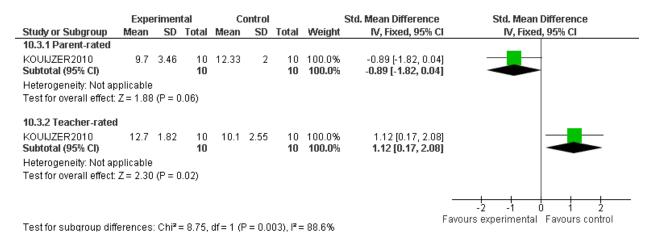
Test for subgroup differences: $Chi^2 = 3.03$, df = 1 (P = 0.08), $I^2 = 67.0\%$

Syntax (CCC-2)

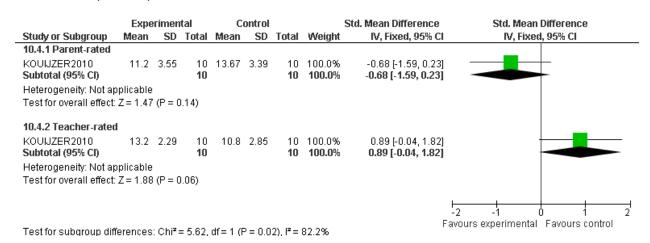
	Expe	erimen	tal	C	ontrol		!	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.2.1 Parent-rated									
KOUIJZER2010	10.7	3.74	10	12.56	2.74	10	100.0%	-0.54 [-1.44, 0.35]	
Subtotal (95% CI)			10			10	100.0%	-0.54 [-1.44, 0.35]	
Heterogeneity: Not a	pplicable)							
Test for overall effect	: Z = 1.19	9 (P = 0	1.23)						
10.2.2 Teacher-rate	d								<u></u>
KOUIJZER2010	12.5	4.06	10	11.8	2.25	10	100.0%	0.20 [-0.68, 1.08]	-
Subtotal (95% CI)			10			10	100.0%	0.20 [-0.68, 1.08]	
Heterogeneity: Not ap	pplicable)							
Test for overall effect	Z = 0.48	6 (P = 0	1.65)						
								-2	-
								-	rs experimental Favours control
Test for subgroup dif	ferences	: Chi²:	= 1.36.	df = 1 (F	9 = 0.2	4), $ ^2 =$	26.6%	ravou	no experimentar Favours Control

Testion subgroup differences. Citi = 1.30, di = 1 (F = 0.24), 1 = 20.0

Semantics (CCC-2)



Coherence (CCC-2)

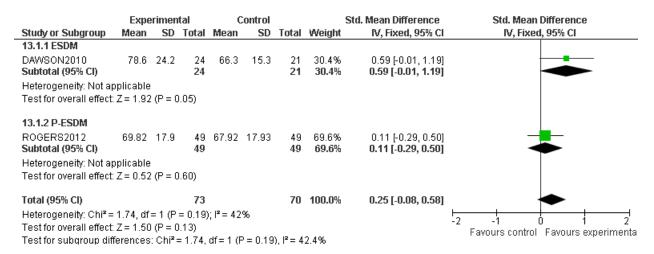


1.18PSYCHOSOCIAL INTERVENTIONS AIMED AT IQ AND ACADEMIC SKILLS

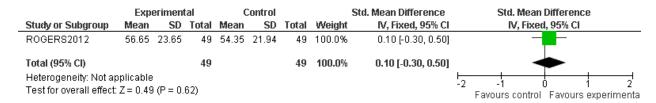
1.18.1 Behavioural interventions for IQ and/or academic skills as a direct or indirect outcome

EIBI or EBI (ESDM or P-ESDM) versus treatment-as-usual for IQ as a direct or indirect outcome

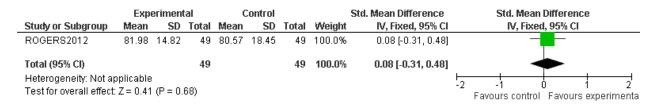
IQ (MSEL - Early-learning composite score; Developmental quotient)



Verbal developmental quotient (MSEL)

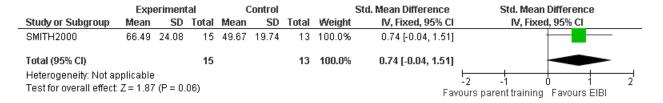


Non-verbal developmental quotient (MSEL)

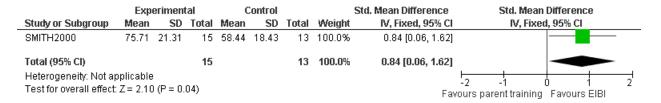


EIBI versus parent training for IQ and academic skills as an indirect outcome

IQ (Bayley Scales of Infant Development - Mental Development Index)

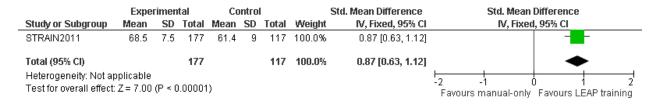


Academic skills (WIAT total score)



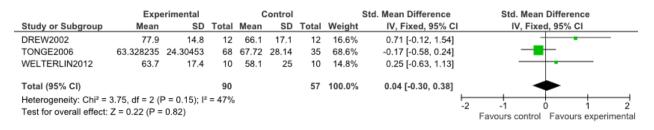
1.18.2Educational interventions for IQ as an indirect outcome

LEAP training versus manual-only control for IQ as an indirect outcome

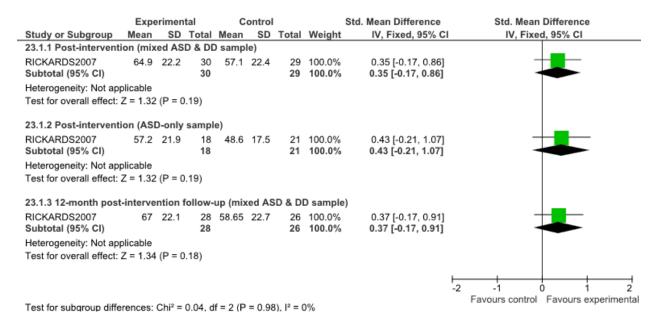


1.18.3 Parent training for IQ as an indirect outcome

Parent training versus treatment-as-usual for IQ as an indirect outcome

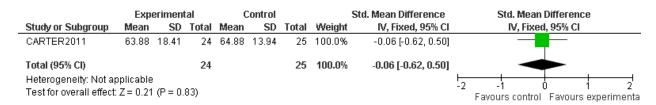


Combined parent training and early intervention centre programme versus early intervention centre programme only for IQ as an indirect outcome

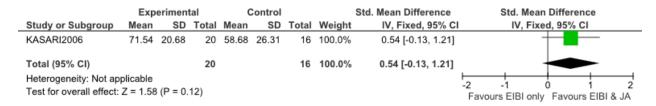


1.18.4 Social-communication interventions for IQ as an indirect outcome

Caregiver-mediated social communication intervention versus treatment-asusual for IQ as an indirect outcome



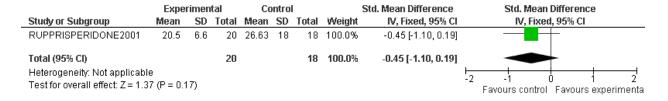
Joint attention training and EIBI versus EIBI only for IQ as an indirect outcome



1.19PHARMACOLOGICAL INTERVENTIONS AIMED AT ACADEMIC SKILLS

1.19.1 Antipsychotics for academic skills as an indirect outcome

Risperidone versus placebo for academic skills as an indirect outcome



1.20BIOMEDICAL INTERVENTIONS AIMED AT IQ

1.20.1 Complementary therapies for IQ as a direct outcome

Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for IQ as a direct outcome

Study or Subgroup	Expe Mean	eriment SD	al Total		ontrol SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
13.1.1 General quotie									11,111111111111111111111111111111111111
WONG2010A	13.66	10.06	25	10.2	9.65	25	47.5%	0.35 [-0.21, 0.90]	
WONG2010B Subtotal (95% CI)	4.6	10.47	30 55	3.24	10.46	25 50	52.5% 100.0 %	0.13 [-0.40, 0.66] 0.23 [-0.15, 0.62]	•
Heterogeneity: Chi ² = Test for overall effect:		,		²=0%					
13.1.2 Mental age in r	nonths	(Griffith	s Menta	al Deve	lopmen	t Scale	e)		
WONG2010A Subtotal (95% CI)	8.95	5.93	25 25	6.41	5.66		100.0% 100.0 %	0.43 [-0.13, 0.99] 0.43 [-0.13, 0.99]	
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.1	13)						
13.1.3 Locomotor (Gr	iffiths M	lental D	evelopi	nent S	cale)				
WONG2010A Subtotal (95% Cl)	2.7	5.78	25 25	3.9	5.94		100.0% 100.0 %	-0.20 [-0.76, 0.35] - 0.20 [-0.76, 0.35]	-
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.4	48)						
13.1.4 Personal-Socia	al (Griffit	ths Mer	ıtal Dev	elopmo	ent Sca	e)			
WONG2010A Subtotal (95% CI)	9.48	6.62	25 25	6.12	5.76	25 25	100.0% 100.0 %	0.53 [-0.03, 1.10] 0.53 [-0.03, 1.10]	
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.0	06)						
13.1.5 Hearing and sp	eech (G	iriffiths	Mental	Develo	pment	Scale)			
WONG2010A Subtotal (95% CI)	6.48	9.69	25 25	5.15	7.14	25 25	100.0% 100.0 %	0.15 [-0.40, 0.71] 0.15 [-0.40, 0.71]	-
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.5	59)						
13.1.6 Eye and hand o	coordina	ntion (G	riffiths I	Mental	Develor	ment :	Scale)		
WONG2010A	7.36	6.23	25		11.01		100.0%	0.12 [-0.44, 0.67]	 _
Subtotal (95% CI)			25			25	100.0%	0.12 [-0.44, 0.67]	-
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.6	67)						
13.1.7 Performance (Griffiths	Menta	l Develo	nnment	Scale)				
WONG2010A Subtotal (95% CI)	13.64		25 25	-	10.29		100.0% 100.0 %	0.41 [-0.15, 0.97] 0.41 [-0.15, 0.97]	
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.1	16)						
13.1.8 Practical reas	nnina (G	riffiths	Mental	Develo	nment !	Scale)			
WONG2010A Subtotal (95% CI)	15.92		25 25		16.54		100.0% 100.0 %	0.32 [-0.23, 0.88] 0.32 [-0.23, 0.88]	
Heterogeneity: Not ap Test for overall effect:		(P = 0.3	25)						
13.1.0 Attention and	nomor.	(LIDE I	٥١						
13.1.9 Attention and r WONG2010B Subtotal (95% CI)	0.97	6.17	30 30	1.28	9.78		100.0% 100.0 %	-0.04 [-0.57, 0.49] - 0.04 [-0.57, 0.49]	*
Heterogeneity: Not ap Test for overall effect:	-	(P = 0 f							Ţ
	•	,	-,						
									-2 -1 0 1 2
Test for subgroup diffe	erences	: Chi²=	5.58, df	= 8 (P	= 0.69),	I² = 0%	5		Favours control Favours experimen

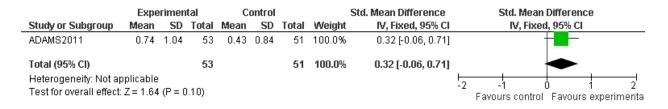
1.20.2 Hormones for IQ as an indirect outcome

Secretin versus placebo for IQ as an indirect outcome

	Experimental			Control				Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
MOLLOY2002	25.7	31.6	19	36.3	35.6	23	100.0%	-0.31 [-0.92, 0.30]	-		
Total (95% CI)			19			23	100.0%	-0.31 [-0.92, 0.30]			
Heterogeneity: Not ap Test for overall effect).32)						-2 -1 0 1 2 Favours control Favours experimenta		

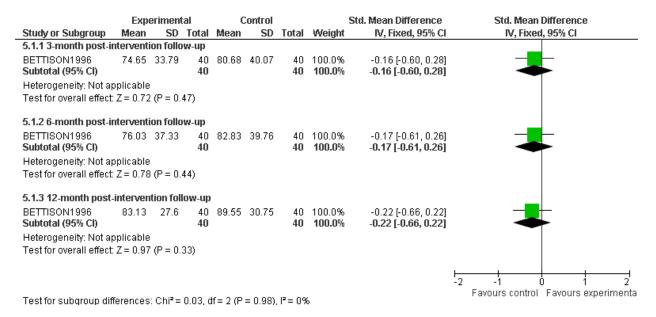
1.20.3 Nutritional intervention for IQ as an indirect outcome

Multivitamin/ mineral supplement versus placebo for IQ as an indirect outcome



1.20.4 Sensory intervention for IQ as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for IQ as an indirect outcome

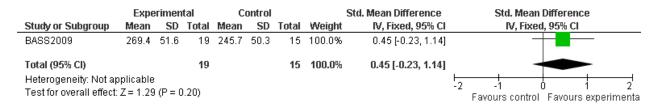


1.21PSYCHOSOCIAL INTERVENTIONS AIMED AT SENSORY SENSITIVITIES

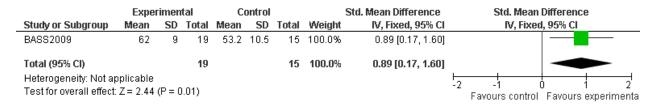
1.21.1 Animal-based interventions for sensory sensitivities as an indirect outcome

Horseback riding versus waitlist control for sensory sensitivities as an indirect outcome

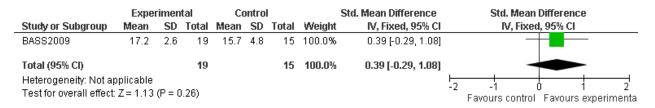
Sensory problems (Sensory Profile Total)



Sensory seeking (Sensory Profile)

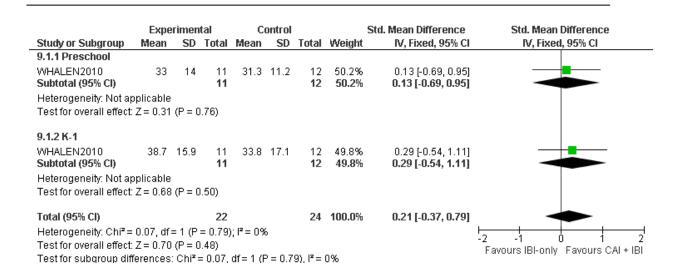


Sensory sensitivity (Sensory Profile)



1.21.2Educational interventions for sensory sensitivities as an indirect outcome

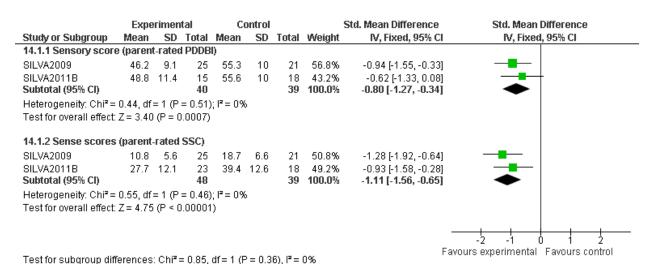
Combined TeachTown and IBI versus IBI-only for sensory sensitivities as an indirect outcome



1.22BIOMEDICAL INTERVENTIONS AIMED AT SENSORY SENSITIVITIES

1.22.1 Complementary therapies for sensory sensitivities as a direct outcome

Qigong massage training versus waitlist for sensory sensitivities as a direct outcome



1.22.2Sensory interventions for sensory sensitivities as a direct outcome

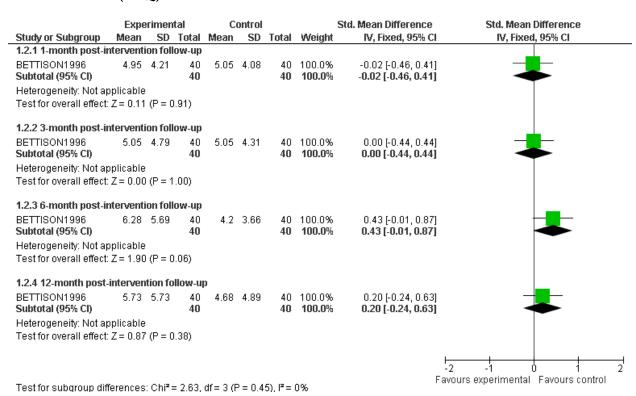
Auditory integration training versus attention-placebo (structured listening) for sensory sensitivities as a direct outcome

Sound sensitivity (SSQ)

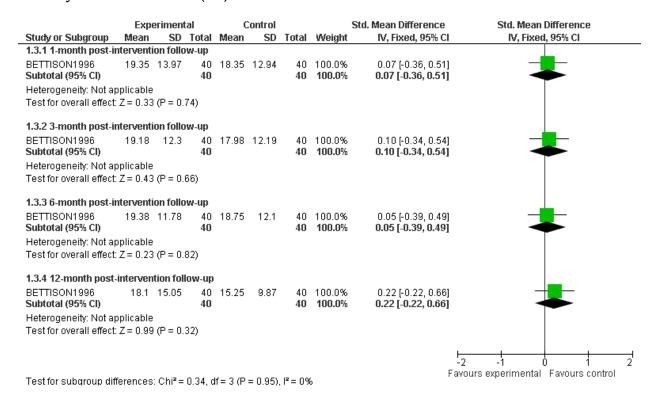
		riment			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 1-month post-in	iterventi	on follo	ow-up						
BETTISON1996	6.19	4.35	40	7.58	5.72		100.0%	-0.27 [-0.71, 0.17]	— —
Subtotal (95% CI)			40			40	100.0%	-0.27 [-0.71, 0.17]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.21	(P = 0.	23)						
1.1.2 3-month post-in	nterventi	on follo	w-up						
BETTISON1996	6.85	5.75	40	7.63	5.88		100.0%	-0.13 [-0.57, 0.31]	— —
Subtotal (95% CI)			40			40	100.0%	-0.13 [-0.57, 0.31]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.59	(P=0.	55)						
1.1.3 6-month post-in	nterventi	on follo	w-up						
BETTISON1996	7.73	6.93	40	6.95	6.17		100.0%	0.12 [-0.32, 0.56]	-
Subtotal (95% CI)			40			40	100.0%	0.12 [-0.32, 0.56]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.53	(P=0.	60)						
1.1.4 12-month post-	interven	tion fol	low-up)					
BETTISON1996	8.85	7.43	40	7.45	6.45	40	100.0%	0.20 [-0.24, 0.64]	-
Subtotal (95% CI)			40			40	100.0%	0.20 [-0.24, 0.64]	*
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.89	(P = 0.	37)						
								-2	-1 1
								_	rs experimental Favours control

Test for subgroup differences: $Chi^2 = 2.84$, df = 3 (P = 0.42), $I^2 = 0\%$

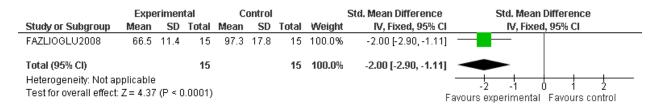
Sound distress (SSQ)



Sensory self-stimulation (SP)



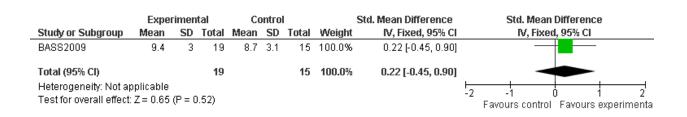
Sensory integration therapy versus treatment-as-usual for sensory sensitivities as a direct outcome



1.23PSYCHOSOCIAL INTERVENTIONS AIMED AT MOTOR SKILLS

1.23.1 Animal-based interventions for motor skills as an indirect outcome

Horseback riding versus waitlist control for motor skills as an indirect outcome



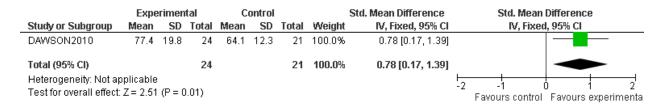
1.23.2Behavioural interventions for motor skills as an indirect outcome

EIBI (ESDM) versus treatment-as-usual for motor skills as an indirect outcome

Fine motor skills (MSEL)

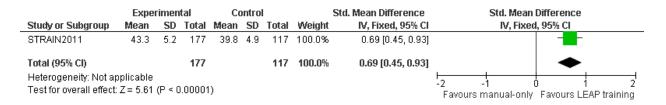
	Ехре	Experimental						Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
DAWSON2010	33.5	12.2	24	28.5	9.5	21	100.0%	0.45 [-0.15, 1.04]	+ -
Total (95% CI)			24			21	100.0%	0.45 [-0.15, 1.04]	-
Heterogeneity: Not ap Test for overall effect:	•).14)						-2 -1 0 1 2 Favours control Favours experimenta

Motor skills (VABS)



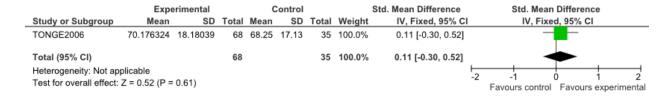
1.23.3 Educational interventions for motor skills as an indirect outcome

LEAP training versus manual-only control for motor skills as an indirect outcome



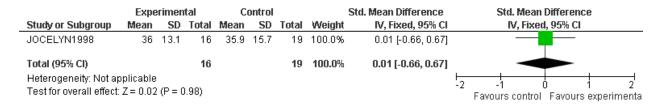
1.23.4 Parent training for motor skills as an indirect outcome

Parent training versus treatment-as-usual for motor skills as an indirect outcome

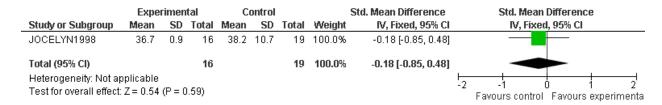


Parent and day-care staff training versus standard day-care for motor skills as an indirect outcome

Perceptual/Fine Motor Skills (EIDP/PSDP developmental age)



Gross Motor Skills (EIDP/PSDP developmental age)



1.23.5 Social-communication interventions for motor skills as an indirect outcome

Caregiver-mediated social-communication intervention versus treatment-asusual for motor skills as an indirect outcome

Fine motor skills (MSEL age [months])

	Experimental			C	ontrol			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
CARTER2011	22	3.5	25	21.92	4.09	25	100.0%	0.02 [-0.53, 0.58]		_	
Total (95% CI)			25			25	100.0%	0.02 [-0.53, 0.58]		-	
Heterogeneity: Not ap Test for overall effect			0.94)						-2 F	-1 0 1 Favours control Favours expe	2 rimenta

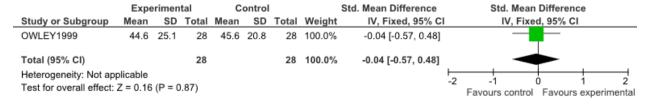
Motor skills (VABS)

	Expe	Experimental SD Tatal			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CARTER2011	83.16	7.36	19	81.55	9.26	20	100.0%	0.19 [-0.44, 0.82]	
Total (95% CI)			19			20	100.0%	0.19 [-0.44, 0.82]	
Heterogeneity: Not ag Test for overall effect:).56)						-2 -1 0 1 2 Favours control Favours experimenta

1.24BIOMEDICAL INTERVENTIONS AIMED AT MOTOR SKILLS

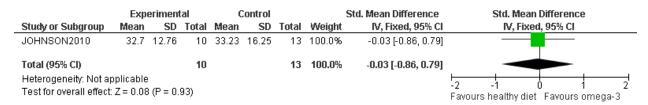
1.24.1 Hormones for motor skills as an indirect outcome

Secretin versus placebo for motor skills as an indirect outcome

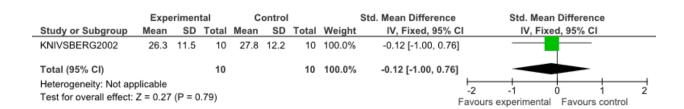


1.24.2 Nutritional interventions for motor skills as an indirect outcome

Omega-3 fatty acids versus healthy diet control for motor skills as an indirect outcome



Gluten-free and casein-free diet versus treatment-as-usual for motor skills as an indirect outcome



1.25PSYCHOSOCIAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

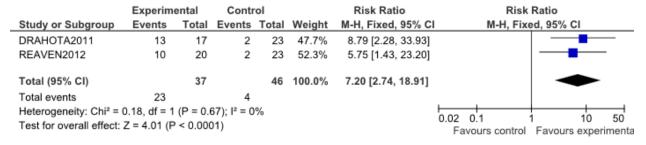
1.25.1 Cognitive-behavioural interventions for anxiety as a direct outcome

CBT versus treatment-as-usual for anxiety as a direct outcome

No longer meet anxiety disorder diagnosis

	Experime	ental	Contr	ol		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H, Fixe	ed, 95% CI	<u> </u>
CHALFANT2007	20	28	0	19	25.8%	28.28 [1.81, 440.96]				
DRAHOTA2011	9	17	2	23	74.2%	6.09 [1.50, 24.64]			-	
Total (95% CI)		45		42	100.0%	11.82 [3.14, 44.50]			•	-
Total events	29		2							
Heterogeneity: Chi ² =			,.	0%			0.002	0.1	1 10	500
Test for overall effect:	Z = 3.65 (P	= 0.000	13)				Fav	ours control	Favours 6	experimental

Improvement in anxiety symptoms (CGI- Improvement)

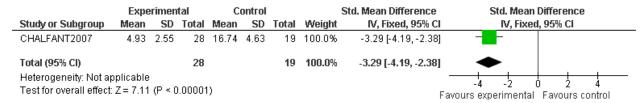


Anxiety

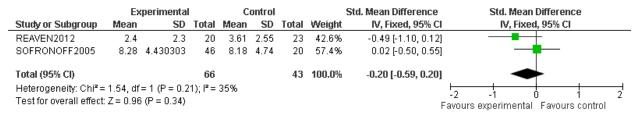
	Experi	mental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 Self-reported (S	SCAS; MASC)								
CHALFANT2007	13.79	10.96	28	41.37	9.09	19	40.8%	-2.64 [-3.45, -1.84]	-
DRAHOTA2011	46.93	14.76	14	46.5	15.83	22	59.2%	0.03 [-0.64, 0.70]	, - •
Subtotal (95% CI)			42			41	100.0%	-1.06 [-1.58, -0.55]	•
Heterogeneity: Chi2 =	24.92, df = 1 (P	< 0.0000	1); I2 =	96%					
Test for overall effect:	Z = 4.04 (P < 0	.0001)							
1.3.2 Parent-reported	d (SCAS-P; MA	SC)							
CHALFANT2007	13.96	5.11	28	44.16	9.04	19	13.6%	-4.27 [-5.34, -3.20]	
DRAHOTA2011	58.48	14.72	14	76.57	14.65	22	29.3%	-1.21 [-1.94, -0.47]	-
SOFRONOFF2005	34.124783 1	5.36961	46	35.61	13.34	20	57.0%	-0.10 [-0.62, 0.43]	, *
Subtotal (95% CI)			88			61	100.0%	-0.99 [-1.39, -0.60]	•
Heterogeneity: Chi2 =	47.24, df = 2 (P	< 0.0000	1); I ² =	96%					
Test for overall effect:	Z = 4.91 (P < 0	.00001)							
1.3.3 Clinician-rated	anxiety (ADIS-	P/C)							
DRAHOTA2011	2.36	1.15	14	4.77	0.81	22	31.6%	-2.47 [-3.37, -1.57]	
REAVEN2012	2.25	0.91	20	2.83	0.98	23	68.4%	-0.60 [-1.21, 0.01]	-
Subtotal (95% CI)			34			45	100.0%	-1.19 [-1.70, -0.68]	•
Heterogeneity: Chi2 =	11.26, df = 1 (P	= 0.0008); I ² = 9	91%					
Test for overall effect:	Z = 4.60 (P < 0	.00001)							
									-4 -2 0 2 4
Test for subgroup diffe	propose: Chi² = I	0.37 df =	2 (P =	0.837 1	2 - 0%			Fa	avours experimental Favours control
reat for adaptioup diffe	orences. Crit = 1	0.57, ui –	211	0.037. 1	- 0 /6				

rest for subgroup differences. Off = 0.07, df = 2 (f = 0.00), f

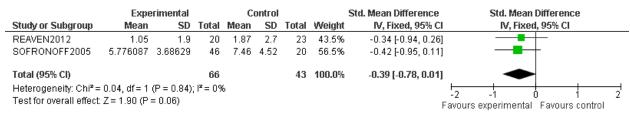
Chronic anxiety (RCMAS)



Social anxiety (ADIS-P or SCAS-P; post-treatment)



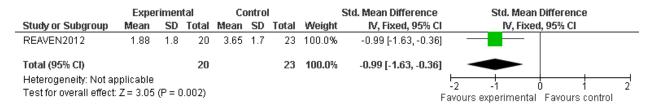
Separation anxiety (ADIS-P or SCAS-P; post-treatment)



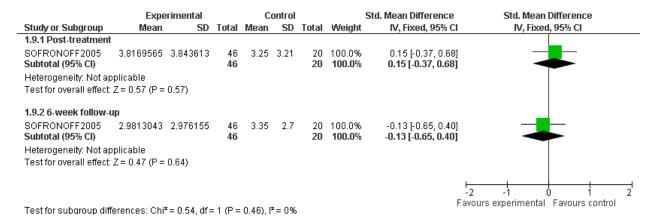
Generalized Anxiety Disorder (ADIS-P or SCAS-P; post-treatment)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	l, 95% CI	
REAVEN2012	2.55	2.5	20	4.61	1.7	23	47.1%	-0.96 [-1.59, -0.32]			
SOFRONOFF2005	5.28	2.53	24	6.42	3.19	20	52.9%	-0.39 [-0.99, 0.21]			
Total (95% CI)			44			43	100.0%	-0.66 [-1.10, -0.22]	•		
Heterogeneity: Chi²=		,		; I² = 38	%				-2 -1	\	$-\frac{1}{2}$
Test for overall effect:	Z = 2.96	i (P = 0	1.003)					F	avours experimental	Favours control	

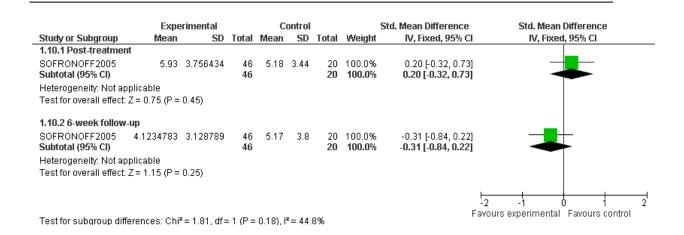
Anxiety relating to a specific phobia (ADIS-P)



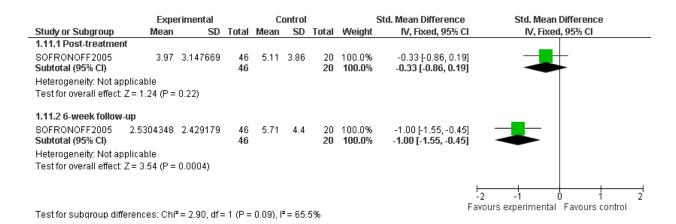
Panic (SCAS-P; child-only and child and parent combined)



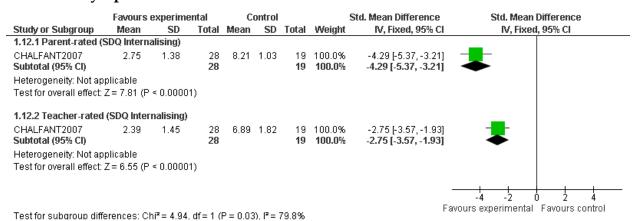
Fear of personal injury (SCAS-P; child-only and child and parent combined)



OCD (SCAS-P; child-only and child and parent combined)



Emotional symptoms



Self-directed negative thoughts (CATS: internalising)

	Ехре	erimen	tal	C	ontrol		9	Std. Mean Difference	Std. Mean	Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI
CHALFANT2007	10.39	5.56	28	51	11.87	19	100.0%	-4.61 [-5.75, -3.48]	-	
Total (95% CI)			28			19	100.0%	-4.61 [-5.75, -3.48]	•	
Heterogeneity: Not a Test for overall effect			0.00001)				F	+ + + + + + + + + + + + + + + + + + +	

Outward-directed negative thoughts (CATS: Hostile Intent)

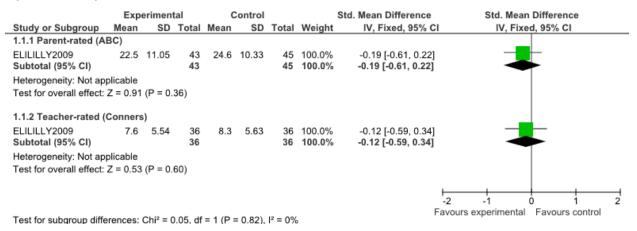
	Experimental				ontrol			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
CHALFANT2007	9.54	5.64	28	11.37	5.25	19	100.0%	-0.33 [-0.91, 0.26]			
Total (95% CI)			28			19	100.0%	-0.33 [-0.91, 0.26]	-		
Heterogeneity: Not ap Test for overall effect:			1.27)						-2 -1 0 1 2		
			,					ŀ	Favours experimental Favours control		

1.26PHARMACOLOGICAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.26.1 SNRIs for ADHD as a direct outcome

Atomoxetine versus placebo for ADHD as a direct outcome

Hyperactivity



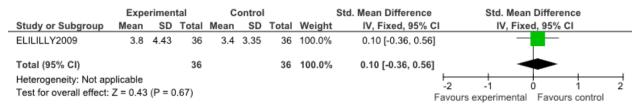
ADHD symptoms

	Exp	eriment	tal	С	ontrol		5	Std. Mean Difference	Std. Mean	Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% (IV, Fixe	d, 95% CI
1.2.1 Parent-rated (D	SM-IV ra	iting sc	ale)							
ELILILLY2009	32.3	10.97	43	37.3	9.57	47	100.0%	-0.48 [-0.90, -0.06	_ _	
Subtotal (95% CI)			43			47	100.0%	-0.48 [-0.90, -0.06]	•	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.26	(P = 0.	02)							
1.2.2 Teacher-rated (Conners	s)								
ELILILLY2009	15.8	9.85	36	17.2	8.69	36	100.0%	-0.15 [-0.61, 0.31	_	_
Subtotal (95% CI)			36			36	100.0%	-0.15 [-0.61, 0.31]	•	-
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.63	(P = 0.	53)							
									-2 -1 (1
									Favours experimental	Favours control

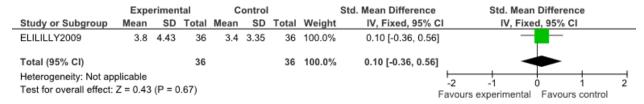
Inattention (Conners)

	Expe	Experimental			ontrol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed	d, 95% CI	
ELILILLY2009	6.1	4.56	34	4.6	3.53	36	100.0%	0.37 [-0.11, 0.84]	-		
Total (95% CI)			34			36	100.0%	0.37 [-0.11, 0.84]	-	◆	
Heterogeneity: Not ap Test for overall effect:		(P = 0	.13)					ı	-2 -1 (Favours experimental) 1 Favours control	2

Oppositional (Conners)



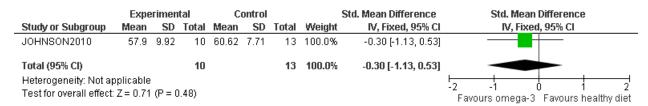
Improvement in ADHD symptoms (CGI-ADHD-I)



1.27BIOMEDICAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.27.1 Nutritional interventions for ADHD as an indirect outcome

Omega-3 fatty acids versus healthy diet control for ADHD as an indirect outcome

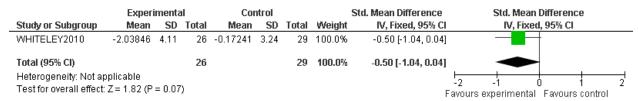


Gluten-free and casein-free diet versus treatment-as-usual for ADHD as an indirect outcome

Inattention (change score; ADHD-IV)

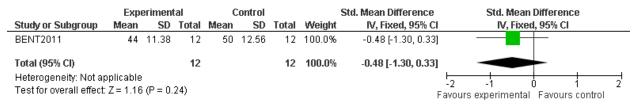
	Experi	imenta	al					Std. Mean Difference	Std. Mea	n Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fixe	ed, 95% CI	
WHITELEY2010	-2.15385	4.67	26	0.31034	3.52	29	100.0%	-0.59 [-1.13, -0.05]] —		
Total (95% CI)			26			29	100.0%	-0.59 [-1.13, -0.05]		-	
Heterogeneity: Not ap Test for overall effect:	•	= 0.03)					I	-2 -1 Favours experiments	0 1 I Favours cont	2 trol

Hyperactivity (change score; ADHD-IV)

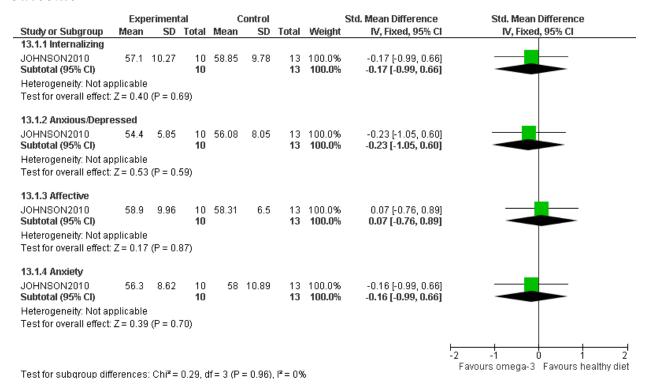


1.27.2 Nutritional interventions for anxiety as an indirect outcome

Omega-3 fatty acids versus placebo for anxiety as an indirect outcome

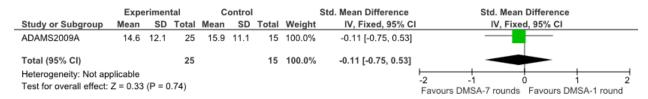


Omega-3 fatty acids versus healthy diet control for anxiety as an indirect outcome



1.27.3 Medical procedures for anxiety as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for anxiety as an indirect outcome



1.28PSYCHOSOCIAL AND PHARMACOLOGICAL INTERVENTIONS AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

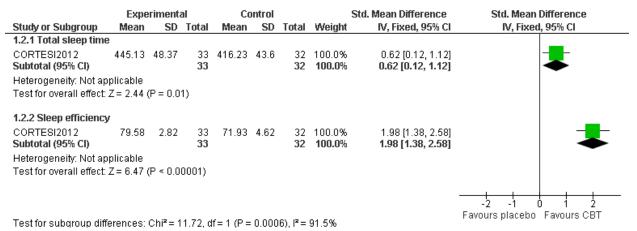
1.28.1 Cognitive-behavioural interventions for sleep problems as a direct outcome

CBT versus placebo for sleep problems as a direct outcome

Sleep problems (actigraph)

	Expo	eriment	tal	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 Sleep onset la	tency								
CORTESI2012 Subtotal (95% CI)	59.13	27.6	33 33	79.6	31.85	32 32	100.0% 100.0 %	-0.68 [-1.18, -0.18] - 0.68 [-1.18, -0.18]	-
Heterogeneity: Not a	pplicable								
Test for overall effect	t: Z= 2.66	(P = 0.	008)						
1.1.2 Wake after sle	eep onset	:							
CORTESI2012 Subtotal (95% CI)	61.17	28.93	33 33	70.15	42.76	32 32	100.0% 100.0 %	-0.24 [-0.73, 0.24] - 0.24 [-0.73, 0.24]	
Heterogeneity: Not a	nnlicable								
Test for overall effect			33)						
1.1.3 Nap time									
CORTESI2012 Subtotal (95% CI)	12.29	24.24	33 33	36.1	33.2	32 32	100.0% 100.0 %	-0.81 [-1.32, -0.30] - 0.81 [-1.32, -0.30]	.
Heterogeneity: Not a	pplicable							•	
Test for overall effec			002)						
1.1.4 Bedtime									
CORTESI2012	22.55	1.01	33	23.51	1.12	32	100.0%	-0.89 [-1.40, -0.38]	
Subtotal (95% CI)	22.00		33	20.01	2	32	100.0%	-0.89 [-1.40, -0.38]	-
Heterogeneity: Not a	pplicable								
Test for overall effect			0006)						
									-2 -1 0 1
Test for subgroup di	fforoncoo	· Chiz –	201 ^	lf = 2 /□	- 0.27V	Z = 22	204		Favours CBT Favours plac
restini sandinah di	merences	. Oni =	3.81,0	n – 3 (F	-0.27)	. 1 – 23	.570		

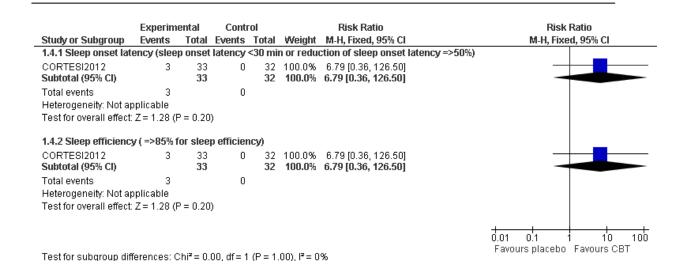
Positive sleep behaviour (actigraph)



Sleep problems (Childrens Sleep Habits Questionnaire)

	Expe	rimen	ıtal	Ci	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 Total score									_
CORTESI2012 Subtotal (95% CI)	60.06	4.71	33 33	64.8	4.52	32 32	100.0% 100.0 %	-1.01 [-1.53, -0.50] - 1.01 [-1.53, -0.50]	•
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z = 3.83	(P = 0	0.0001)						
1.3.2 Bed resistance									
CORTESI2012	11.62	2.22	33	14.1	1.93		100.0%	-1.18 [-1.71, -0.65]	
Subtotal (95% CI)	ماطممناهم		33			32	100.0%	-1.18 [-1.71, -0.65]	
Heterogeneity: Not ap Test for overall effect:			0.0001)						
			,						
1.3.3 Sleep onset de	_	0.57	22	2.02	0.25	22	400.00	0.04.14.45.0.42	
CORTESI2012 Subtotal (95% CI)	2.51	0.57	33 33	2.93	0.25		100.0% 100.0 %	-0.94 [-1.45, -0.42] - 0.94 [-1.45, -0.42]	-
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z= 3.58	(P = 0	0.0003)						
1.3.4 Sleep anxiety									_
CORTESI2012	7.17	1.48	33	7.93	1.99		100.0%	-0.43 [-0.92, 0.06]	
Subtotal (95% CI) Heterogeneity: Not as	nnlicable		33			32	100.0%	-0.43 [-0.92, 0.06]	
Test for overall effect:			0.09)						
4.0.5 Nicolate constitue con									
1.3.5 Night-wakings CORTESI2012	7.06	1.06	33	7.86	0.91	22	100.0%	-0.84 [-1.34, -0.33]	
Subtotal (95% CI)	7.00	1.00	33	7.00	0.01		100.0%	-0.84 [-1.34, -0.33]	•
Heterogeneity: Not ap									
Test for overall effect:	: Z = 3.22	! (P = 0	J.001)						
1.3.6 Sleep duration									<u></u>
CORTESI2012	6.68	1.16	33	6.4	1.29		100.0%	0.23 [-0.26, 0.71]	
Subtotal (95% CI) Heterogeneity: Not as	nnlicable		33			32	100.0%	0.23 [-0.26, 0.71]	
Test for overall effect:			0.36)						
1.3.7 Parasomnias									
CORTESI2012	9.82	2.25	33	9.16	1.53	32	100.0%	0.34 [-0.15, 0.83]	
Subtotal (95% CI)			33			32	100.0%	0.34 [-0.15, 0.83]	
Heterogeneity: Not ap			140						
Test for overall effect	.∠=1.35	(r=(ມ. 1 ປັ)						
1.3.8 Sleep disorder		_							<u></u>
CORTESI2012 Subtotal (95% CI)	3.2	0.41	33 33		0.44		100.0% 100.0%	0.00 [-0.49, 0.49] 0.00 [-0.49, 0.49]	
Heterogeneity: Not as	oplicable		33			JZ	100.070	0.00 [-0.43, 0.43]	
Test for overall effect			(00.1						
1.3.9 Daytime sleepii	ness								
CORTESI2012	11.96	1.97	33	12.96	1.97	32	100.0%	-0.50 [-1.00, -0.01]	———
Subtotal (95% CI)			33			32	100.0%	-0.50 [-1.00, -0.01]	
Heterogeneity: Not ap Test for overall effect:			1.05)						
restroi overali ellett.	. ೭ – 1.38	(i – t	,.03)						
									-2 -1 0 1 2
Test for subgroup dif	ferences	: Chi≅-	= 38 11	df = 8 4	(P < ∩	000011	2 <u> </u>	%	Favours CBT Favours placebo
ւ Ժու յու ոսով լոսի Այլ	ierentes	. Om	- 50.11	, ui – 0 i	,ı= → U.	00001)	.1 - 78.0	70	

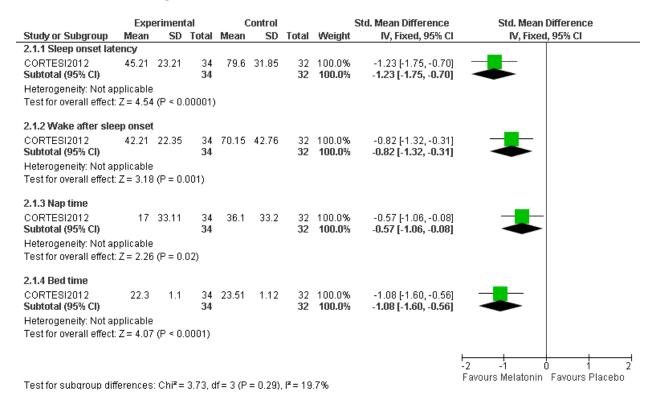
Positive treatment response



1.28.2 Melatonin for sleep problems as a direct outcome

Melatonin versus placebo for sleep problems as a direct outcome

Sleep problems (actigraph)



Positive sleep behaviour (actigraph)

Exbe	eriment	al	Co	ntrol		St	d. Mean Difference	Std. Mean Difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
481.1	45.07	34 34	416.23	43.6	32 32	100.0% 100.0 %	1.45 [0.90, 1.99] 1.45 [0.90, 1.99]	👢
olicable Z= 5.19		00001)						
82.71	4	34 34	71.93	4.62	32 32	100.0% 100.0 %	2.47 [1.82, 3.12] 2.47 [1.82, 3.12]	👢
olicable Z= 7.46		00001)						
								-4 -2 0 2
	481.1 olicable Z = 5.19 82.71 olicable	481.1 45.07 blicable Z = 5.19 (P < 0.00) 82.71 4 blicable	481.1 45.07 34 34 blicable Z = 5.19 (P < 0.00001) 82.71 4 34 34 blicable	481.1 45.07 34 416.23 34 blicable Z = 5.19 (P < 0.00001) 82.71 4 34 71.93 34	481.1 45.07 34 416.23 43.6 34 blicable Z = 5.19 (P < 0.00001) 82.71 4 34 71.93 4.62 34 blicable	481.1 45.07 34 416.23 43.6 32 34 32 blicable Z= 5.19 (P < 0.00001) 82.71 4 34 71.93 4.62 32 34 32 blicable	481.1 45.07 34 416.23 43.6 32 100.0% 34 32 100.0% 32 100.0% 32 100.0% 32 100.0% 32 32 100.0% 32 32 100.0% 34 32 100.0% 32 100.0% 31 32 100.0% 31 32 100.0% 31 32 32 32 32 33 33 33 34 32 34 33 32 34 33 34 34 34 34 34 34 34 34 34 34 34	481.1 45.07 34 416.23 43.6 32 100.0% 1.45 [0.90, 1.99] 34 32 100.0% 1.45 [0.90, 1.99] blicable Z = 5.19 (P < 0.00001) 82.71 4 34 71.93 4.62 32 100.0% 2.47 [1.82, 3.12] 34 32 100.0% 2.47 [1.82, 3.12] blicable

Sleep problems (Children's Sleep Habits Questionnaire)

Chucks on Creberross		rimen			ontrol	Total	Mainh	Std. Mean Difference	Std. Mean Difference
Study or Subgroup 2.3.1 Total score	Mean	30	rutal	Mean	ÐΝ	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CORTESI2012 Subtotal (95% CI)	54.78	6.22	34 34	64.8	4.52		100.0% 100.0 %	-1.81 [-2.39, -1.23] - 1.81 [- 2.39 , - 1.23]	.
Heterogeneity: Not ap Test for overall effect:			.00001)				. , .	
2.3.2 Bed resistance									
CORTESI2012 Subtotal (95% CI)	10.5	2.2	34 34	14.1	1.93		100.0% 100.0 %	-1.72 [-2.29, -1.15] - 1.72 [-2.29, -1.15]	.
Heterogeneity: Not ap Test for overall effect:			.00001)					
2.3.3 Sleep onset del	av								
CORTESI2012 Subtotal (95% CI)	-	0.68	34 34	2.93	0.25		100.0% 100.0 %	-1.58 [-2.14, -1.03] - 1.58 [-2.14, -1.03]	-
Heterogeneity: Not ap Test for overall effect:			.00001)					
2.3.4 Sleep anxiety									
CORTESI2012 Subtotal (95% CI)	7.21	1.87	34 34	7.93	1.99		100.0% 100.0 %	-0.37 [-0.86, 0.12] - 0.37 [-0.86, 0.12]	-
Heterogeneity: Not ap Test for overall effect:			.14)						
2.3.5 Night-wakings									
CORTESI2012 Subtotal (95% CI)	5.03	1.1	34 34	7.86	0.81		100.0% 100.0 %	-2.88 [-3.58, -2.18] - 2.88 [-3.58, -2.18]	
Heterogeneity: Not ap Test for overall effect:			.00001)					
2.3.6 Sleep duration									
CORTESI2012 Subtotal (95% CI)	4.82	0.94	34 34	6.4	1.29		100.0% 100.0 %	-1.39 [-1.93, -0.85] - 1.39 [- 1.93 , - 0.85]	.
Heterogeneity: Not ap			00004	,					
Test for overall effect:	Z = 5.03	(P < U	.00001)					
2.3.7 Parasomnias									
CORTESI2012 Subtotal (95% CI)		1.78	34 34	9.16	1.53		100.0% 100.0 %	0.11 [-0.37, 0.60] 0.11 [-0.37, 0.60]	-
Heterogeneity: Not ap Test for overall effect:			.65)						
2.3.8 Sleep disordere	ed breatl	hing							
CORTESI2012 Subtotal (95% CI)		0.48	34 34	3.2	0.44	32 32	100.0% 100.0 %	-0.11 [-0.59, 0.38] - 0.11 [-0.59, 0.38]	
Heterogeneity: Not ap Test for overall effect:			.66)						
2.3.9 Daytime sleepin	2291								
2.3.9 Daytime sleepiii CORTESI2012 Subtotal (95% CI)	11.39	2.34	34 3 4	12.96	1.97		100.0% 100.0 %	-0.72 [-1.21, -0.22] - 0.72 [-1.21, -0.22]	.
Heterogeneity: Not ap Test for overall effect:						-	3.6.1		
	_ 2.01	V - 0	.500)						
									-4 -2 0 2
									Favours Melatonin Favours Placet

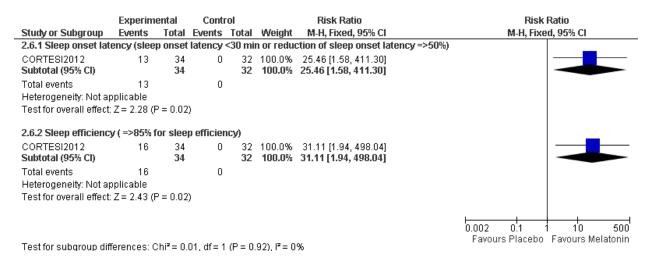
Sleep onset latency (sleep diary)

	Exp	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
GRINGRAS2012	47.13	44.21	25	88.6	61.45	24	100.0%	-0.76 [-1.35, -0.18]	_
Total (95% CI)	nlicable		25			24	100.0%	-0.76 [-1.35, -0.18]	
Heterogeneity: Not ap Test for overall effect:			010)						'-2 -1 0 1 2' Favours Melatonin Favours Placebo

Total sleep time (sleep diary)

	Expe	rimenta	al	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
GRINGRAS2012	567.36	73.85	23	556.43	73.57	24	100.0%	0.15 [-0.43, 0.72]	
Total (95% CI)			23			24	100.0%	0.15 [-0.43, 0.72]	-
Heterogeneity: Not ap Test for overall effect:		(P = 0.6	2)						-2 -1 0 1 2 Favours Placebo Favours Melatonin

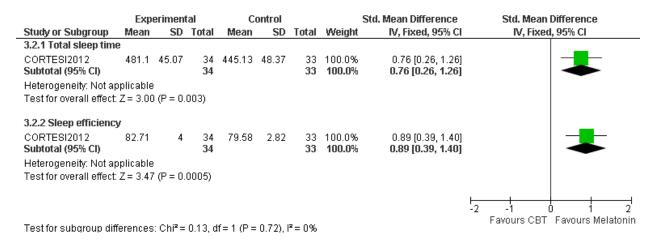
Positive treatment response



Melatonin versus CBT for sleep problems as a direct outcome Sleep problems (actigraph)

		eriment			ontrol			Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
.1.1 Sleep onset late	ency								
ORTE8I2012	45.21	23.21		59.13	27.6		100.0%	-0.54 [-1.03, -0.05]	
ubtotal (95% CI)			34			33	100.0%	-0.54 [-1.03, -0.05]	-
leterogeneity: Not ap	plicable								
est for overall effect:	Z = 2.17	(P = 0.	03)						
.1.2 Wake after slee	p onset								
ORTESI2012	42.21	22.35	34	61.17	28.93	33	100.0%	-0.73 [-1.22, -0.23]	— — —
ubtotal (95% CI)			34			33	100.0%	-0.73 [-1.22, -0.23]	-
leterogeneity: Not ap	plicable								
est for overall effect:	Z= 2.87	(P = 0.	004)						
.1.3 Nap time									
ORTESI2012	17	33.11	34	12.29	24.24	33	100.0%	0.16 [-0.32, 0.64]	
ubtotal (95% CI)			34			33	100.0%	0.16 [-0.32, 0.64]	-
leterogeneity: Not ap	plicable								
est for overall effect:	Z = 0.65	(P = 0.1)	51)						
.1.4 Bed time									
ORTESI2012	22.3	1.1	34	22.55	1.01	33	100.0%	-0.23 [-0.71, 0.25]	———
ubtotal (95% CI)			34			33	100.0%	-0.23 [-0.71, 0.25]	-
leterogeneity: Not ap	plicable								
est for overall effect:			34)						
									-2 -1 1 1

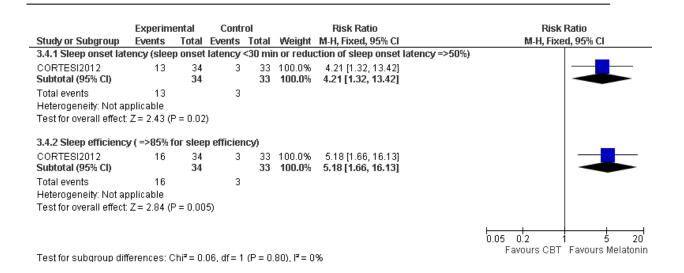
Positive sleep behaviour (actigraph)



Sleep problems (Children's sleep habits questionnaire)

Cturks or Cuberous		rimen			ontrol	Total		Std. Mean Difference	Std. Mean Difference
Study or Subgroup 3.3.1 Total score	Mean	30	rotal	Mean	Эυ	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CORTESI2012	54.78	6 22	34	60.06	1 71	22	100.00	0.0414.45.0.441	
Subtotal (95% CI)		0.22	34	60.06	4.71	33 33	100.0% 100.0 %	-0.94 [-1.45, -0.44] - 0.94 [-1.45, -0.4 4]	
Heterogeneity: Not ap Test for overall effect:		(P = 0	.0003)						
3.3.2 Bed resistance									_
CORTESI2012 Subtotal (95% Cl)	10.5	2.2	34 34	11.62	2.22		100.0% 100.0 %	-0.50 [-0.99, -0.01] - 0.50 [-0.99, -0.01]	-
Heterogeneity: Not ap Test for overall effect:	•	(P = 0	.04)						
3.3.3 Sleep onset del	ay								
CORTESI2012 Subtotal (95% CI)	2.1	0.68	34 34	2.51	0.57		100.0% 100.0 %	-0.65 [-1.14, -0.15] - 0.65 [-1.14 , - 0.15]	
Heterogeneity: Not ap Test for overall effect:	•	(P = 0	.01)						
3.3.4 Sleep anxiety									\perp
CORTESI2012 Subtotal (95% CI)	7.21	1.87	34 34	7.17	1.48		100.0% 100.0 %	0.02 [-0.46, 0.50] 0.02 [-0.46, 0.50]	-
Heterogeneity: Not ap Test for overall effect:		(P = 0	.92)						
3.3.5 Night-wakings									
CORTESI2012 Subtotal (95% CI)	5.03	1.1	34 34	7.06	1.06		100.0% 100.0 %	-1.86 [-2.44, -1.28] - 1.86 [-2.44, -1.28]	
Heterogeneity: Not ap Test for overall effect:	•	(P < 0)				,	
3.3.6 Sleep duration									
CORTESI2012 Subtotal (95% CI)	4.82	0.94	34 34	6.68	1.16		100.0% 100.0 %	-1.74 [-2.31, -1.18] - 1.74 [-2.31 , - 1.18]	<u> </u>
Heterogeneity: Not ap Test for overall effect:	•	(P < 0)					
3.3.7 Parasomnias									
CORTESI2012 Subtotal (95% CI)	9.35	1.78	34 34	9.82	2.25		100.0% 100.0 %	-0.23 [-0.71, 0.25] - 0.23 [-0.71, 0.25]	.
Heterogeneity: Not ap Test for overall effect:	•	(P = 0				-			
3.3.8 Sleep disordere		•	•						
5.5.6 Sieep disordere CORTESI2012 Subtotal (95% CI)	3.15	_	34 34	3.2	0.41		100.0% 100.0 %	-0.11 [-0.59, 0.37] - 0.11 [-0.59, 0.37]	#
Heterogeneity: Not ap Test for overall effect:		/p = 0				33	100.070	-0.11 [-0.35, 0.31]	
		(r − 0	.00)						
3.3.9 Daytime sleepin CORTESI2012	11.39	234	31	11.96	1 97	22	100.0%	-0.26 [-0.74, 0.22]	
Subtotal (95% CI)		2.34	34	11.30	1.01		100.0%	-0.26 [-0.74, 0.22]	-
Heterogeneity: Not ap Test for overall effect:		(P = 0	.29)						
									-2 -1 0 1 2

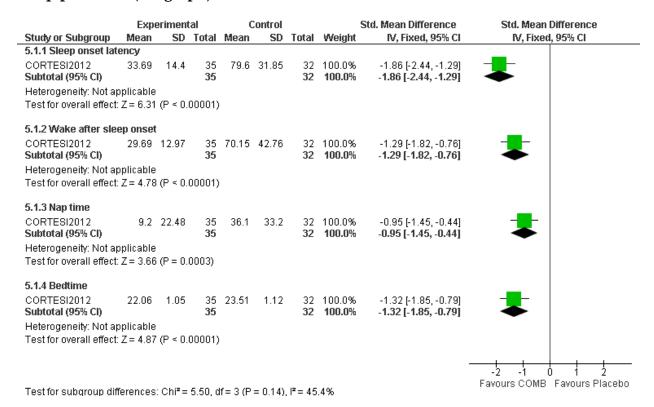
Positive treatment response



1.28.3 Combined cognitive-behavioural intervention and melatonin for sleep problems as a direct outcome

COMB versus placebo for sleep problems as a direct outcome

Sleep problems (actigraph)



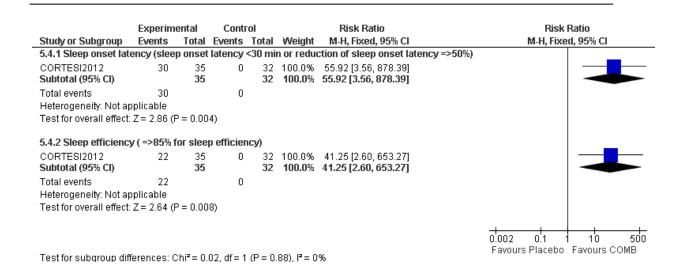
Positive sleep behaviour (actigraph)

	Expe	riment	al	Co	ntrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.2.1 Total sleep time	1								
CORTESI2012 Subtotal (95% CI)	505.01	31.18	35 35	416.23	43.6	32 32	100.0% 100.0 %	2.33 [1.70, 2.96] 2.33 [1.70, 2.96]	
Heterogeneity: Not ap	plicable								
Test for overall effect: 1	Z = 7.27 ((P < 0.0	0001)						
5.2.2 Sleep efficiency	,								
CORTESI2012 Subtotal (95% CI)	84.46	4.23	35 35	71.93	4.62	32 32	100.0% 100.0 %	2.80 [2.12, 3.49] 2.80 [2.12, 3.49]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 8.02 ((P < 0.0	0001)						
TOSTION OVERAIL CHECK.									
restror overall ellect.									
Test for everall effect.								ŀ	.4 -2 0 2

Sleep problems (Children's sleep habits questionnaire)

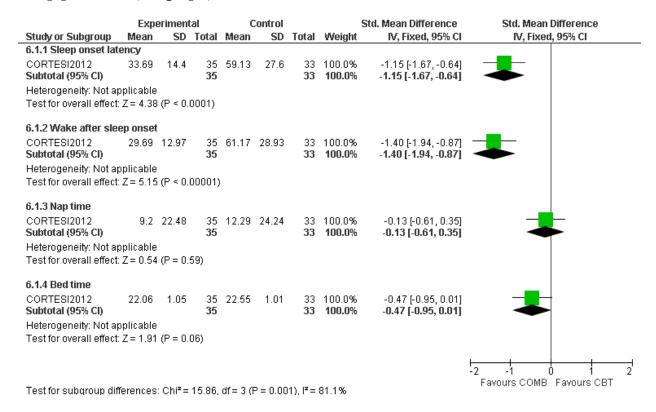
Study or Subgroup	Expe Mean	rimen SD		Co Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
5.3.1 Total score	1110 011		10101			Total		11,111104,001101	11,111104,1001101
CORTESI2012 Subtotal (95% CI)	47.84	2.94	35 35	64.8	4.52		100.0% 100.0 %	-4.44 [-5.35, -3.53] -4.44 [-5.35, -3.53]	‡
Heterogeneity: Not ap Test for overall effect:			0.00001)					
5.3.2 Bed resistance									_
CORTESI2012 Subtotal (95% CI)	8.46	1.39	35 35	14.1	1.93		100.0% 100.0 %	-3.34 [-4.09, -2.58] - 3.34 [-4.09, -2.58]	
Heterogeneity: Not ap Test for overall effect:	•		0.00001)					
5.3.3 Sleep onset del	ay								
CORTESI2012 Subtotal (95% CI)	1.69	0.73	35 35	2.93	0.25		100.0% 100.0 %	-2.21 [-2.82, -1.59] - 2.21 [-2.82, -1.59]	
Heterogeneity: Not ap Test for overall effect:			0.00001)					
5.3.4 Sleep anxiety									_
CORTESI2012 Subtotal (95% CI)	5.23	0.95	35 35	7.93	1.99	32 32	100.0% 100.0 %	-1.74 [-2.30, -1.17] - 1.74 [-2.30, -1.17]	
Heterogeneity: Not ap Test for overall effect:			0.00001)					
5.3.5 Night-wakings									_
CORTESI2012 Subtotal (95% CI)	4.42	0.9	35 35	7.86	0.81		100.0% 100.0 %	-3.96 [-4.80, -3.12] - 3.96 [-4.80, -3.12]	
Heterogeneity: Not ap Test for overall effect:).00001)					
5.3.6 Sleep duration									_
CORTESI2012 Subtotal (95% CI)	4.38	1.02	35 35	6.4	1.29	32 32	100.0% 100.0 %	-1.73 [-2.29, -1.16] - 1.73 [-2.29, -1.16]	
Heterogeneity: Not ap Test for overall effect:			0.00001)					
5.3.7 Parasomnias									
CORTESI2012 Subtotal (95% CI)	8.92	1.38	35 35	9.16	1.53	32 32	100.0% 100.0 %	-0.16 [-0.64, 0.32] - 0.16 [-0.64, 0.32]	
Heterogeneity: Not ap Test for overall effect:).51)						
5.3.8 Sleep disordere	ed breati	hina							
CORTESI2012 Subtotal (95% CI)		0.95	35 35	3.2	0.44		100.0% 100.0 %	0.03 [-0.45, 0.51] 0.03 [-0.45, 0.51]	
Heterogeneity: Not ap Test for overall effect:).91)						
5.3.9 Daytime sleepir	ness								
CORTESI2012 Subtotal (95% CI)	10.84	1.68	35 35	12.96	1.97		100.0% 100.0 %	-1.15 [-1.67, -0.63] - 1.15 [-1.67 , - 0.63]	-
Heterogeneity: Not ap Test for overall effect:).0001)					- · ·	
									-4 -2 0 2 4
Fest for subgroup diff	oroncoc	: Chi≅:	= 172 4	9 df= 9	! (P < (1 00001	I) P= 95	4%	-4 -2 U 2 4 Favours COMB Favours Placek

Positive treatment response



COMB versus CBT-only for sleep problems as a direct outcome

Sleep problems (actigraph)



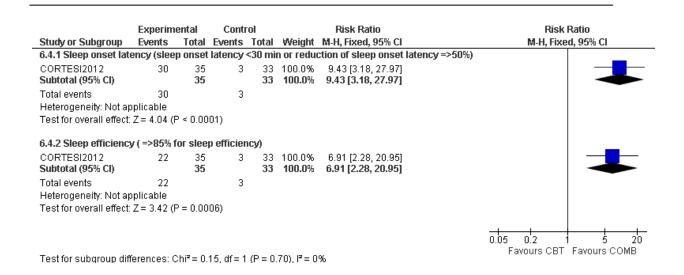
Positive sleep behaviour (actigraph)

	Exbe	erimenta	al	Ci	ontrol		Si	td. Mean Difference	Std. Mean Difference	ž
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
6.2.1 Total sleep time										
CORTESI2012 Subtotal (95% CI)	505.01	31.18	35 35	445.13	48.37	33 33	100.0% 100.0 %	1.46 [0.93, 2.00] 1.46 [0.93, 2.00]	🚚	<u> </u>
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z= 5.32 ((P < 0.0	0001)							
6.2.2 Sleep efficiency CORTESI2012	84.46	4.23	35	79.58	2.82	33	100.0%	1.33 [0.81, 1.86]	-	_
Subtotal (95% CI)			35			33	100.0%	1.33 [0.81, 1.86]	•	۰
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z = 4.95 ((P < 0.0	0001)							
								_	-2 -1 0 1	+
									Favours CBT Favours (201

Sleep problems (Children's sleep habits questionnaire)

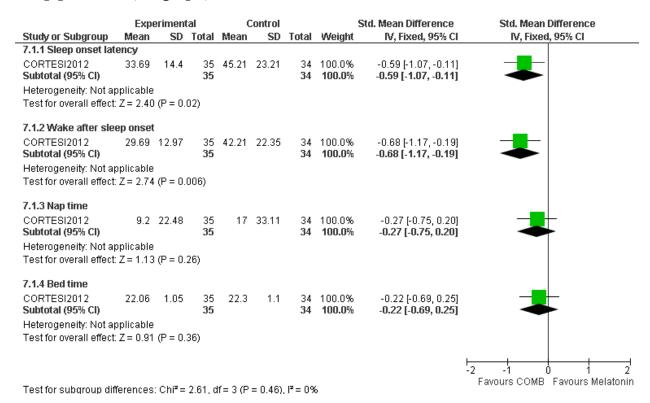
Study or Subgroup	Expe Mean	erimen SD		Co Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
6.3.1 Total score									_
CORTESI2012 Subtotal (95% CI)	47.84	2.94	35 35	60.06	4.71		100.0% 100.0 %	-3.10 [-3.81, -2.38] - 3.10 [-3.81, -2.38]	-
Heterogeneity: Not ap									
Test for overall effect:	Z = 8.47	'(P < 0	.00001	1)					
6.3.2 Bed resistance									
CORTESI2012	8.46	1.39	35	11.62	2.22	33	100.0%	-1.70 [-2.26, -1.14]	
Subtotal (95% CI)			35			33	100.0%	-1.70 [-2.26, -1.14]	•
Heterogeneity: Not ap				13.					
Test for overall effect:	. ∠= 5.95)(P < U	.00001)					
6.3.3 Sleep onset de	lay								_
CORTESI2012	1.69	0.73	35	2.51	0.57		100.0%	-1.23 [-1.75, -0.71]	-
Subtotal (95% CI)			35			33	100.0%	-1.23 [-1.75, -0.71]	•
Heterogeneity: Not ap Test for overall effect:			. 00004	D.					
restroi overali ellect	4.04	, (r = U	.00001	'/					
6.3.4 Sleep anxiety									
CORTESI2012	5.23	0.95	35	7.17	1.48		100.0%	-1.55 [-2.10, -1.01]	_
Subtotal (95% CI)	1 1 - 1 - 1 - 1 - 1 - 1 - 1 -		35			33	100.0%	-1.55 [-2.10, -1.01]	—
Heterogeneity: Not ap Test for overall effect:			00001	D.					
restror overall effect.	. 2 – 5.51	(1 - 0		' /					
6.3.5 Night-wakings									
CORTESI2012	4.42	0.9	35	7.06	1.06		100.0%	-2.66 [-3.32, -2.00]	
Subtotal (95% CI)	ملطممناهم		35			JJ	100.0%	-2.66 [-3.32, -2.00]	•
Heterogeneity: Not ap Test for overall effect:			00001	I)					
restroi overan enece	2-1.00	, (,		'/					
6.3.6 Sleep duration									
CORTESI2012	4.38	1.02	35	6.68	1.16		100.0%	-2.09 [-2.68, -1.49]	
Subtotal (95% CI)	anliaahla		35			33	100.0%	-2.09 [-2.68, -1.49]	•
Heterogeneity: Not ap Test for overall effect:			00001	D)					
, cotion overall effect	0.00	, (i = 0		'/					
6.3.7 Parasomnias									
CORTESI2012	8.92	1.38	35	9.82	2.25		100.0%	-0.48 [-0.96, 0.00]	
Subtotal (95% CI) Heterogeneity: Not as	onlicable		35			33	100.0%	-0.48 [-0.96, 0.00]	•
Test for overall effect:			105)						
		,, ,	,						
6.3.8 Sleep disorder		_							
CORTESI2012 Subtotal (95% CI)	3.22	0.95	35 35	3.2	0.41	33 33	100.0% 100.0 %	0.03 [-0.45, 0.50] 0.03 [-0.45, 0.50]	T
Heterogeneity: Not as	nnlicable	,	JJ			JJ	100.070	0.05 [-0.45, 0.50]	T
Test for overall effect:			.91)						
		, -							
6.3.9 Daytime sleepi									
CORTESI2012 Subtotal (95% CI)	10.84	1.68	35 35	11.96	1.97		100.0% 100.0 %	-0.61 [-1.09, -0.12] - 0.61 [-1.09, -0.12]	
Heterogeneity: Not as	oplicable	!	33			33	100.070	-0.0 1 [-1.05, -0.12]	
Test for overall effect:			.01)						
		-							
									-4 -2 0 2
Toot for outparous dif	foronces	e ∩ki≇ -	- 00 20) df = 0 :	/D ~ 0 !	000043	IX = 04 0	ov.	Favours COMB Favours CBT
Test for subgroup dif	ierences	. Office	- უნ.ქს	ı, uı = 8 ı	رr ۶ U.	00001)	, ⊨= 91.9	70	

Positive treatment response



COMB versus melatonin-only for sleep problems as a direct outcome

Sleep problems (actigraph)



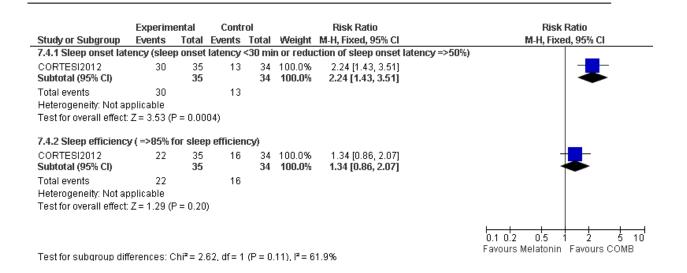
Positive sleep behaviour (actigraph)

	Expe	riment	al	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.2.1 Total sleep time	!								
CORTESI2012 Subtotal (95% CI)	505.01	31.18	35 35	481.1	45.07	34 34	100.0% 100.0 %	0.61 [0.13, 1.10] 0.61 [0.13, 1.10]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z= 2.48 i	(P = 0.0)	1)						
7.2.2 Sleep efficiency	,								
CORTESI2012 Subtotal (95% CI)	84.46	4.23	35 35	82.71	4	34 34	100.0% 100.0 %	0.42 [-0.06, 0.90] 0.42 [-0.06, 0.90]	
Heterogeneity: Not ap	plicable							• / •	
Test for overall effect:		(P = 0 0	8)						
			-,						
								<u>⊢</u>	
								_	ours Melatonin Favours COME
Test for subgroup diffe	erences:	$Chi^2 = 0$).31, df	= 1 (P =	0.58), I	² =0%		гач	outs Melatoriii Favours COME

Sleep problems (Children's sleep habits questionnaire)

		erimen			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup 7.3.1 Total score	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CORTESI2012 Subtotal (95% CI)	47.84	2.94	35 35	54.78	6.22	34 34	100.0% 100.0 %	-1.42 [-1.95, -0.89] - 1.42 [-1.95, -0.89]	+
Heterogeneity: Not ap Test for overall effect:			.00001)				- , -	
7.3.2 Bed resistance	!								
CORTESI2012 Subtotal (95% CI)	8.46	1.39	35 35	10.5	2.2	34 34	100.0% 100.0 %	-1.10 [-1.61, -0.59] - 1.10 [-1.61, -0.59]	-
Heterogeneity: Not ap Test for overall effect:			1.0001)						
7.3.3 Sleep onset de	lau								
CORTESI2012 Subtotal (95% CI)		0.73	35 35	2.1	0.68	34 34	100.0% 100.0 %	-0.57 [-1.06, -0.09] - 0.57 [-1.06, -0.09]	<u> </u>
Heterogeneity: Not ap						01	100.072	-0.01 [-1.00, -0.00]	
			,						
7.3.4 Sleep anxiety	5.00	0.05	25	7.04	4.07	24	400.00	4 22 1 4 05 0 00	
CORTESI2012 Subtotal (95% CI)	5.23	0.95	35 35	1.21	1.87	34 34	100.0% 100.0 %	-1.33 [-1.85, -0.80] - 1.33 [-1.85, - 0.80]	•
Heterogeneity: Not ap Test for overall effect:			.00001)					
7.3.5 Night-wakings									
CORTESI2012 Subtotal (95% CI)	4.42	0.9	35 35	5.03	1.1	34 34	100.0% 100.0 %	-0.60 [-1.08, -0.12] - 0.60 [-1.08, -0.12]	-
Heterogeneity: Not ap Test for overall effect:			1.01)						
7.3.6 Sleep duration									
CORTESI2012 Subtotal (95% CI)	4.38	1.02	35 35	4.82	0.94	34 34	100.0% 100.0 %	-0.44 [-0.92, 0.03] - 0.44 [-0.92, 0.03]	
Heterogeneity: Not ap						54	100.07	-0.44 [-0.02, 0.00]	
Test for overall effect:	Z = 1.82	! (P = L	1.07)						
7.3.7 Parasomnias									_
CORTESI2012 Subtotal (95% CI)	8.92	1.38	35 35	9.35	1.78		100.0% 100.0 %	-0.27 [-0.74, 0.21] - 0.27 [-0.74, 0.21]	-
Heterogeneity: Not ap Test for overall effect:			1.27)						
7.3.8 Sleep disorder	nd broat	hina							
CORTESI2012 Subtotal (95% CI)		0.95	35 35	3.15	0.48	34 34	100.0% 100.0 %	0.09 [-0.38, 0.56] 0.09 [-0.38, 0.56]	<u> </u>
Heterogeneity: Not ap	•					34	100.078	0.09 [-0.30, 0.30]	
Test for overall effect:	∠ — 0.38	, (r = L	1.70)						
7.3.9 Daytime sleeping									_
CORTESI2012 Subtotal (95% CI)	10.84	1.68	35 35	11.39	2.34		100.0% 100.0 %	-0.27 [-0.74, 0.21] - 0.27 [-0.74, 0.21]	-
Heterogeneity: Not ap Test for overall effect:			1.27)						
									-2 -1 0 1 2 Favours COMB Favours Melatonin
Test for subgroup dif	ferences	: Chi²:	= 32.58	. df = 8	(P < 0.	0001).	I ² = 75.49	6	Tarana madamin

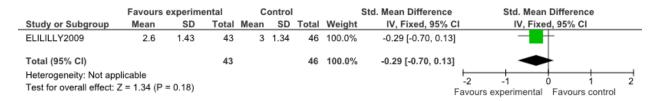
Positive treatment response



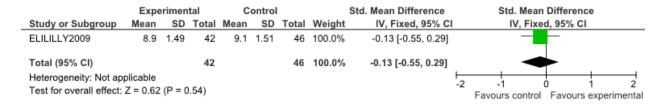
1.28.4SNRIs for sleep problems as an indirect outcome

Atomoxetine versus placebo for sleep problems as an indirect outcome

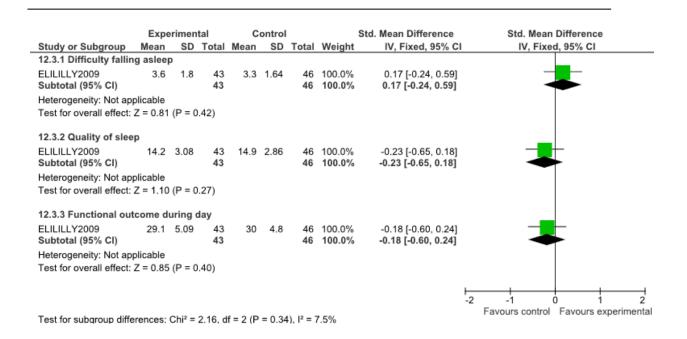
Time to fall asleep



Total hours of sleep



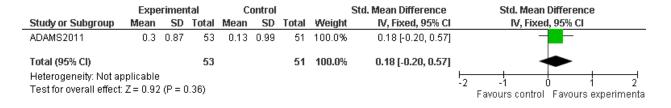
Sleep problems



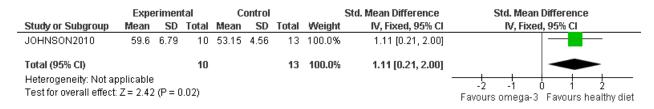
1.29BIOMEDICAL INTERVENTIONS AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

1.29.1 Nutritional interventions for sleep problems as an indirect outcome

Multivitamin/mineral supplement versus placebo for sleep problems as an indirect outcome

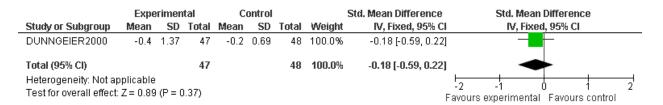


Omega-3 fatty acids versus healthy diet control for sleep problems as an indirect outcome



1.29.2 Hormones for gastrointestinal symptoms as an indirect outcome

Secretin versus placebo for gastrointestinal symptoms as an indirect outcome



1.29.3 Nutritional interventions for gastrointestinal symptoms as a direct or indirect outcome

Immunoglobulin versus placebo for gastrointestinal symptoms as a direct outcome

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HANDEN2009	31	94	14	31	100.0%	0.73 [0.45, 1.18]	-
Total (95% CI)		94		31	100.0%	0.73 [0.45, 1.18]	•
Total events	31		14				
Heterogeneity: Not as	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.28 (F	P = 0.20)				Favours control Favours experimenta

Multivitamin/ mineral supplement versus placebo for gastrointestinal symptoms as an indirect outcome

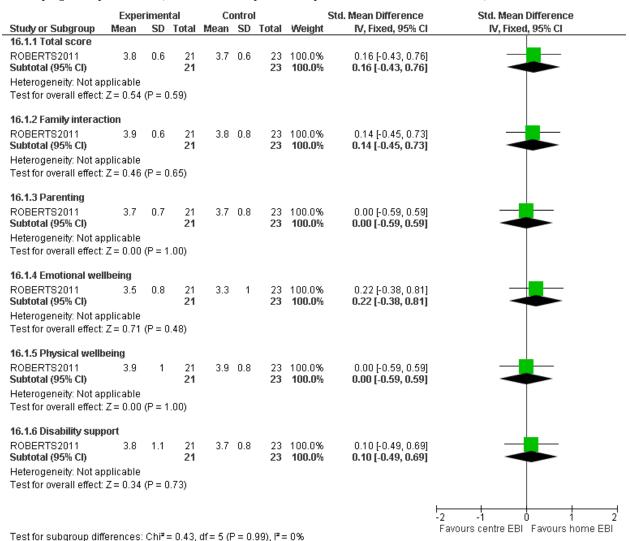
	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ADAMS2011	0.68	1.11	53	0.35	1.09	51	100.0%	0.30 [-0.09, 0.68]	+
Total (95% CI)			53			51	100.0%	0.30 [-0.09, 0.68]	-
Heterogeneity: Not ap Test for overall effect:).13)						-2 -1 0 1 2 Favours control Favours experimenta

1.30PSYCHOSOCIAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

1.30.1 Behavioural interventions for improving the impact of autism on the family as an indirect outcome

Home-based EBI versus centre-based EBI for improving the impact of autism on the family as an indirect outcome

Family quality of life (Beach Family Quality of Life Questionnaire)

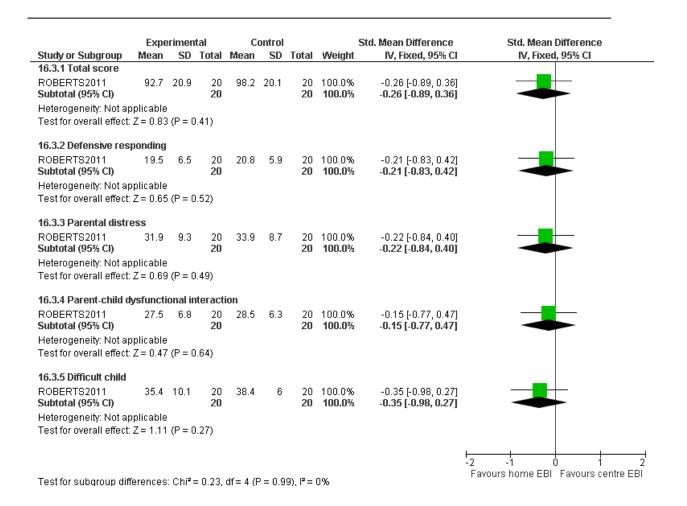


Parental coping skills (study-specific questionnaire)

	Experimental		Control			9	Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
16.2.1 Total score									
ROBERTS2011 Subtotal (95% CI)	3.7	0.7	23 23	3.8	0.6	23 23	100.0% 100.0 %	-0.15 [-0.73, 0.43] - 0.15 [-0.73, 0.43]	<u> </u>
Heterogeneity: Not a									
Test for overall effect	Z = 0.51	(P = (0.61)						
16.2.2 Confidence									
ROBERTS2011	3.7	0.8	23	3.7	0.7	23	100.0%	0.00 [-0.58, 0.58]	
Subtotal (95% CI)			23			23	100.0%	0.00 [-0.58, 0.58]	
Heterogeneity: Not a									
Test for overall effect	Z = 0.00	(P = 1)	1.00)						
16.2.3 Coping									
ROBERTS2011	3.6	0.9	23	3.3	0.9		100.0%	0.33 [-0.25, 0.91]	
Subtotal (95% CI)			23			23	100.0%	0.33 [-0.25, 0.91]	
Heterogeneity: Not a									
Test for overall effect	:: Z = 1.10	(P = 0	0.27)						
16.2.4 Knowledge									
ROBERTS2011	3.9	0.7	23	4.2	0.4		100.0%	-0.52 [-1.11, 0.07]	
Subtotal (95% CI)			23			23	100.0%	-0.52 [-1.11, 0.07]	
Heterogeneity: Not a									
Test for overall effect	:: Z = 1.72	(P = (J.08)						
16.2.5 Understandin	g								
ROBERTS2011	3.9	0.8	23	4.1	0.7	23	100.0%	-0.26 [-0.84, 0.32]	
Subtotal (95% CI)			23			23	100.0%	-0.26 [-0.84, 0.32]	
Heterogeneity: Not a									
Test for overall effect	:: Z= 0.88	(P = 0	0.38)						
16.2.6 Family issues	;								
ROBERTS2011	3.8	0.7	23	3.6	1		100.0%	0.23 [-0.35, 0.81]	
Subtotal (95% CI)			23			23	100.0%	0.23 [-0.35, 0.81]	
Heterogeneity: Not a		_							
Test for overall effect	Z = 0.77	(P = 0)	J.44)						
16.2.7 Planning									
ROBERTS2011	3.6	1	23	3.7	1.2	23	100.0%	-0.09 [-0.67, 0.49]	
Subtotal (95% CI)			23			23	100.0%	-0.09 [-0.67, 0.49]	
Heterogeneity: Not a									
Test for overall effect	Z = 0.30	(P = 0)	0.76)						
									-2 -1 0 1
Toot for oubgroup dit	foronooo	- Ohiz	_ = = =	df _ C /I	n = 0	471 12 -	. 00/		Favours centre EBI Favours home El

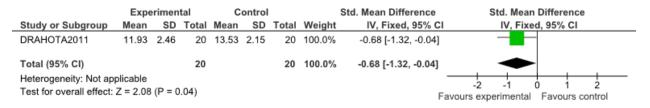
Test for subgroup differences: $Chi^2 = 5.57$, df = 6 (P = 0.47), $I^2 = 0\%$

Parental stress (PSI)



1.30.2 Cognitive-behavioural interventions for improving the impact of autism on the family as an indirect outcome

CBT versus waitlist for improving the impact of autism on the family as an indirect outcome



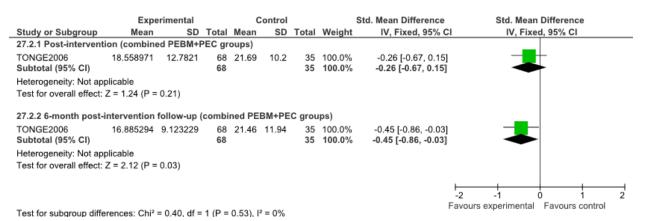
1.30.3 Parent training for improving the impact of autism on the family as a direct or indirect outcome

Parent training versus treatment as usual for improving the impact of autism on the family as a direct or indirect outcome

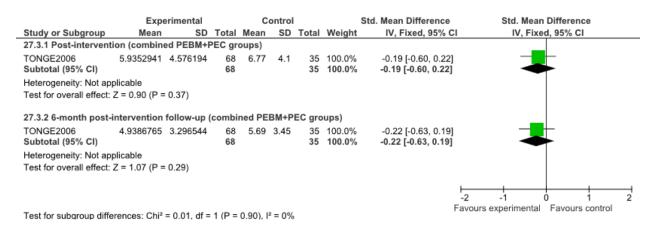
Parental stress

	Expe	rimental		С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95%	CI IV, Fixed, 95% CI
27.1.1 Direct outcome	e: combined	PEBM+PE	C (stre	ss ther	mome	eter; po	st-interv	ention)	
TONGE2006 Subtotal (95% CI)	1.8405882	0.925576	68 68	2.26	1.09	35 35	69.7% 69.7%	-0.42 [-0.84, -0.01 -0.42 [-0.84, -0.01	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 2.01 (P =	0.04)							
27.1.2 Indirect outcor	ne (Parentin	g Stress In	ventor	y/PSI-3	3)				
DREW2002	104.3	20	10	112.1	20.1	10	15.1%	-0.37 [-1.26, 0.51	ı
WELTERLIN2012	242.4	41.5	10	256.2	70	10	15.3%	-0.23 [-1.11, 0.65	<u> </u>
Subtotal (95% CI)			20			20	30.3%	-0.30 [-0.93, 0.32	i 🔷
Heterogeneity: Chi2 = 0	0.05, df = 1 (F	e = 0.82); l ²	= 0%						
Test for overall effect:	Z = 0.94 (P =	0.35)							
Total (95% CI)			88			55	100.0%	-0.39 [-0.73, -0.04	1
Heterogeneity: Chi ² = 0	0.15, df = 2 (F	e = 0.93); l ²	= 0%						
Test for overall effect:	Z = 2.20 (P =	0.03)							Favours experimental Favours control
Test for subgroup diffe	rences: Chi ²	= 0.10, df =	1 (P =	0.75), I	² = 0%				ravours experimental ravours control

Parental mental health (GHQ-28)



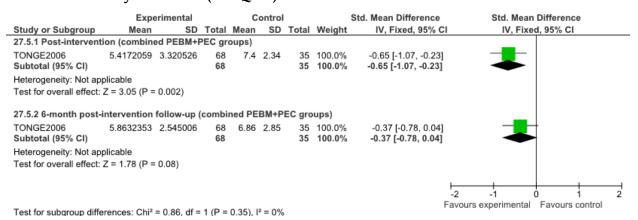
Parental somatic symptoms (GHQ-28)



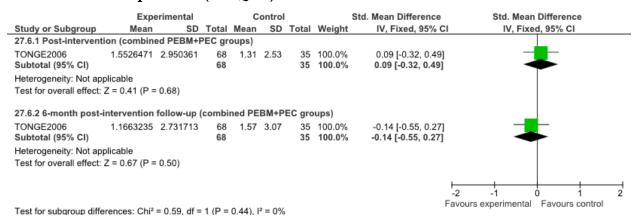
Parental anxiety and insomnia (GHQ-28)

	Expe	erimental		С	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95%	CI IV, Fixed, 95% CI	
27.4.1 Post-interventi	ion (combine	ed PEBM+F	PEC gr	oups)						
TONGE2006 Subtotal (95% CI)	5.6173529	4.302236	68 68	6.26	3.31	35 35	100.0% 100.0%	-0.16 [-0.57, 0.25 -0.16 [-0.57, 0.25		
Heterogeneity: Not app Test for overall effect:		0.44)								
27.4.2 6-month post-i	ntervention	follow-up (combi	ned PE	BM+P	EC gro	ups)			
TONGE2006 Subtotal (95% CI)	4.7294118	3.325824	68 68	6.91	5.15	35 35	100.0% 100.0%	-0.54 [-0.95, -0.12 -0.54 [-0.95, -0.12]		
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z = 2.54 (P =	0.01)								
									-2 -1 0 1	
Test for subgroup diffe	rences: Chi²	= 161 df =	1 (P =	0.20) 1	² = 38	0%			Favours experimental Favours co	ntrol

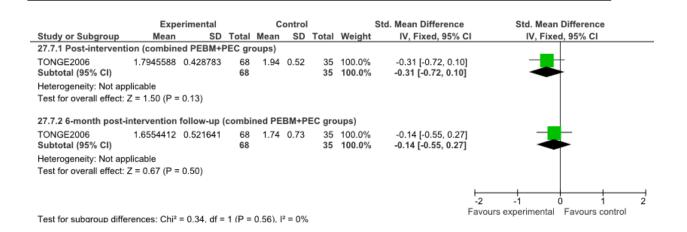
Parental social dysfunction (GHQ-28)



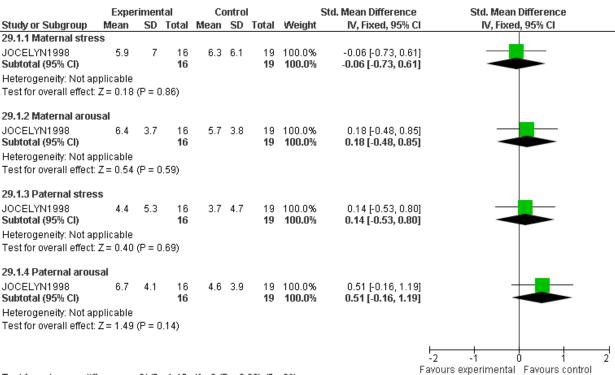
Parental severe depression (GHQ-28)



General family function (FAD)



Parent and day-care staff training versus standard day-care for improving the impact of autism on the family as an indirect outcome

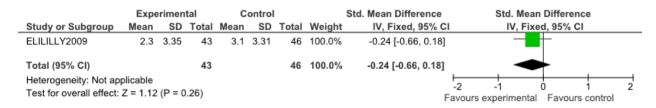


1.31PHARMACOLOGICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

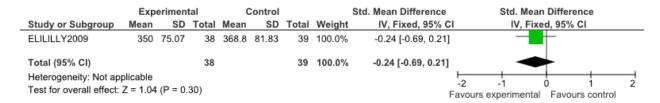
1.31.1SNRIs for improving the impact of autism on the family as an indirect outcome

Atomoxetine versus placebo for improving the impact of autism on the family as an indirect outcome

Parental mental health (GHQ)



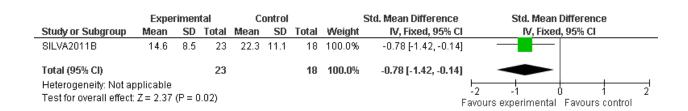
Parental stress (NOSI)



1.32BIOMEDICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

1.32.1 Complementary therapies for improving the impact of autism on the family as an indirect outcome

Qigong massage training versus waitlist for improving the impact of autism on the family as an indirect outcome



1.33ADVERSE EVENTS ASSOCIATED WITH PHARMACOLOGICAL INTERVENTIONS

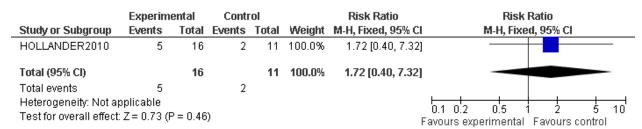
1.33.1 Adverse events associated with anticonvulsants

Adverse events associated with divalproex versus placebo

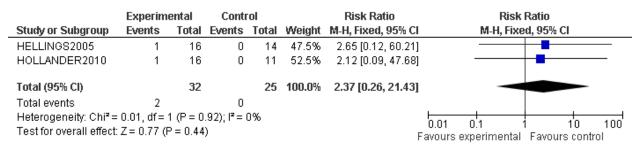
Any adverse event

	Experim	ental	Contr	ol		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1		M-H, Fixe	d, 95%	CI		
HELLINGS2005	15	16	11	14	100.0%	1.19 [0.88, 1.61]		-	-			
Total (95% CI)		16		14	100.0%	1.19 [0.88, 1.61]		•	•			
Total events	15		11										
Heterogeneity: Not ap	oplicable						⊢ 0.1	 -	0.5	<u> </u>		<u> </u>	10
Test for overall effect	Z = 1.15 (F	P = 0.25)				٠.,	0.2	o.o erimental	Favol	: ırs cont	rol	10

More than one adverse event



Discontinuation due to adverse event



Weight gain (in kg or lb)

	Expe	erimen	ıtal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
HELLINGS2005	1.98	1.88	16	1.1	1.1	14	52.3%	0.55 [-0.19, 1.28]	
HOLLANDER2010	3.02	6.41	16	2.95	3.37	11	47.7%	0.01 [-0.76, 0.78]	
Total (95% CI)			32			25	100.0%	0.29 [-0.24, 0.82]	-
Heterogeneity: Chi²=	0.97, df	= 1 (P	= 0.32)); I² = 0%	6				1 1 1 2
Test for overall effect:	Z = 1.08	P = 0	0.28)					F	avours experimental Favours control

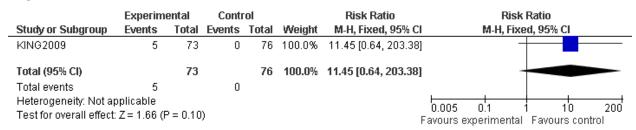
1.33.2 Adverse events associated with antidepressants

Adverse events associated with citalogram versus placebo

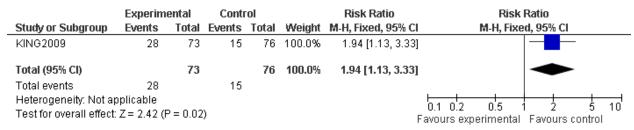
Any adverse event

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl	
KING2009	71	73	66	76	100.0%	1.12 [1.02, 1.23		
Total (95% CI)		73		76	100.0%	1.12 [1.02, 1.23]	1 ♦	
Total events	71		66					
Heterogeneity: Not as	oplicable						01 02 05 1 2 5 1	┧
Test for overall effect:	Z = 2.32 (F	P = 0.02)				Favours experimental Favours control	U

Nightmares



Increased energy level



Anger or irritability

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
KING2009	18	73	13	76	100.0%	1.44 [0.76, 2.73	1 +
Total (95% CI)		73		76	100.0%	1.44 [0.76, 2.73]	-
Total events	18		13				
Heterogeneity: Not a	pplicable						01 02 05 1 2 5 10
Test for overall effect	:: Z = 1.13 (F	P = 0.26)				Favours experimental Favours control

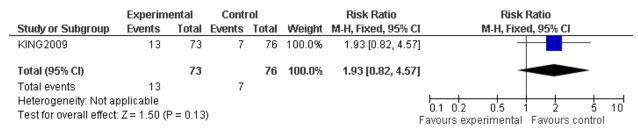
Aggression or hostility

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
KING2009	17	73	13	76	100.0%	1.36 [0.71, 2.60	
Total (95% CI)		73		76	100.0%	1.36 [0.71, 2.60]	1 🔷
Total events	17		13				
Heterogeneity: Not ap							01 02 05 1 2 5 10
Test for overall effect	Z = 0.94 (F	P = 0.35)				Favours experimental Favours control

Headache or migraine

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
KING2009	15	73	10	76	100.0%	1.56 [0.75, 3.25	
Total (95% CI)		73		76	100.0%	1.56 [0.75, 3.25]	
Total events	15		10				
Heterogeneity: Not ap	pplicable						01 02 05 1 2 5 10
Test for overall effect	: Z = 1.19 (F	P = 0.23)				Favours experimental Favours control

Restlessness or difficulty settling down



Disinhibited, impulsive, or intrusive behaviour

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
KING2009	14	73	5	76	100.0%	2.92 [1.11, 7.68	
Total (95% CI)		73		76	100.0%	2.92 [1.11, 7.68	
Total events	14		5				
Heterogeneity: Not as	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 2.16 (F	P = 0.03)				Favours experimental Favours control

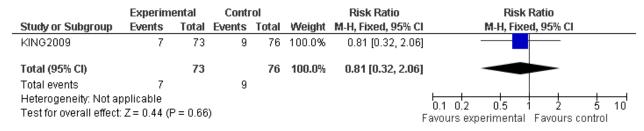
Silliness

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
KING2009	9	73	10	76	100.0%	0.94 [0.40, 2.17	
Total (95% CI)		73		76	100.0%	0.94 [0.40, 2.17]	
Total events	9		10				
Heterogeneity: Not ap	pplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 0.15 (F	P = 0.88)				Favours experimental Favours control

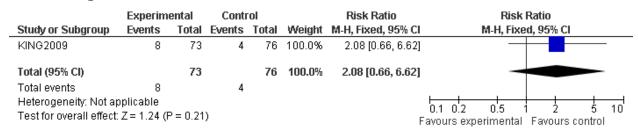
Anxiety

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
KING2009	8	73	9	76	100.0%	0.93 [0.38, 2.27	
Total (95% CI)		73		76	100.0%	0.93 [0.38, 2.27]	
Total events	8		9				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.87)				0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control

Mood lability



Increased speech



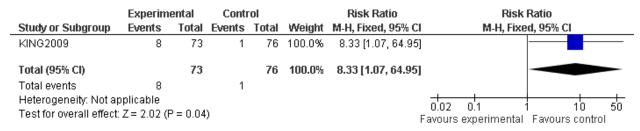
Decreased attention and concentration

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2009	9	73	2	76	100.0%	4.68 [1.05, 20.96]	
Total (95% CI)		73		76	100.0%	4.68 [1.05, 20.96]	
Total events	9		2				
Heterogeneity: Not ap	pplicable						0.05 0.2 1 5 20
Test for overall effect	Z = 2.02 (F	P = 0.04)				Favours experimental Favours control

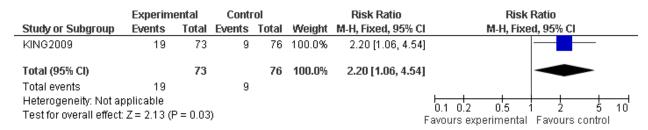
Hyperactivity

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2009	9	73	2	76	100.0%	4.68 [1.05, 20.96]	
Total (95% CI)		73		76	100.0%	4.68 [1.05, 20.96]	
Total events	9		2				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5 20
Test for overall effect	Z = 2.02 (F	P = 0.04)				Favours experimental Favours control

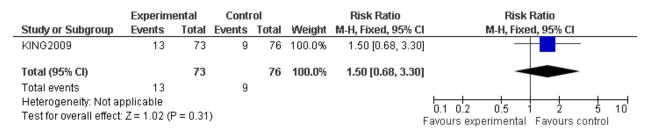
Stereotypy



Diarrhoea or loose stools



Abdominal discomfort



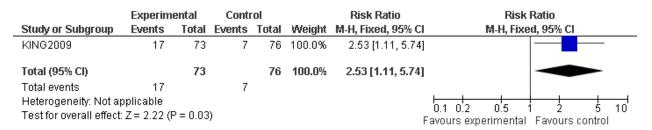
Vomiting or nausea

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
KING2009	14	73	6	76	100.0%	2.43 [0.99, 5.98	
Total (95% CI)		73		76	100.0%	2.43 [0.99, 5.98]	
Total events	14		6				
Heterogeneity: Not ap Test for overall effect:	•) – n ns	3				0.1 0.2 0.5 1 2 5 10
restion overall ellect	. Z = 1.85 (r	- 0.00	,				Favours experimental Favours control

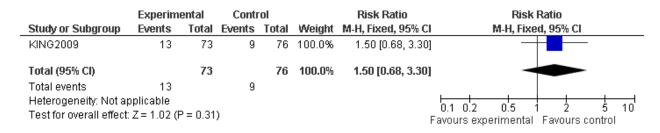
Any insomnia

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
KING2009	28	73	17	76	100.0%	1.71 [1.03, 2.86	1
Total (95% CI)		73		76	100.0%	1.71 [1.03, 2.86]	•
Total events	28		17				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 2.07 (F	P = 0.04)				Favours experimental Favours control

Initial insomnia or difficulty falling asleep



Midcycle or other insomnia



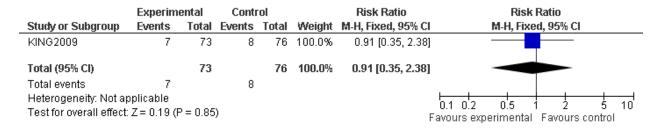
Cold, flu or other systemic infection

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
KING2009	31	73	26	76	100.0%	1.24 [0.82, 1.87]	1 -
Total (95% CI)		73		76	100.0%	1.24 [0.82, 1.87]	ı
Total events	31		26				
Heterogeneity: Not ap	pplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 1.03 (F	P = 0.30)				Favours experimental Favours control

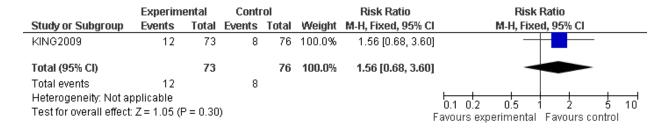
Decreased appetite

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
KING2009	11	73	10	76	100.0%	1.15 [0.52, 2.53]	
Total (95% CI)		73		76	100.0%	1.15 [0.52, 2.53]	
Total events	11		10				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.33 (F	P = 0.74)				Favours experimental Favours control

Increased appetite



Rash



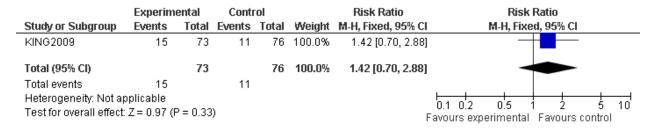
Other skin or subcutaneous tissue disorder

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	l M-H, Fixe	ed, 95% CI
KING2009	9	73	1	76	100.0%	9.37 [1.22, 72.12]	1	
Total (95% CI)		73		76	100.0%	9.37 [1.22, 72.12]	I	
Total events	9		1					
Heterogeneity: Not ap	pplicable						0.02 0.1	1 10 50
Test for overall effect	Z = 2.15 (F	P = 0.03)				Favours experimental	

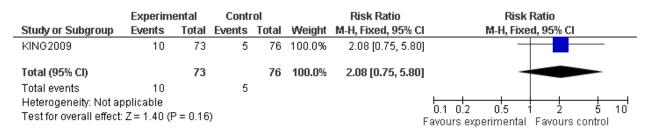
Fatigue

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
KING2009	10	73	10	76	100.0%	1.04 [0.46, 2.35	1 —
Total (95% CI)		73		76	100.0%	1.04 [0.46, 2.35	
Total events	10		10				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.10 (F	P = 0.92)				Favours experimental Favours control

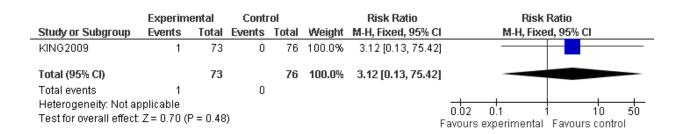
Allergies



Cough



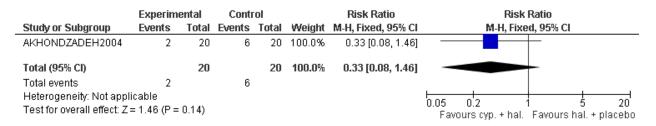
Any serious adverse event



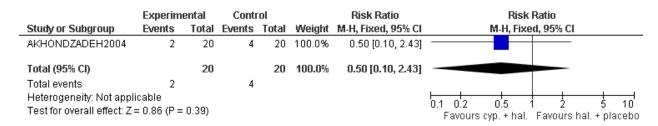
1.33.3 Adverse events associated with antihistamines

Adverse events associated with cyproheptadine and haloperidol versus placebo and haloperidol

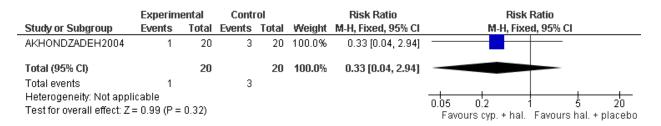
Extrapyramidal symptoms



Trouble swallowing



Stiffness



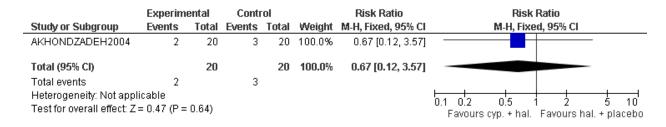
Slow movement

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2004	1	20	3	20	100.0%	0.33 [0.04, 2.94]	
Total (95% CI)		20		20	100.0%	0.33 [0.04, 2.94]	
Total events	1		3				
Heterogeneity: Not appl	icable						0.05 0.2 1 5 20
Test for overall effect: Z	= 0.99 (P =	0.32)					Favours cyp. + hal. Favours hal. + placebo

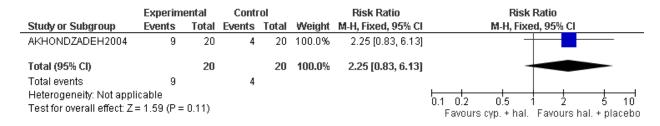
Constipation

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2004	4	20	2	20	100.0%	2.00 [0.41, 9.71]	
Total (95% CI)		20		20	100.0%	2.00 [0.41, 9.71]	
Total events	4		2				
Heterogeneity: Not appli	icable						01 02 05 1 2 5 10
Test for overall effect: Z	= 0.86 (P =	0.39)					Favours cyp. + hal. Favours hal. + placebo

Diarrhoea



Increased appetite



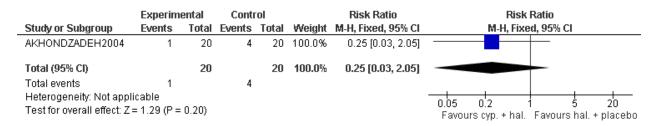
Morning drowsiness

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2004	3	20	2	20	100.0%	1.50 [0.28, 8.04]	
Total (95% CI)		20		20	100.0%	1.50 [0.28, 8.04]	
Total events	3		2				
Heterogeneity: Not appl	licable						01 02 05 1 2 5 10
Test for overall effect: Z	= 0.47 (P =	0.64)					0.1 0.2 0.5 1 2 5 10 Favours cyp. + hal. Favours hal. + placeb

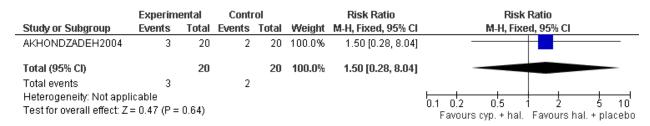
Day time drowsiness

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2004	1	20	2	20	100.0%	0.50 [0.05, 5.08]	
Total (95% CI)		20		20	100.0%	0.50 [0.05, 5.08]	
Total events	1		2				
Heterogeneity: Not appl Test for overall effect: Z		0.56)					0.05 0.2 1 5 20 Favours cyp. + hal. Favours hal. + placebo

Restlessness



Fatigue



1.33.4 Adverse events associated with antioxidants

Adverse events associated with N-acetylcysteine versus placebo

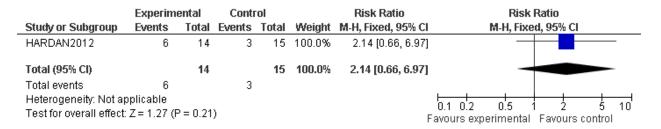
Any gastrointestinal side effect

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HARDAN2012	11	14	7	15	100.0%	1.68 [0.92, 3.09	1
Total (95% CI)		14		15	100.0%	1.68 [0.92, 3.09]	
Total events	11		7				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.68 (F	P = 0.09)				Favours experimental Favours control

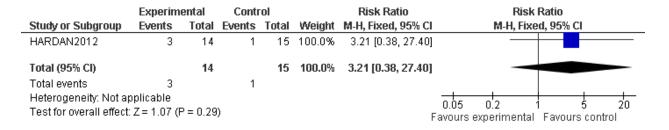
Constipation

	Experimental		Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HARDAN2012	3	14	2	15	100.0%	1.61 [0.31, 8.24]
Total (95% CI)		14		15	100.0%	1.61 [0.31, 8.24	
Total events	3		2				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.57 (F	P = 0.57)				Favours experimental Favours control

Nausea



Diarrhoea



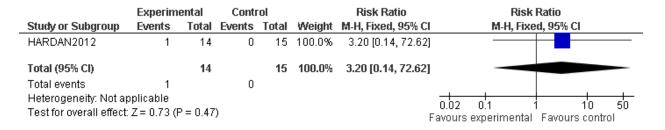
Increased appetite

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HARDAN2012	2	14	0	15	100.0%	5.33 [0.28, 102.26]	
Total (95% CI)		14		15	100.0%	5.33 [0.28, 102.26]	
Total events	2		0				
Heterogeneity: Not as	oplicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 1.11 (F	P = 0.27)			F	Favours experimental Favours control

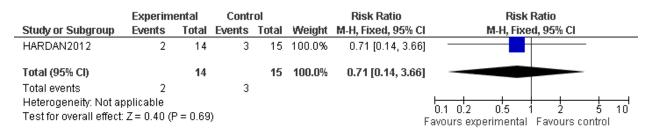
Loss of appetite

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HARDAN2012	2	14	3	15	100.0%	0.71 [0.14, 3.66]
Total (95% CI)		14		15	100.0%	0.71 [0.14, 3.66]	
Total events	2		3				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.40 (F	P = 0.69)				Favours experimental Favours control

Akathisia



Increased motor activity



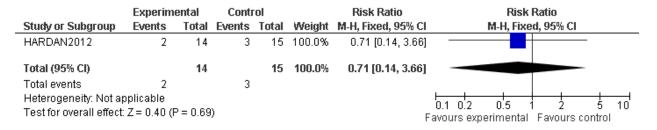
Tremor

	Ехрегіт	ental	Contr	rol		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
HARDAN2012	0	14	1	15	100.0%	0.36 [0.02, 8.07]		
Total (95% CI)		14		15	100.0%	0.36 [0.02, 8.07]		
Total events	0		1					
Heterogeneity: Not ap	pplicable						1 0 0 2 0 1	1 10 50
Test for overall effect	Z = 0.65 (F	P = 0.52)			1	0.02 0.1 Favours experimental	

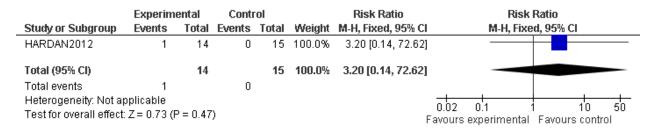
Dizziness

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HARDAN2012	0	14	1	15	100.0%	0.36 [0.02, 8.07]	
Total (95% CI)		14		15	100.0%	0.36 [0.02, 8.07]	
Total events	0		1				
Heterogeneity: Not ap	plicable						002 01 1 10 50
Test for overall effect:	Z = 0.65 (F	P = 0.52)				Favours experimental Favours control

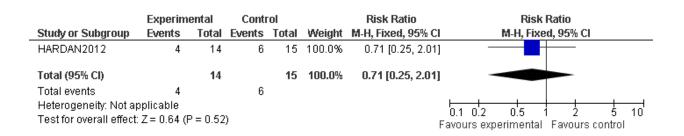
Excitement/agitation



Depressed affect



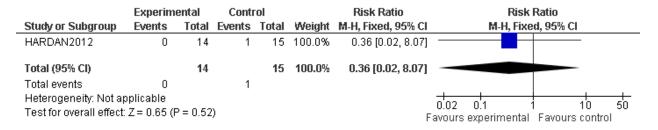
Nasal congestion



Increased salivation

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HARDAN2012	0	14	2	15	100.0%	0.21 [0.01, 4.09]	
Total (95% CI)		14		15	100.0%	0.21 [0.01, 4.09]	
Total events	0		2				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 1.03 (F	P = 0.31)				Favours experimental Favours control

Sweating

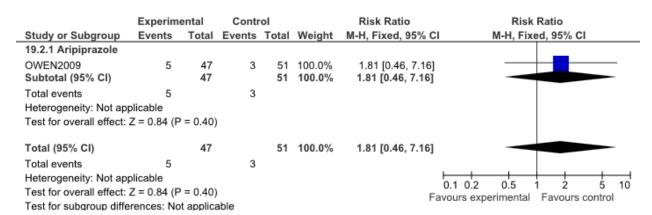


1.33.5 Adverse events associated with antipsychotics

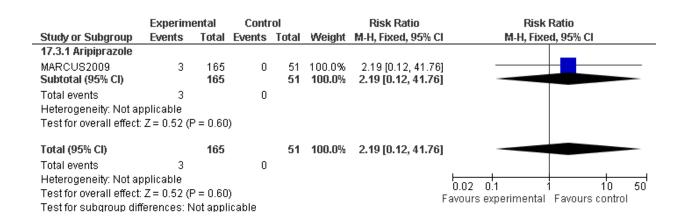
Adverse events associated with antipsychotics versus placebo Any side effect

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.1.1 Aripiprazole							
MARCUS2009	145	165	37	51	36.5%	1.21 [1.01, 1.45]	-
OWEN2009	43	47	36	50	22.5%	1.27 [1.05, 1.54]	-
Subtotal (95% CI)		212		101	59.0%	1.23 [1.08, 1.41]	◆
Total events	188		73				
Heterogeneity: Chi ² = 0.13, df	= 1 (P = 0.7	2); I ² =	0%				
Test for overall effect: Z = 3.11	(P = 0.002)					
19.1.2 Haloperidol							
CAMPBELL1978	16	20	5	20	3.2%	3.20 [1.45, 7.05]	
Subtotal (95% CI)		20		20	3.2%	3.20 [1.45, 7.05]	
Total events	16		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.89	P = 0.004)					
19.1.3 Risperidone							
JOHNSON&JOHNSON2011	39	61	21	35	17.2%	1.07 [0.77, 1.48]	-
SHEA2004	40	40	31	39	20.6%	1.25 [1.06, 1.48]	-
Subtotal (95% CI)		101		74	37.8%	1.17 [0.98, 1.39]	◆
Total events	79		52				
Heterogeneity: Chi2 = 1.02, df	= 1 (P = 0.3	1); I ² =	2%				
Test for overall effect: Z = 1.78	B (P = 0.07)						
Total (95% CI)		333		195	100.0%	1.27 [1.14, 1.42]	•
Total events	283		130				
Heterogeneity: Chi ² = 6.67, df	= 4 (P = 0.1	5); I ² = -	40%			<u> </u>	
Test for overall effect: Z = 4.43	(P < 0.000	01)				0.1	0.2 0.5 1 2 5 s experimental Favours control
Test for subgroup differences:	Chi ² = 5.98	df = 2	(P = 0.05), I ² = 6	6.5%	ravour	s experimental Favours control

Discontinuation due to adverse events



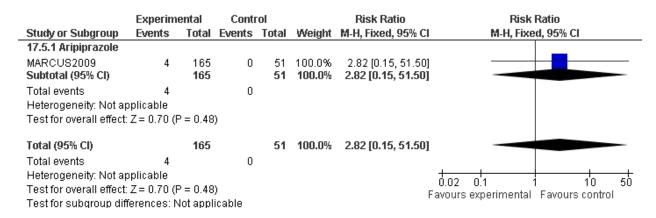
Discontinuation due to drooling



Discontinuation due to sedation

	Experim	Experimental		rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
17.4.1 Aripiprazole							
MARCUS2009 Subtotal (95% CI)	7	165 165	0	51 51	100.0% 100.0 %	4.70 [0.27, 80.88 4.70 [0.27, 80.88	
Total events	7		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 1.07 (P = 0.29)				
Total (95% CI)		165		51	100.0%	4.70 [0.27, 80.88	
Total events	7		0				
Heterogeneity: Not a	pplicable						0.01 0.1 1 10 10
Test for overall effect	Z = 1.07 (P = 0.29)				0.01 0.1 1 10 10 Favours experimental Favours control
Test for subgroup dif	ferences: N	Not appl	icable				ravours experimental ravours control

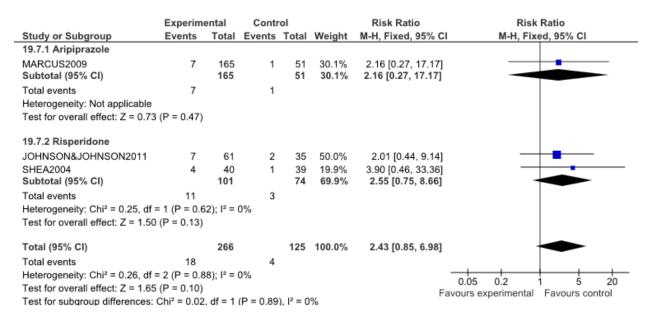
Discontinuation due to tremor



Clinically relevant (>=7%) weight gain

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
19.6.1 Aripiprazole							
MARCUS2009	42	165	4	51	67.8%	3.25 [1.22, 8.62]	
OWEN2009	14	47	3	50	32.2%	4.96 [1.52, 16.18]	
Subtotal (95% CI)		212		101	100.0%	3.80 [1.79, 8.05]	•
Total events	56		7				
Heterogeneity: Chi2 =	0.30, df = 1	(P = 0.9)	59); I ² = 0	%			
Test for overall effect:	Z = 3.49 (P	= 0.000	05)				
Total (95% CI)		212		101	100.0%	3.80 [1.79, 8.05]	•
Total events	56		7				
Heterogeneity: Chi2 =	0.30, df = 1	(P = 0.9)	59); I ² = 0	%			0.05 0.2 1 5 20
Test for overall effect:	Z = 3.49 (P	= 0.000	05)			_	0.05 0.2 1 5 20 avours experimental Favours control
Test for subgroup diffe	erences: No	t applica	able				avours experimental Pavours control

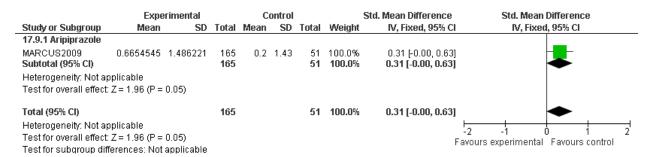
Weight gain



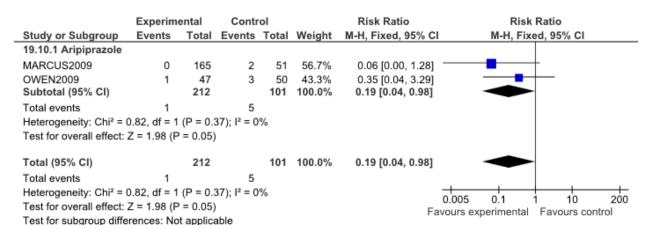
Weight gain (in kg)

						DI L D d	Bl. I. B. d.
	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.7.1 Aripiprazole							
MARCUS2009	7	165	1	51	30.1%	2.16 [0.27, 17.17]	
Subtotal (95% CI)		165		51	30.1%	2.16 [0.27, 17.17]	
Total events	7		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.73	(P = 0.47)						
19.7.2 Risperidone							
JOHNSON&JOHNSON2011	7	61	2	35	50.0%	2.01 [0.44, 9.14]	
SHEA2004	4	40	1	39	19.9%	3.90 [0.46, 33.36]	-
Subtotal (95% CI)		101		74	69.9%	2.55 [0.75, 8.66]	
Total events	11		3				
Heterogeneity: Chi2 = 0.25, df =	= 1 (P = 0.6	2); I ² =	0%				
Test for overall effect: Z = 1.50	(P = 0.13)						
Total (95% CI)		266		125	100.0%	2.43 [0.85, 6.98]	
Total events	18		4				
Heterogeneity: Chi ² = 0.26, df =	= 2 (P = 0.8	8); I ² =	0%				
Test for overall effect: Z = 1.65						-	0.05 0.2 1 5 20
Test for subgroup differences:	, ,	. df = 1	(P = 0.89), I ² = 0	1%	Fa	avours experimental Favours control

BMI change (kg/m-squared)



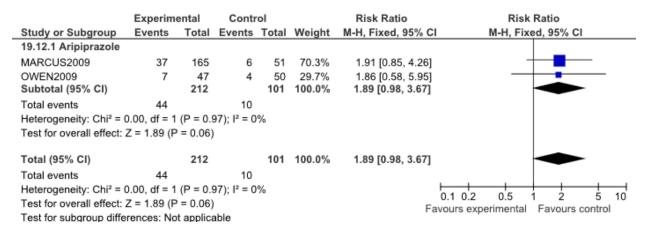
Clinically relevant prolactin elevation (above upper limit of normal for age & gender)



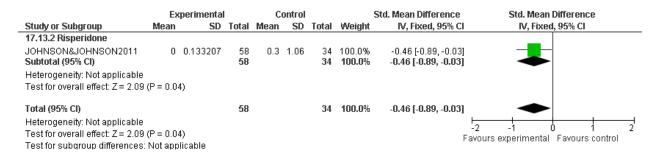
Prolactin concentration (ng/ml)

	Exp	erimen	tal	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean SD		Total	Mean SI		Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
17.11.1 Risperidone									
LUBY2006	33.38	14.48	11	11.11	18.74	12	21.4%	1.27 [0.36, 2.19]	-
RUPPRISPERIDONE2001	39	19.2	49	10.1	8.8	52	78.6%	1.94 [1.46, 2.42]	_
Subtotal (95% CI)			60			64	100.0%	1.80 [1.38, 2.22]	•
Heterogeneity: Chi² = 1.61, o	df = 1 (P =	0.21);	$I^2 = 389$	%					
Test for overall effect: $Z = 8.3$	34 (P < 0.	00001)							
Total (95% CI)			60			64	100.0%	1.80 [1.38, 2.22]	•
Heterogeneity: Chi ² = 1.61, d	f=1 (P=	0.21);	l² = 389	%				-	_ <u> </u>
Test for overall effect: $Z = 8.3$	34 (P < 0.	00001)						Fox	2 -۱ U ۱ 2 vours experimental Favours contro
Test for subgroup difference	s: Not ap	plicabl	е					Fa	ours experimental Favours confic

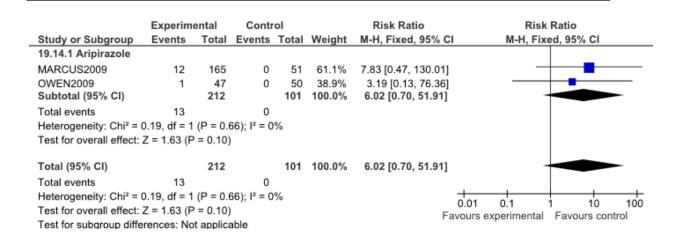
Any treatment-emergent extrapyramidal symptom



Extrapyramidal symptoms



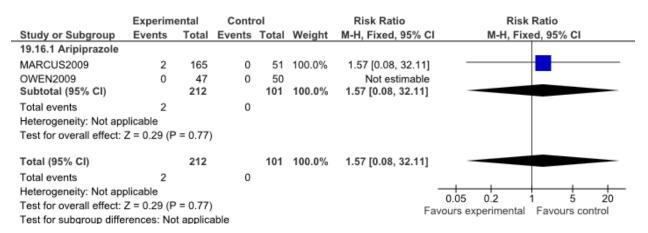
Extrapyramidal disorder



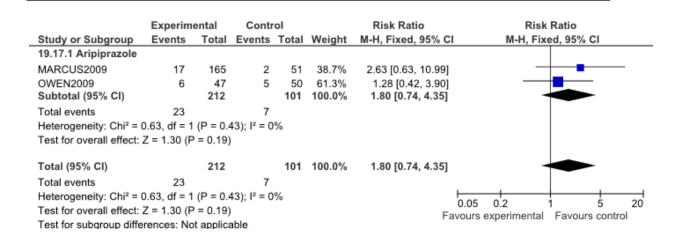
Fasting glucose (mg/dL) change score

	Ex	perimental	I	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
17.15.1 Risperidone									_L
JOHNSON&JOHNSON2011	-0.2	9.286649	46	-0.4	8.2	22	100.0%	0.02 [-0.49, 0.53]	_
Subtotal (95% CI)			46			22	100.0%	0.02 [-0.49, 0.53]	-
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.09 (F	P = 0.90	3)							
Total (95% CI)			46			22	100.0%	0.02 [-0.49, 0.53]	•
Heterogeneity: Not applicable								<u> </u>	
Test for overall effect: Z = 0.09 (F	P = 0.93	3)						-2 Favou	rs experimental Favours control
Test for subgroup differences: N	lot app	licable						ravou	is experimental Favours control

Fasting glucose (=>115 mg/dL)



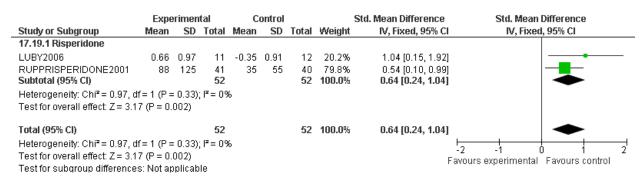
Fasting triglycerides (=>120 mg/dL for females or 160 mg/dL for males)



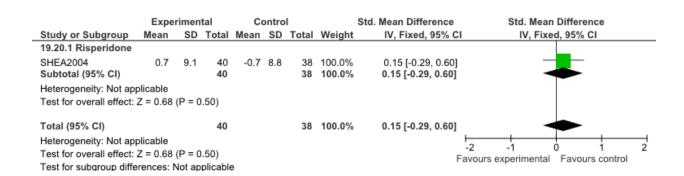
Insulin resistance (HOMA-IR) change score

	Expe	rimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	CI IV, Fixed, 95% CI
17.18.1 Risperidone									
JOHNSON&JOHNSON2011	0.1813953	1.429791	43	0.36	1.59	22	100.0%	-0.12 [-0.63, 0.40	oj —
Subtotal (95% CI)			43			22	100.0%	-0.12 [-0.63, 0.40	oj 🔷
Heterogeneity: Not applicable									
Test for overall effect: $Z = 0.45$	(P = 0.65)								
Total (95% CI)			43			22	100.0%	-0.12 [-0.63, 0.40	01
Heterogeneity: Not applicable									1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect: $Z = 0.45$	(P = 0.65)								Favours experimental Favours control
Test for subgroup differences:	: Not applicab	le							ravours experimental ravours contion

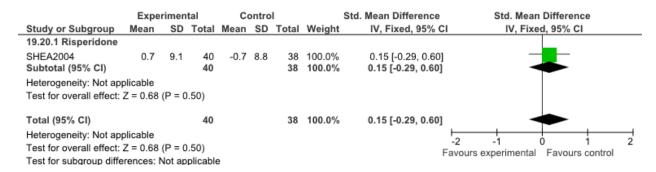
Leptin (mg/L) change score



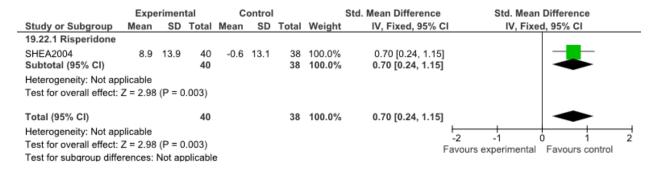
Diastolic blood pressure (mm Hg) change scores



Systolic blood pressure (mm Hg) change scores



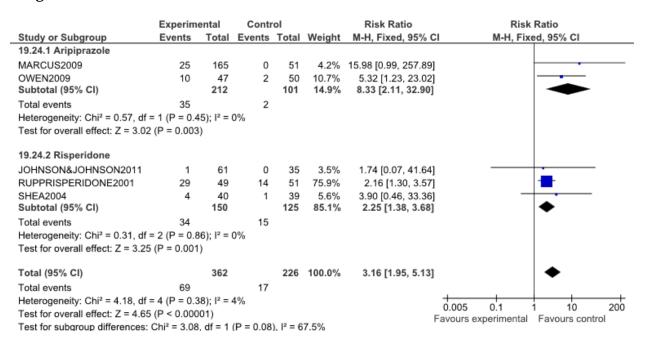
Pulse (bpm) change score



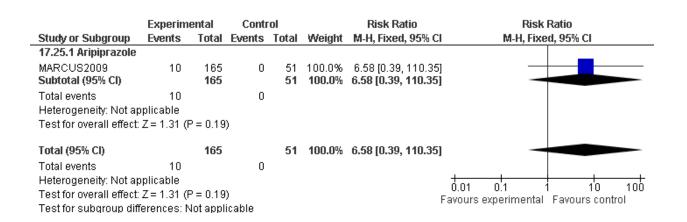
Somnolence/Drowsiness

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.23.1 Aripiprazole							
MARCUS2009	14	165	2	51	20.1%	2.16 [0.51, 9.20]	-
OWEN2009	8	47	2	50	12.8%	4.26 [0.95, 19.02]	-
Subtotal (95% CI)		212		101	32.9%	2.98 [1.07, 8.31]	
Total events	22		4				
Heterogeneity: Chi2 = 0.41, df	= 1 (P = 0.5	52); I ² =	0%				
Test for overall effect: Z = 2.08	3 (P = 0.04)						
19.23.2 Risperidone							
JOHNSON&JOHNSON2011	7	61	1	35	8.4%	4.02 [0.52, 31.31]	•
RUPPRISPERIDONE2001	24	49	6	51	38.7%	4.16 [1.86, 9.30]	-
SHEA2004	29	40	3	39	20.0%	9.43 [3.13, 28.42]	
Subtotal (95% CI)		150		125	67.1%	5.71 [3.08, 10.60]	•
Total events	60		10				
Heterogeneity: Chi ² = 1.50, df	= 2 (P = 0.4)	17); I ² =	0%				
Test for overall effect: Z = 5.53	3 (P < 0.000	01)					
Total (95% CI)		362		226	100.0%	4.81 [2.85, 8.13]	•
Total events	82		14				
Heterogeneity: Chi2 = 2.78, df	= 4 (P = 0.6	60); I ² =	0%				
est for overall effect: Z = 5.88	3 (P < 0.000	01)				E/	0.05 0.2 1 5 20 avours experimental Favours control
Test for subgroup differences:	4		(P = 0.29), I ² = 1	2.2%	F	avours experimental rayours control

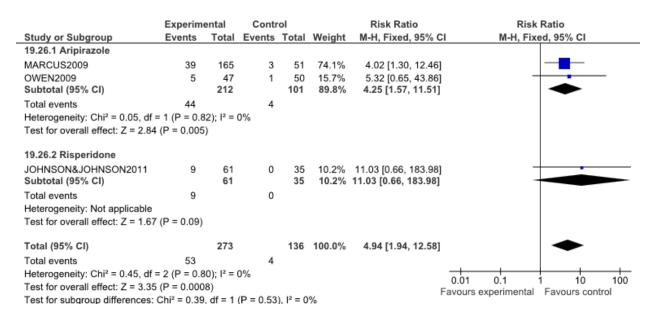
Fatigue



Lethargy



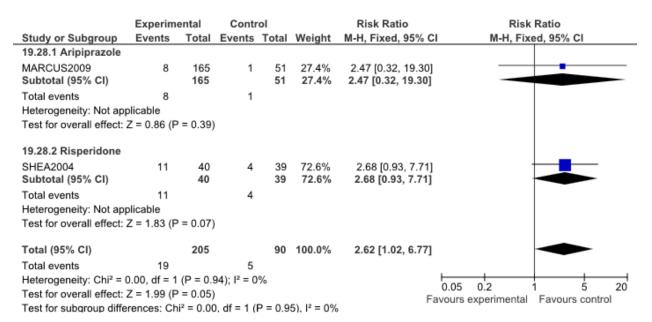
Sedation



Upper respiratory tract infection

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
19.27.1 Aripiprazole							
MARCUS2009	5	165	0	51	5.1%	3.45 [0.19, 61.28]	
OWEN2009	1	47	5	50	32.5%	0.21 [0.03, 1.75]	
Subtotal (95% CI)		212		101	37.6%	0.65 [0.16, 2.58]	
Total events	6		5				
Heterogeneity: Chi ² = 2.37, df	= 1 (P = 0.1	2); I ² = 5	58%				
Test for overall effect: Z = 0.61	(P = 0.54)						
19.27.2 Risperidone							
JOHNSON&JOHNSON2011	4	61	1	35	8.5%	2.30 [0.27, 19.73]	
RUPPRISPERIDONE2001	5	49	2	51	13.1%	2.60 [0.53, 12.79]	
SHEA2004	15	40	6	39	40.7%	2.44 [1.05, 5.63]	
Subtotal (95% CI)		150		125	62.4%	2.45 [1.21, 4.96]	•
Total events	24		9				
Heterogeneity: Chi ² = 0.01, df	= 2 (P = 1.0	0); I ² =	0%				
Test for overall effect: Z = 2.49	(P = 0.01)						
Total (95% CI)		362		226	100.0%	1.78 [0.97, 3.25]	•
Total events	30		14				
Heterogeneity: Chi ² = 4.91, df	= 4 (P = 0.3	0); I ² =	19%				0.02 0.1 1 10 5
Test for overall effect: Z = 1.86	(P = 0.06)					E	0.02 0.1 1 10 5 avours experimental Favours control
Test for subgroup differences:	Chi ² = 2.82	. df = 1	(P = 0.09)), $I^2 = 6$	4.6%	Г	avours experimental Pavours control

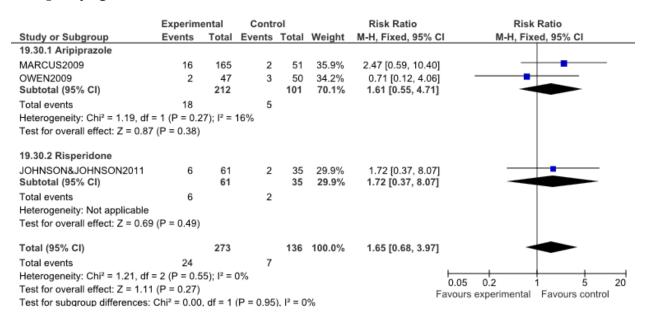
Rhinitis/rhinorrhea



Nasal congestion

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
19.29.1 Aripiprazole							
MARCUS2009	6	165	1	51	6.9%	1.85 [0.23, 15.05]	· ·
OWEN2009	3	47	1	50	4.4%	3.19 [0.34, 29.62]	-
Subtotal (95% CI)		212		101	11.3%	2.37 [0.52, 10.77]	
Total events	9		2				
Heterogeneity: Chi ² = 0.12, d	f = 1 (P = 0)).73); l ² :	= 0%				
Test for overall effect: Z = 1.1	2 (P = 0.26	6)					
19.29.2 Risperidone							
RUPPRISPERIDONE2001	25	49	20	51	88.7%	1.30 [0.84, 2.02]	· •
Subtotal (95% CI)		49		51	88.7%	1.30 [0.84, 2.02]	•
Total events	25		20				
Heterogeneity: Not applicable	•						
Test for overall effect: Z = 1.1	8 (P = 0.24	4)					
Total (95% CI)		261		152	100.0%	1.42 [0.92, 2.19]	•
Total events	34		22				
Heterogeneity: Chi ² = 0.73, d	f = 2 (P = 0).70); l ²	= 0%				1 1 1
Test for overall effect: Z = 1.6						,	0.05 0.2 1 5 20
Test for subgroup differences		,	1 (P = 0.4	15), I ² =	0%	1	Favours experimental Favours control

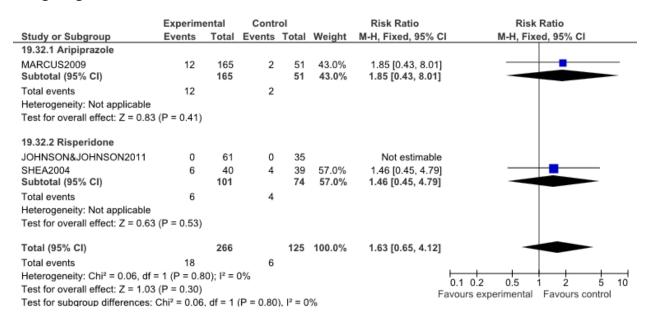
Nasopharyngitis



Nose bleed

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
17.31.1 Aripiprazole							
MARCUS2009	5	165	0	51	54.6%	3.45 [0.19, 61.28	3]
Subtotal (95% CI)		165		51	54.6%	3.45 [0.19, 61.28	
Total events	5		0				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.84$	(P = 0.40)						
17.31.2 Risperidone							
JOHNSON&JOHNSON2011	2	61	0	35	45.4%	2.90 [0.14, 58.81	1
Subtotal (95% CI)		61		35	45.4%	2.90 [0.14, 58.81	i
Total events	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69	(P = 0.49)						
Total (95% CI)		226		86	100.0%	3.20 [0.40, 25.77	
Total events	7		0				
Heterogeneity: Chi² = 0.01, df =	: 1 (P = 0.9	4); $I^2 = I$	0%				0.02 0.1 1 10 5
Test for overall effect: $Z = 1.09$	(P = 0.27)						0.02 0.1 1 10 5 Favours experimental Favours control
Test for subgroup differences:	$Chi^2 = 0.0^\circ$	l, df = 1	(P = 0.94)	4), $I^2 = 0$	0%		i avouis experimental Favouis control

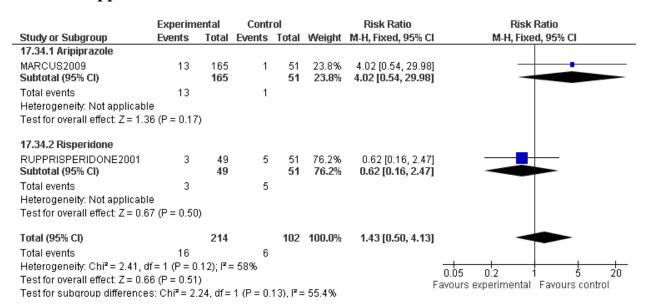
Coughing



Increased appetite

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
19.33.1 Aripiprazole							
MARCUS2009	20	165	2	51	18.6%	3.09 [0.75, 12.78]	ı • • • • • • • • • • • • • • • • • •
OWEN2009	7	47	5	50	29.4%	1.49 [0.51, 4.37]	i -
Subtotal (95% CI)		212		101	48.0%	2.11 [0.89, 5.01]	
Total events	27		7				
Heterogeneity: Chi ² = 0.68, df	= 1 (P = 0.4	1); I ² = 1	0%				
Test for overall effect: Z = 1.69	P = 0.09						
19.33.2 Risperidone							
JOHNSON&JOHNSON2011	16	61	2	35	15.4%	4.59 [1.12, 18.80]	ı —
RUPPRISPERIDONE2001	12	49	2	51	11.9%	6.24 [1.47, 26.48]	i
SHEA2004	9	40	4	39	24.6%	2.19 [0.74, 6.54]	i +
Subtotal (95% CI)		150		125	52.0%	3.83 [1.84, 8.01]	•
Total events	37		8				
Heterogeneity: Chi ² = 1.50, df	= 2 (P = 0.4	7); $I^2 = 0$	0%				
Test for overall effect: Z = 3.58	B (P = 0.000	3)					
Total (95% CI)		362		226	100.0%	3.01 [1.73, 5.24]	•
Total events	64		15				
Heterogeneity: Chi ² = 3.29, df	= 4 (P = 0.5	1); I ² = 1	0%				0.05 0.2 1 5 20
Test for overall effect: Z = 3.89	(P = 0.000	1)					0.05 0.2 1 5 20 Favours experimental Favours control
Test for subgroup differences:	Chi ² = 1.06	df = 1	(P = 0.30), I ² = 6	.0%	r	avours experimental Favours control

Decreased appetite



Abdominal pain/Stomachache

	Experime	ental	Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
19.35.1 Aripiprazole							
MARCUS2009	7	165	1	51	10.9%	2.16 [0.27, 17.17]	
Subtotal (95% CI)		165		51	10.9%	2.16 [0.27, 17.17]	
Total events	7		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.73	(P = 0.47)						
19.35.2 Risperidone							
JOHNSON&JOHNSON2011	3	61	0	35	4.5%	4.06 [0.22, 76.47]	
RUPPRISPERIDONE2001	5	49	9	51	62.9%	0.58 [0.21, 1.60]	
SHEA2004	8	40	3	39	21.7%	2.60 [0.74, 9.09]	+-
Subtotal (95% CI)		150		125	89.1%	1.25 [0.61, 2.54]	*
Total events	16		12				
Heterogeneity: Chi2 = 4.13, df =	2 (P = 0.1	3); I ² = 5	52%				
Test for overall effect: Z = 0.61	(P = 0.54)						
Total (95% CI)		315		176	100.0%	1.35 [0.69, 2.64]	•
Total events	23		13				
Heterogeneity: Chi2 = 4.44, df =	3 (P = 0.2	2); I ² = 3	32%				1 1 1
Test for overall effect: Z = 0.87	(P = 0.39)	-				_	0.02 0.1 1 10 5 avours experimental Favours control
Test for subgroup differences: (Chi² = 0.24	. df = 1	P = 0.62), I ² = 0	%	Г	avours experimental Pavours control

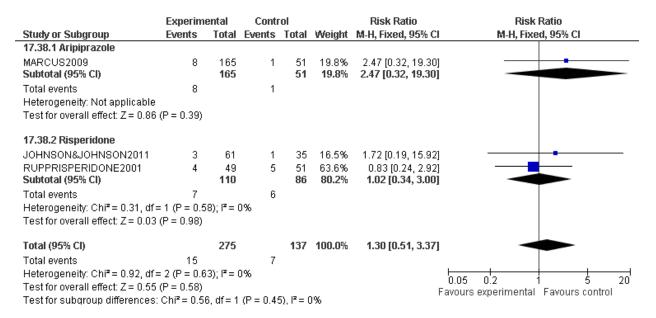
Abdominal discomfort

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
17.36.1 Risperidone							
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	61 61	3	35 35	100.0% 100.0 %	0.08 [0.00, 1.56 0.08 [0.00, 1.5 6	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.66 (0 (P = 0.10)		3				
Total (95% CI)		61		35	100.0%	0.08 [0.00, 1.56	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.66 (Test for subgroup differences:		ahla	3				0.005 0.1 10 200 Favours experimental Favours control

Vomiting

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total			Weight	M-H, Fixed, 95% C	
19.37.1 Aripiprazole							
MARCUS2009	22	165	4	51	21.5%	1.70 [0.61, 4.71]	
OWEN2009	7	47	2	50	6.8%	3.72 [0.81, 17.03]	
Subtotal (95% CI)		212		101	28.3%	2.19 [0.95, 5.03]	
Total events	29		6				
Heterogeneity: Chi2 = 0.71, df =	= 1 (P = 0.4	0); I ² =	0%				
Test for overall effect: Z = 1.84	(P = 0.07)						
19.37.2 Risperidone							
JOHNSON&JOHNSON2011	4	61	2	35	8.9%	1.15 [0.22, 5.95]	· ·
RUPPRISPERIDONE2001	16	49	12	51	41.4%	1.39 [0.73, 2.63]	· I _
SHEA2004	6	40	6	39	21.4%	0.97 [0.34, 2.76]	· -
Subtotal (95% CI)		150		125	71.7%	1.23 [0.74, 2.07]	*
Total events	26		20				
Heterogeneity: Chi2 = 0.33, df =	= 2 (P = 0.8	5); I ² = 1	0%				
Test for overall effect: Z = 0.80	(P = 0.42)						
Total (95% CI)		362		226	100.0%	1.50 [0.97, 2.34]	•
Total events	55		26				
Heterogeneity: Chi2 = 2.25, df =	= 4 (P = 0.6	9); I ² = 1	0%				105 00
Test for overall effect: Z = 1.82	(P = 0.07)	-					0.05 0.2 1 5 20 Favours experimental Favours control
Test for subgroup differences:	Chi ² = 1.31	. df = 1	P = 0.25), I ² = 2	3.6%		avours experimental Pavours control

Nausea



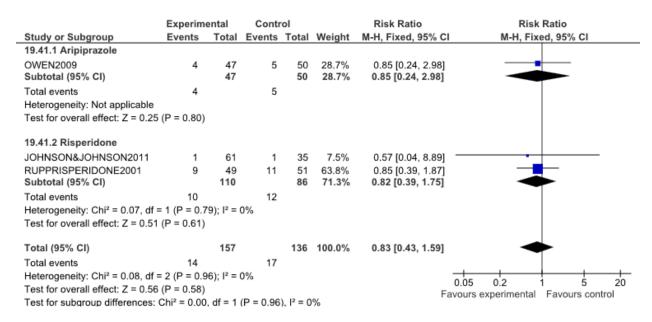
Gastroenteritis viral

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
17.39.1 Aripiprazole							
MARCUS2009	5	165	0	51	100.0%	3.45 [0.19, 61.28	31
Subtotal (95% CI)		165		51	100.0%	3.45 [0.19, 61.28	
Total events	5		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 0.84 (F	o = 0.40)				
Total (95% CI)		165		51	100.0%	3.45 [0.19, 61.28	
Total events	5		0				
Heterogeneity: Not a	pplicable						1 1 1
Test for overall effect	: Z= 0.84 (F	P = 0.40)				0.02 0.1 1 10 50 Favours experimental Favours control
Test for subgroup dit	fferences: N	lot appl	icable				ravours experimental ravours control

Constipation

	Experim	Contr	ol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI	
19.40.1 Risperidone								
JOHNSON&JOHNSON2011	2	61	1	35	15.6%	1.15 [0.11, 12.20	ı	_
RUPPRISPERIDONE2001	14	49	6	51	72.0%	2.43 [1.02, 5.81	j —	
SHEA2004	5	40	1	39	12.4%	4.88 [0.60, 39.86	i +	
Subtotal (95% CI)		150		125	100.0%	2.53 [1.19, 5.39	i	
Total events	21		8					
Heterogeneity: Chi2 = 0.81, df	= 2 (P = 0.6	67); I ² =	0%					
Test for overall effect: Z = 2.41	(P = 0.02)							
Total (95% CI)		150		125	100.0%	2.53 [1.19, 5.39	ı -	
Total events	21		8					
Heterogeneity: Chi ² = 0.81, df	= 2 (P = 0.6	67); I ² =	0%				005 00	20
Test for overall effect: Z = 2.41	(P = 0.02)						0.05 0.2 1 5 Favours experimental Favours con	
Test for subgroup differences:	Not applica	able					ravours experimental ravours con	ILIOI

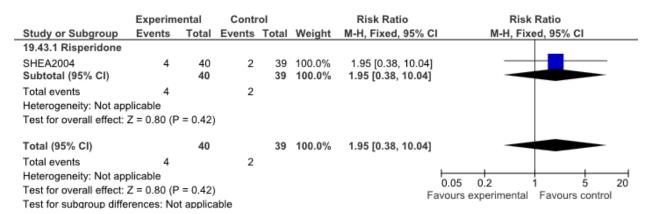
Diarrhoea



Fever

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
19.42.1 Aripiprazole							
MARCUS2009	15	165	0	51	8.1%	9.71 [0.59, 159.51	1 + •
OWEN2009	4	47	1	50	10.3%	4.26 [0.49, 36.71	i +
Subtotal (95% CI)		212		101	18.3%	6.66 [1.13, 39.20]	
Total events	19		1				
Heterogeneity: Chi2 = 0.24, df =	1 (P = 0.6	3); I ² = (0%				
Test for overall effect: Z = 2.10	(P = 0.04)						
19.42.2 Risperidone							
JOHNSON&JOHNSON2011	2	61	0	35	6.7%	2.90 [0.14, 58.81	1 -
SHEA2004	8	40	7	39	75.0%	1.11 [0.45, 2.78	i —
Subtotal (95% CI)		101		74	81.7%	1.26 [0.53, 3.02]	i 🌩
Total events	10		7				
Heterogeneity: Chi ² = 0.37, df =	1 (P = 0.5	5); I ² = (0%				
Test for overall effect: Z = 0.52	(P = 0.60)						
Total (95% CI)		313		175	100.0%	2.25 [1.04, 4.87]	ı -
Total events	29		8				
Heterogeneity: Chi2 = 3.68, df =	3 (P = 0.3	0); I ² = 1	19%				10 10
Test for overall effect: Z = 2.06	(P = 0.04)						0.01 0.1 1 10 100 Favours experimental Favours control
Test for subgroup differences:	Chi ² = 2.72	df = 1	(P = 0.10), I ² = 6	3.3%		Favours experimental Favours control

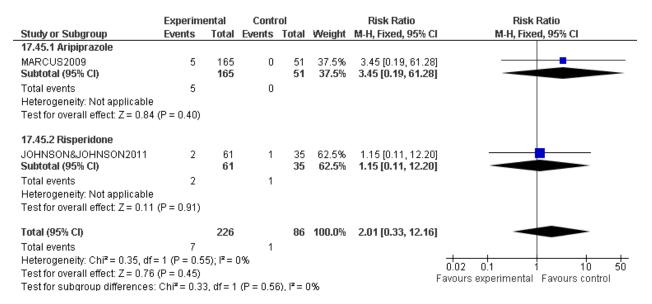
Influenza-like symptoms



Insomnia

	Favours experim	nental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
19.44.1 Aripiprazole							
OWEN2009	3	47	4	50	13.9%	0.80 [0.19, 3.38]	-
Subtotal (95% CI)		47		50	13.9%	0.80 [0.19, 3.38]	-
Total events	3		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.31	(P = 0.76)						
19.44.2 Risperidone							
JOHNSON&JOHNSON2011	0	61	2	35	11.4%	0.12 [0.01, 2.35]	· · · ·
RUPPRISPERIDONE2001	7	49	15	51	52.8%	0.49 [0.22, 1.09]	_ _
SHEA2004	6	40	6	39	21.8%	0.97 [0.34, 2.76]	
Subtotal (95% CI)		150		125	86.1%	0.56 [0.31, 1.03]	•
Total events	13		23				
Heterogeneity: Chi ² = 2.26, df :	= 2 (P = 0.32); I ² = 1	11%					
Test for overall effect: Z = 1.87	(P = 0.06)						
Total (95% CI)		197		175	100.0%	0.59 [0.34, 1.04]	•
Total events	16		27				
Heterogeneity: Chi2 = 2.40, df	= 3 (P = 0.49); I ² = 0)%					0.01 0.1 1 10 10
Test for overall effect: Z = 1.83	(P = 0.07)					-	avours experimental Favours control
Test for subgroup differences:	Chi2 = 0.19, df = 1 (P = 0.66), I ² = 0%			,	avours experimental Favours control

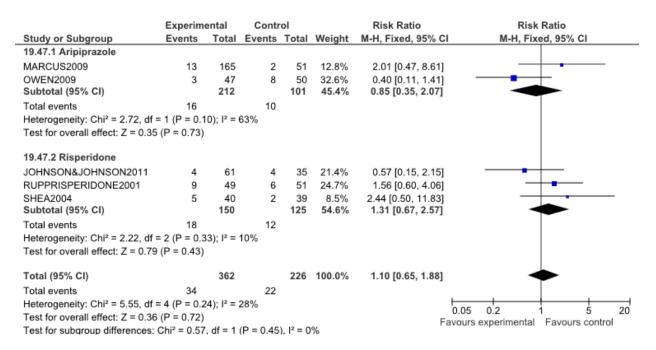
Hypersomnia



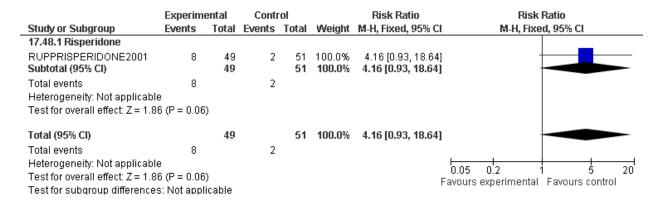
Sleep problems

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
17.46.1 Risperidone							
RUPPRISPERIDONE2001 Subtotal (95% CI)	11	49 49	9	51 51	100.0% 100.0 %	1.27 [0.58, 2.80 1.27 [0.58, 2.8 0	·
Total events Heterogeneity: Not applicable	11 e		9				
Test for overall effect: Z = 0.6	0 (P = 0.55))					
Total (95% CI)		49		51	100.0%	1.27 [0.58, 2.80	0]
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.6		١	9				0.1 0.2 0.5 1 2 5 10
Test for subaroup difference:		_					Favours experimental Favours control

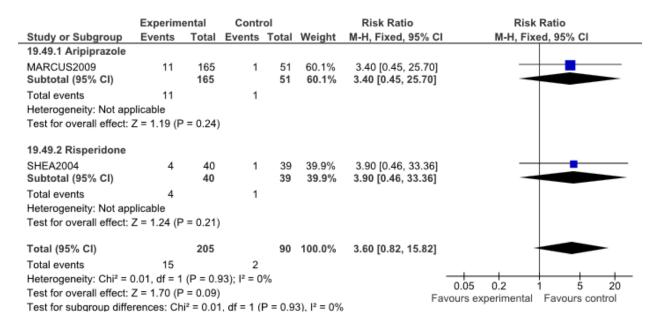
Headache



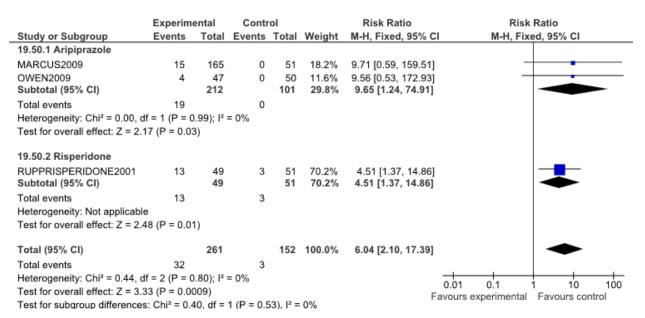
Dizziness



Increased salivation



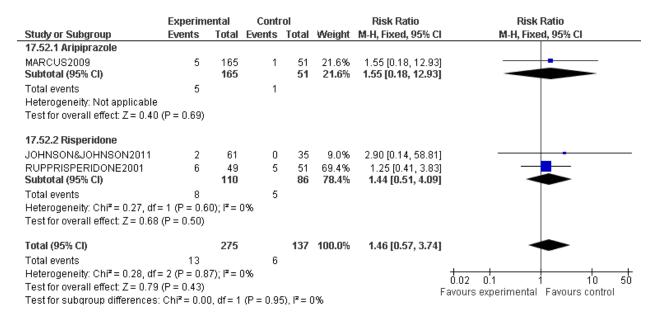
Drooling



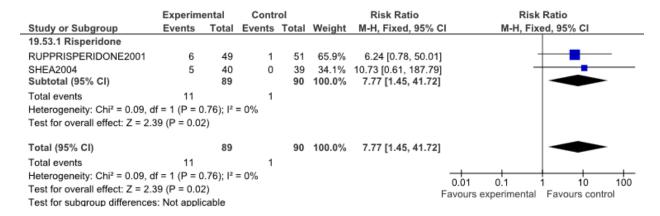
Dry mouth

	Ехрегіте	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
17.51.1 Risperidone							
RUPPRISPERIDONE2001 Subtotal (95% CI)	9	49 49	5	51 51	100.0% 100.0 %	1.87 [0.68, 5.20 1.87 [0.68, 5.2 0	
Total events Heterogeneity: Not applicable	9 le		5				
Test for overall effect: Z = 1.2	21 (P = 0.23))					
Total (95% CI)		49		51	100.0%	1.87 [0.68, 5.20	0]
Total events	9		5				
Heterogeneity: Not applicable	le						
Test for overall effect: $Z = 1.2$ Test for subgroup difference	•	•					0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control

Increased thirst



Tachycardia



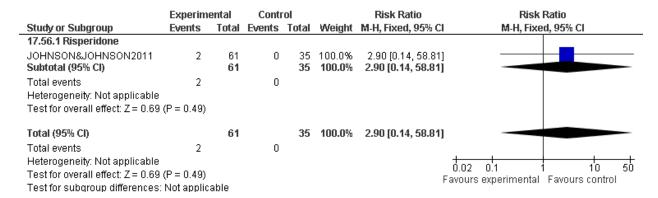
Anorexia

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
19.54.1 Risperidone							
SHEA2004	4	40	1	39	100.0%	3.90 [0.46, 33.36	1
Subtotal (95% CI)		40		39	100.0%	3.90 [0.46, 33.36	
Total events	4		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.24 (P	= 0.21)					
Total (95% CI)		40		39	100.0%	3.90 [0.46, 33.36	
Total events	4		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.24 (P	= 0.21)					0.05 0.2 1 5 20 Favours experimental Favours control
Test for subgroup diffe	erences: No	t applica	able			I	-avours experimental Favours control

Anxiety

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
17.55.1 Risperidone							
RUPPRISPERIDONE2001 Subtotal (95% CI)	12	49 49	10	51 51	100.0% 100.0 %	1.25 [0.59, 2.62 1.25 [0.59, 2.6 2	
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 0.5)	10				
Total (95% CI)		49		51	100.0%	1.25 [0.59, 2.62	2]
Total events Heterogeneity: Not applicabl Test for overall effect: Z = 0.5 Test for subgroup difference	9 (P = 0.56)		10				0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control

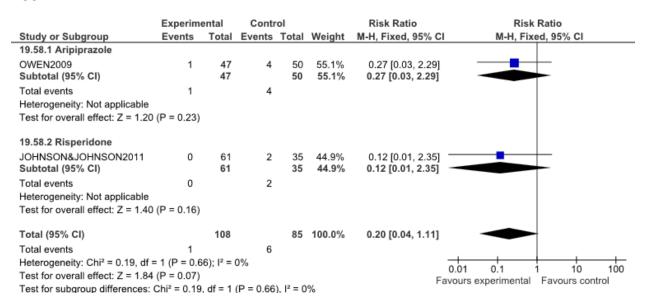
Depression



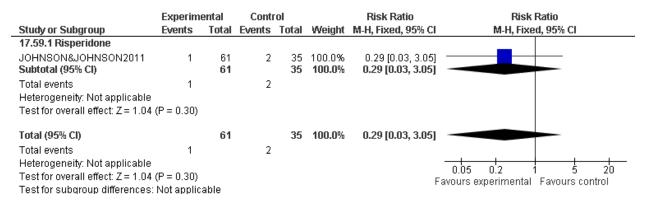
Apathy

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
19.57.1 Risperidone							
SHEA2004	5	40	0	39	100.0%	10.73 [0.61, 187.79	91
Subtotal (95% CI)		40		39	100.0%	10.73 [0.61, 187.79	i –
Total events	5		0				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 1.63 (P	= 0.10)					
Total (95% CI)		40		39	100.0%	10.73 [0.61, 187.79	
Total events	5		0				
Heterogeneity: Not app	licable						004 04 40 40
Test for overall effect: 2	Z = 1.63 (P	= 0.10)					0.01 0.1 1 10 100 Favours experimental Favours control
Test for subgroup differ	rences: No	t applica	ble				ravours experimental ravours control

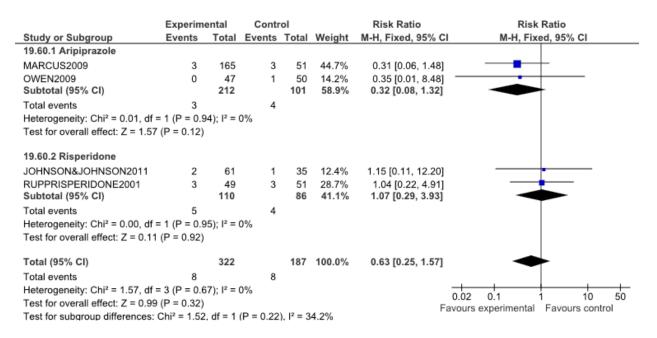
Aggression



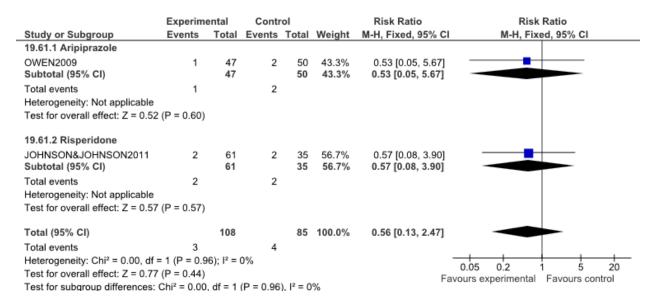
Agitation



Restlessness



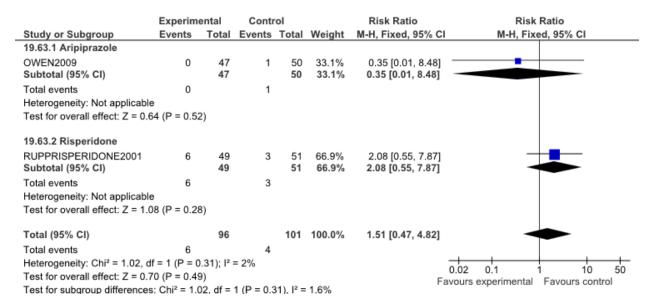
Psychomotor hyperactivity



Tremor

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events		Weight		
19.62.1 Aripirazole							
MARCUS2009	17	165	0	51	27.9%	10.96 [0.67, 179.19]	-
OWEN2009	4	47	0	50	17.7%	9.56 [0.53, 172.93]	+
Subtotal (95% CI)		212		101	45.6%	10.42 [1.33, 81.48]	
Total events	21		0				
Heterogeneity: Chi ² = 0.00, d	If = 1 (P = 0	.95); l ²	= 0%				
Test for overall effect: Z = 2.2	23 (P = 0.03	3)					
19.62.2 Risperidone							
RUPPRISPERIDONE2001	7	49	1	51	35.9%	7.29 [0.93, 57.07]	-
SHEA2004	4	40	0	39	18.5%	8.78 [0.49, 157.85]	-
Subtotal (95% CI)		89		90	54.4%	7.79 [1.46, 41.70]	
Total events	11		1				
Heterogeneity: Chi ² = 0.01, d	If = 1 (P = 0)	.92); l2:	= 0%				
Test for overall effect: Z = 2.4	40 (P = 0.02	2)					
Total (95% CI)		301		191	100.0%	8.99 [2.40, 33.64]	-
Total events	32		1				
Heterogeneity: Chi ² = 0.06, d	If = 3 (P = 1	.00); I2	= 0%				
Test for overall effect: Z = 3.2	26 (P = 0.00	01)					0.01 0.1 1 10 10 Favours experimental Favours control
Test for subgroup differences	s: Chi ² = 0.0)5, df =	1 (P = 0.8	33), I ² =	0%	,	avours experimental Pavours control

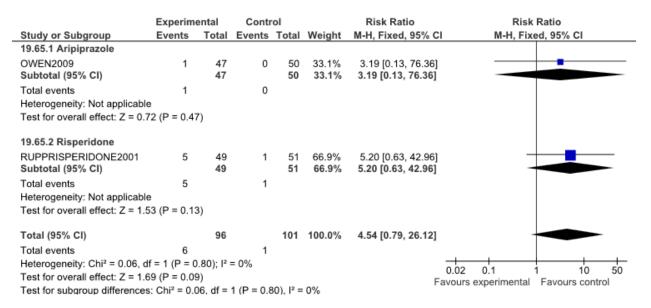
Dyskinesia/Hyperkinesia



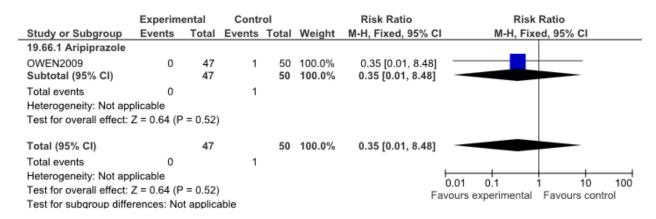
Hypokinesia

	Experimental	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
19.64.1 Aripiprazole						
OWEN2009	1 47	0	50	100.0%	3.19 [0.13, 76.36	31
Subtotal (95% CI)	47		50	100.0%	3.19 [0.13, 76.36]	
Total events	1	0				
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z = 0.72 (P = 0.47	')				
Total (95% CI)	47		50	100.0%	3.19 [0.13, 76.36]	
Total events	1	0				
Heterogeneity: Not app	plicable					1 1 1 1
Test for overall effect:	Z = 0.72 (P = 0.47	')				0.02 0.1 1 10 50
Test for subgroup diffe	,	,				Favours experimental Favours control

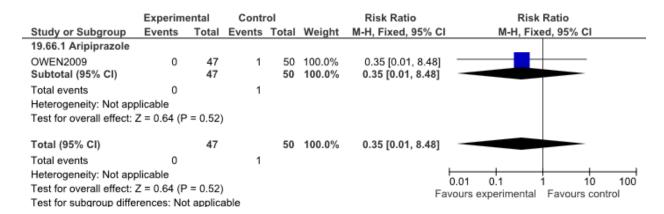
Muscle rigidity



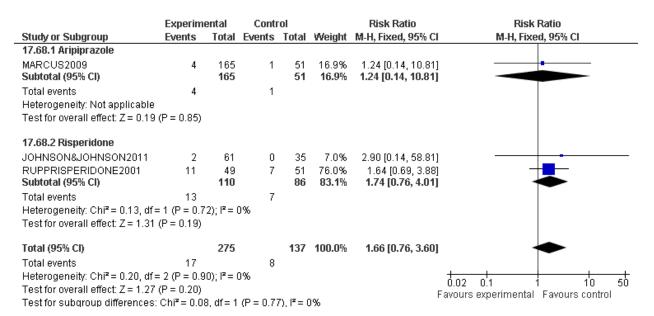
Muscle spasms



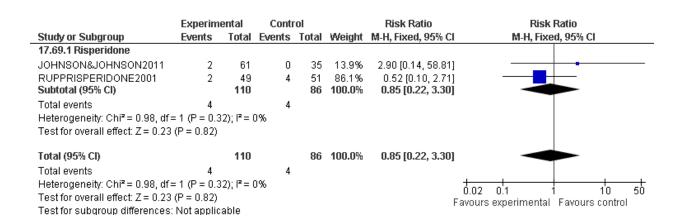
Enuresis



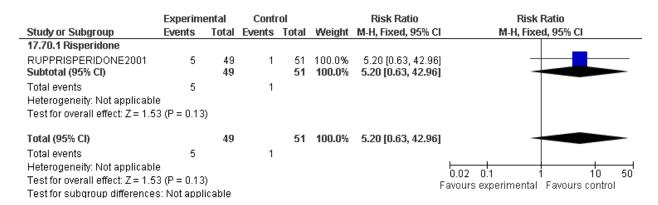
Skin irritation/Rash



Earache/Ear infection



Sore throat



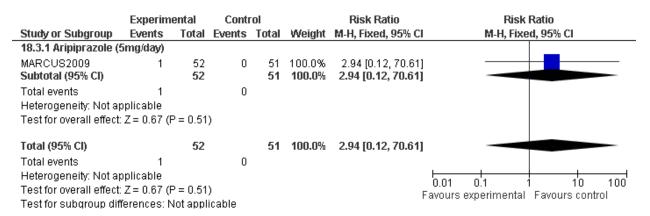
Adverse events associated with low dose antipsychotics versus placebo Any side effect

	Ехрегіте	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
18.1.1 Aripiprazole (5mg/day)							
MARCUS2009 Subtotal (95% CI)	46	52 52	37	51 51	65.8% 65.8 %	1.22 [1.00, 1.48 1.22 [1.00, 1.48	
Total events	46		37				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.99 ((P = 0.05)						
18.1.2 Risperidone (0.125-0.17	75mg/day)						
JOHNSON&JOHNSON2011 Subtotal (95% CI)	12	30 30	21	35 35	34.2% 34.2 %	0.67 [0.40, 1.12 0.67 [0.40, 1.12	
Total events	12		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.54 ((P = 0.12)						
Total (95% CI)		82		86	100.0%	1.03 [0.84, 1.26	· •
Total events	58		58				
Heterogeneity: Chi ² = 5.60, df =	1 (P = 0.0)	$2); I^2 = 0$	32%				01 02 05 1 2 5 10
Test for overall effect: $Z = 0.30$ ((P = 0.77)						0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control
Test for subgroup differences:	Chi ² = 4.62	?, df= 1	(P = 0.00)	3), I² = 3	78.3%		ravouis experimental ravouis control

Discontinuation due to sedation

	Ехрегіт	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (M-H, Fixed, 95% CI
18.2.1 Aripiprazole (5	img/day)						
MARCUS2009 Subtotal (95% CI)	1	52 52	0	51 51	100.0% 100.0 %		
Total events	1	32	0	31	100.0 /4	2.54 [6.12, 16.6]	
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.67 (F	° = 0.51)				
Total (95% CI)		52		51	100.0%	2.94 [0.12, 70.61	
Total events	1		0				
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.67 (F	P = 0.51)				Favours experimental Favours control
Test for subgroup diff	ferences: N	lot appl	icable				Tareare experimental Tareare control

Discontinuation due to drooling



Discontinuation due to tremor

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
18.4.1 Aripiprazole (5mg/day)						
MARCUS2009	2	52	0	51	100.0%	4.91 [0.24, 99.74	1
Subtotal (95% CI)		52		51	100.0%	4.91 [0.24, 99.74	
Total events	2		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	E Z = 1.03 (F	P = 0.30)				
Total (95% CI)		52		51	100.0%	4.91 [0.24, 99.74	
Total events	2		0				
Heterogeneity: Not a	pplicable						0.01 0.1 1 10 1
Test for overall effect	t: Z = 1.03 (F	P = 0.30)				0.01 0.1 1 10 10 Favours experimental Favours control
Test for subgroup dit	fferences: N	lot appl	icable				ravours experimental Favours control

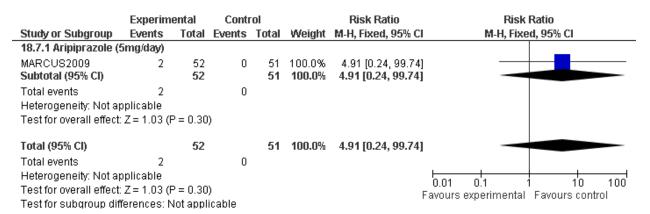
Any treatment-emergent extrapyramidal symptoms

	Ехрегіт	ental	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
18.5.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% CI)	12	52 52	6	51 51	100.0% 100.0 %	1.96 [0.80, 4.83 1.96 [0.80, 4.8 3	
Total events Heterogeneity: Not a	12 policable		6				
Test for overall effect		P = 0.14)				
Total (95% CI)		52		51	100.0%	1.96 [0.80, 4.83	1
Total events	12		6				
Heterogeneity: Not ap	pplicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect Test for subgroup dif							0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control

Extrapyramidal symptoms

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
18.6.1 Risperidone (0.125-0.1)	75mg/da	ry)							
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	0	0.19	29 29	0.3	1.06	34 34	100.0% 100.0 %	-0.37 [-0.87, 0.13 - 0.37 [-0.87, 0.13	
Heterogeneity: Not applicable Test for overall effect: Z = 1.47	(P = 0.14	4)							
Total (95% CI) Heteropeneity: Not applicable Test for overall effect: Z = 1.47 Test for subgroup differences:	,		29			34	100.0%	-0.37 [-0.87, 0.13	Favours experimental Favours control

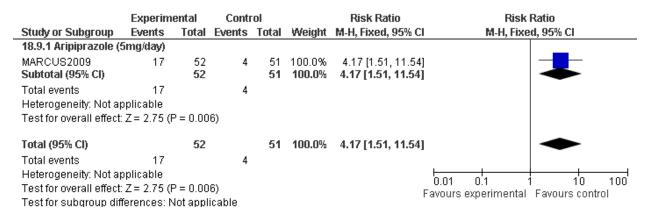
Extrapyramidal disorder



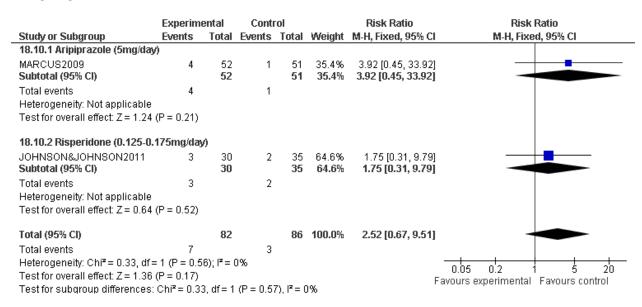
Tremor

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
18.8.1 Aripiprazole (5mg/day)						
MARCUS2009	4	52	0	51	100.0%	8.83 [0.49, 159.93	1 + -
Subtotal (95% CI)		52		51	100.0%	8.83 [0.49, 159.93]	
Total events	4		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 1.47 (F	P = 0.14)				
Total (95% CI)		52		51	100.0%	8.83 [0.49, 159.93]	
Total events	4		0				
Heterogeneity: Not a	pplicable						004 04 4 40 40
Test for overall effect	Z = 1.47 (F	o = 0.14)				0.01 0.1 1 10 100 Favours experimental Favours control
Test for subaroup dif	ferences: N	Jot appl	icable				ravours experimental ravours control

Clinically relevant (>=7%) weight gain



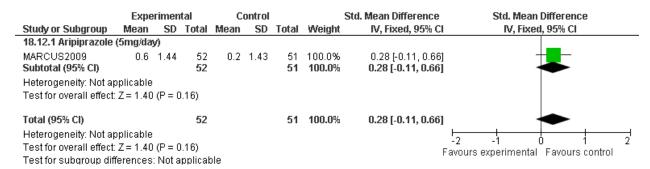
Weight gain



Weight gain (in kg)

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
18.11.1 Aripiprazole (5mg/day))								
MARCUS2009	1.3	2.16	52	0.3	2.14	51	64.9%	0.46 [0.07, 0.85]	
Subtotal (95% CI)			52			51	64.9%	0.46 [0.07, 0.85]	-
Heterogeneity: Not applicable									
Test for overall effect: $Z = 2.31$ ((P = 0.0)	2)							
18.11.2 Risperidone (0.125-0.1	175mg/c	lay)							
JOHNSON&JOHNSON2011	1.2	1.13	24	0.7	1.19	33	35.1%	0.42 [-0.11, 0.96]	
Subtotal (95% CI)			24			33	35.1%	0.42 [-0.11, 0.96]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.56 ((P = 0.1)	2)							
Total (95% CI)			76			84	100.0%	0.45 [0.13, 0.76]	•
Heterogeneity: Chi ² = 0.01, df =	1 (P = 0)	0.91); F	= 0%						
Test for overall effect: $Z = 2.79$ (P = 0.01	05)						,	-2 -1 U 1
Test for subgroup differences:	•		= 1 (P	= 0.91)	$I^2 = 0.9$	6		ŀ	Favours experimental Favours control

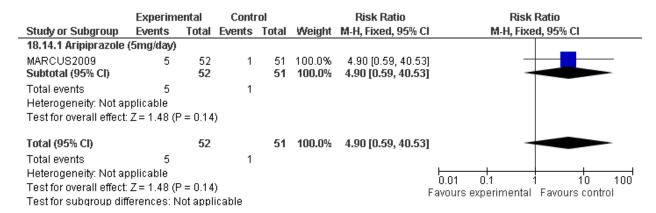
BMI change (kg/m-squared)



Increased appetite

	Ехрегіте	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
18.13.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% CI)	10	52 52	2	51 51	52.2% 52.2 %	4.90 [1.13, 21.29] 4.90 [1.13, 21.29]	
Total events	10		2				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 2.12$	(P = 0.03)						
18.13.2 Risperidone (0.125-0.1	175mg/day	0					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	5	30 30	2	35 35	47.8% 4 7.8 %	2.92 [0.61, 13.96] 2.92 [0.61, 13.96]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.34	5 (P = 0.18)		2				
Total (95% CI)		82		86	100.0%	3.95 [1.36, 11.51]	
Total events Heterogeneity: Chi² = 0.23, df = Test for overall effect: Z = 2.52 offert for subgroup differences:	(P = 0.01)			\$), ²= (0%		0.05 0.2 1 5 20 Favours experimental Favours control

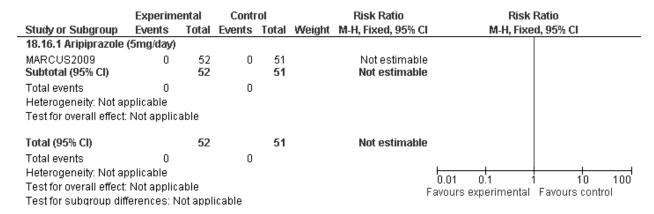
Decreased appetite



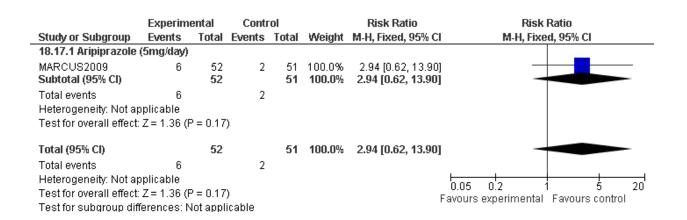
Fasting Glucose (mg/dL) (Change Score)

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
18.15.1 Risperidone (0.125-0.1	75mg/d	ay)							
JOHNSON&JOHNSON2011 Subtotal (95% CI)	-0.1	8.81	23 23	-0.4	8.2	22 22	100.0% 100.0 %	0.03 [-0.55, 0.62] 0.03 [-0.55, 0.62]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (I	P = 0.91)							
Total (95% CI)			23			22	100.0%	0.03 [-0.55, 0.62]	•
Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (I Test for subgroup differences: N			9						-2 -1 0 1 Favours experimental Favours control

Fasting glucose (=>115 mg/dL)



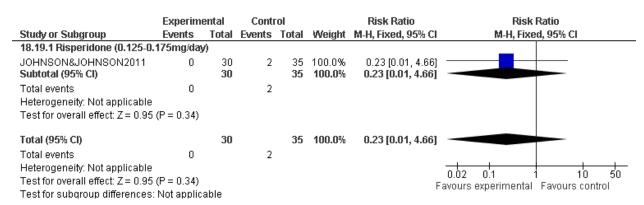
Fasting triglycerides (=>120 mg/dL for females or 160 mg/dL for males)



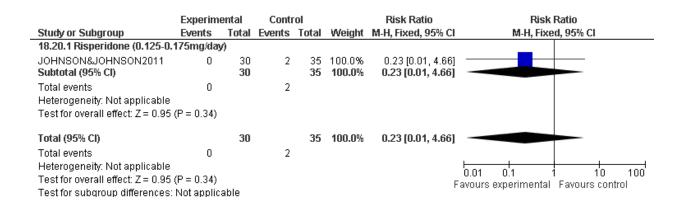
Insulin Resistance (HOMA-IR) (Change Score)

	Exper	imen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup 1	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
18.18.1 Risperidone (0.125-0.17	'5mg/da	ay)							
JOHNSON&JOHNSON2011 Subtotal (95% CI)	-0.1	1.44	21 21	0.36	1.59	22 22	100.0% 100.0 %	-0.30 [-0.90, 0.30] - 0.30 [-0.90, 0.30]	The state of the s
Heterogeneity: Not applicable Test for overall effect: Z = 0.97 (P	= 0.33)							
Total (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.97 (P Test for subgroup differences: N			21			22	100.0%	-0.30 [-0.90, 0.30]	-2 -1 0 Favours experimental Favours control

Aggression



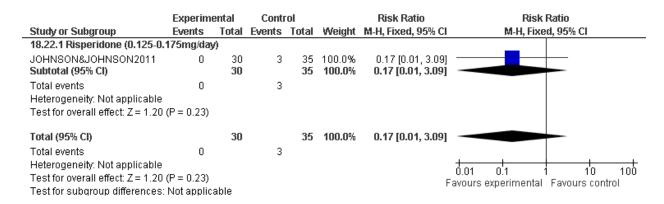
Agitation



Depression

	Ехрегіт	ental	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (I M-H, Fixed, 95% CI
18.21.1 Risperidone (0.125-0.	175mg/day	v)					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	0	35 35		Not estimabl Not estimabl	-
Total events Heterogeneity: Not applicable Test for overall effect: Not appl	0 icable		0				
Total (95% CI)		30		35		Not estimabl	e
Total events	0		0				
Heterogeneity: Not applicable Test for overall effect: Not appl Test for subgroup differences:		able					0.01 0.1 1 10 100 Favours experimental Favours control

Abdominal discomfort



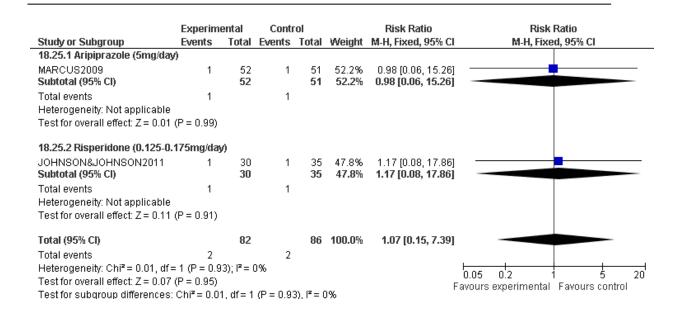
Abdominal pain (upper)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
18.23.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% CI)	2	52 52	1	51 51	68.6% 68.6 %	1.96 [0.18, 20.97 1.96 [0.18, 20.97	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.56 (2 (P = 0.58)		1				
18.23.2 Risperidone (0.125-0.1	175mg/day)					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	1	30 30	0	35 35	31.4% 31. 4%	3.48 [0.15, 82.48 3.48 [0.15, 82.48	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.77 (1 (P = 0.44)		0				
Total (95% CI)		82		86	100.0%	2.44 [0.37, 15.99	
Total events Heterogeneity: Chi ² = 0.08, df = Test for overall effect: Z = 0.93 (Test for subgroup differences:	(P = 0.35)			8), I²= (0%		0.02 0.1 1 10 50 Favours experimental Favours control

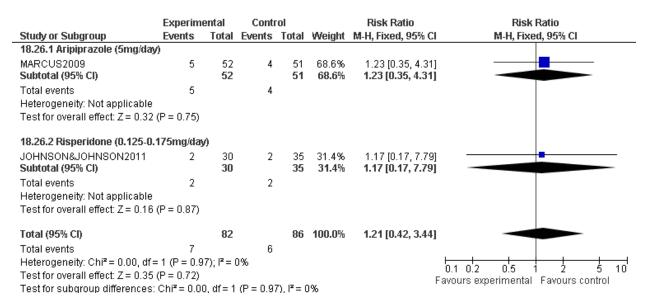
Constipation

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Cl M-H, Fixed, 95% Cl
18.24.1 Risperidone (0.125-0.	175mg/day	0					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	1	35 35	100.0% 100.0 %	0.39 [0.02, 9.16 0.39 [0.02, 9.1 6	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.59	0 (P = 0.56)		1				
Total (95% CI)		30		35	100.0%	0.39 [0.02, 9.16	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.59 Test for subgroup differences:		able	1				0.02 0.1 1 10 50 Favours experimental Favours control

Nausea



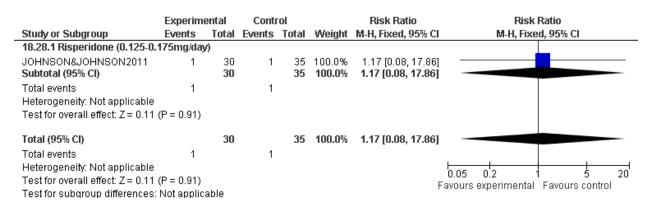
Vomiting



Gastroenteritis viral

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l M-H, Fixed, 95% Cl
18.27.1 Aripiprazole	(5mg/day)						
MARCUS2009	1	52	0	51	100.0%	2.94 [0.12, 70.61]	1 -
Subtotal (95% CI)		52		51	100.0%	2.94 [0.12, 70.61]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.67 (F	9 = 0.51)				
Total (95% CI)		52		51	100.0%	2.94 [0.12, 70.61]	
Total events	1		0				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 5
Test for overall effect:	Z = 0.67 (F	9 = 0.51)				0.02 0.1 1 10 5 Favours experimental Favours control
Test for subgroup diff	ferences: N	ot appl	icable				i avours experimental Favours control

Diarrhoea



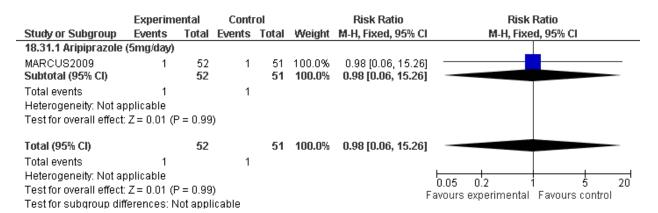
Pyrexia

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
18.29.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% CI)	3	52 52	0	51 51	100.0% 100.0 %	6.87 [0.36, 129.70 6.87 [0.36, 129.70	
Total events Heterogeneity: Not applicable	3		0				
Test for overall effect: Z = 1.29	(P = 0.20)						
18.29.2 Risperidone (0.125-0.	175mg/day)					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	0	35 35		Not estimable Not estimable	- I
Total events Heterogeneity: Not applicable	0		0				
Test for overall effect: Not appli	cable						
Total (95% CI)		82		86	100.0%	6.87 [0.36, 129.70	
Total events	3		0				
Heterogeneity: Not applicable							0.01 0.1 1 10 100
Test for overall effect: Z = 1.29 (Test for subgroup differences:		able					Favours experimental Favours control

Drooling

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
18.30.1 Aripiprazole	(5mg/day)						
MARCUS2009 Subtotal (95% CI)	2	52 52	0	51 51	100.0% 100.0 %	4.91 [0.24, 99.74 4.91 [0.24, 99.7 4	
Total events	2		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	:: Z= 1.03 (F	9 = 0.30)				
Total (95% CI)		52		51	100.0%	4.91 [0.24, 99.74	1]
Total events	2		0				
Heterogeneity: Not a	pplicable						0.01 0.1 1 10 100
Test for overall effect	: Z = 1.03 (F	P = 0.30)				Favours experimental Favours control
Test for subgroup dif	fferences: N	lot appl	icable				i avodio experimentali il avodio contioi

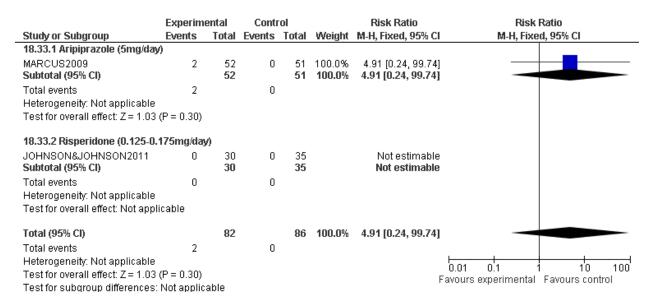
Increased salivation



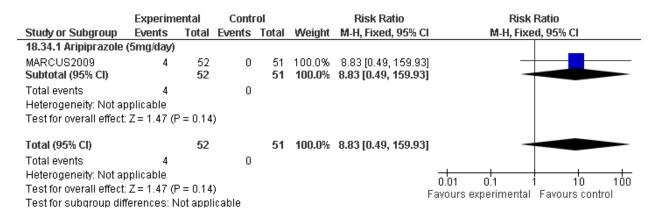
Thirst

	Experime	ental	Contr	ol		Risk Ratio	Risk F	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed	d, 95% CI
18.32.1 Aripiprazole (5mg/day)							
MARCUS2009 Subtotal (95% CI)	3	52 52	1	51 51	100.0% 100.0 %	2.94 [0.32, 27.36] 2.94 [0.32, 27.36]		
Total events	3		1					
Heterogeneity: Not applicable								
Test for overall effect: $Z = 0.95$ ((P = 0.34)							
18.32.2 Risperidone (0.125-0.1	175mg/day)						
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	0	30 30	0	35 35		Not estimable Not estimable	· I	
Total events Heterogeneity: Not applicable Test for overall effect: Not appli	0 cable		0					
Total (95% CI)		82		86	100.0%	2.94 [0.32, 27.36]		
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.95 (Test for subgroup differences:		able	1				0.01 0.1 1 Favours experimental	10 100 Favours control

Fatigue



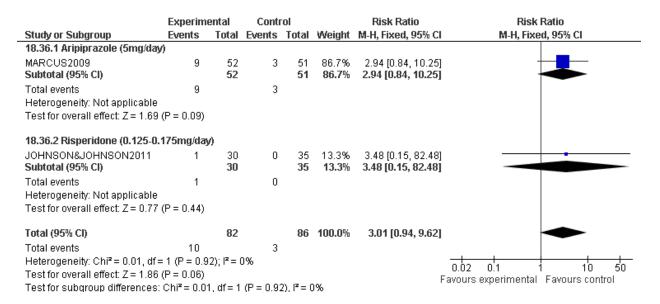
Lethargy



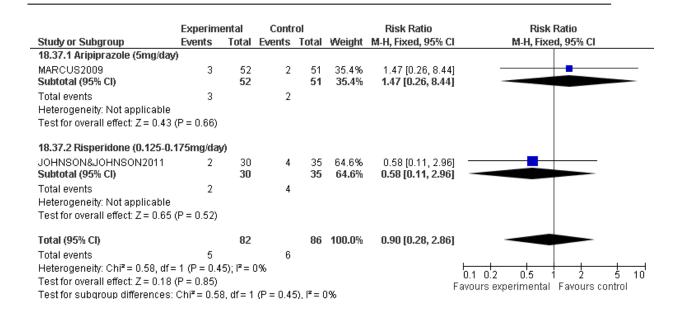
Somnolence

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
18.35.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% Cl)	4	52 52	2	51 51	59.3% 59.3 %	1.96 [0.38, 10.24 1.96 [0.38, 10.2 4	
Total events Heterogeneity: Not applicable	4		2				
Test for overall effect: $Z = 0.80$	(P = 0.42)						
18.35.2 Risperidone (0.125-0.	175mg/day	9					
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	0	30 30	1	35 35	40.7% 4 0.7 %	0.39 [0.02, 9.16 0.39 [0.02, 9.16	
Total events Heterogeneity: Not applicable	0		1				
Test for overall effect: Z = 0.59	(P = 0.56)						
Total (95% CI)		82		86	100.0%	1.32 [0.33, 5.26	1
Total events	4		3				
Heterogeneity: Chi² = 0.80, df=	1 (P = 0.3	7); l² = I	0%				0.02 0.1 1 10 50
Test for overall effect: Z = 0.39	(P = 0.69)						Favours experimental Favours control
Test for subgroup differences:	$Chi^2 = 0.79$	0, df = 1	(P = 0.3)	7), $ z = 0$	0%		Taroaro experimental Taroaro combol

Sedation



Headache



Ear infection

	Ехрегіт	ental	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (Cl M-H, Fixed, 95% Cl
18.38.1 Risperidone (0.125-0.	.175mg/day	0					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	0	35 35		Not estimabl Not estimabl	-
Total events Heterogeneity: Not applicable Test for overall effect: Not app	0 licable		0				
Total (95% CI)		30		35		Not estimabl	e
Total events Heterogeneity: Not applicable Test for overall effect: Not app Test for subgroup differences		able	0				0.01 0.1 1 10 100 Favours experimental Favours control

Upper respiratory tract infection

	Ехрегіте	ental	Conti	ol		Risk Ratio	Risk F	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed	d, 95% CI
18.39.1 Aripiprazole (5mg/day)							
MARCUS2009 Subtotal (95% CI)	2	52 52	0	51 51	35.4% 35. 4%			
Total events Heterogeneity: Not applicable	2		0					
Test for overall effect: $Z = 1.03$	(P = 0.30)							
18.39.2 Risperidone (0.125-0.1	175mg/day)						
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	1	30 30	1	35 35	64.6% 64.6 %	1.17 [0.08, 17.86 1.17 [0.08, 17.86		
Total events Heterogeneity: Not applicable	1		1					
Test for overall effect: $Z = 0.11$	(P = 0.91)							
Total (95% CI)		82		86	100.0%	2.49 [0.36, 17.01	1	
Total events	3		1					
Heterogeneity: Chi ² = 0.49, df =	1 (P = 0.4	8); l² = l	0%				0.01 0.1 1	10 1
Test for overall effect: $Z = 0.93$	(P = 0.35)						0.01 0.1 1 Favours experimental	
Test for subgroup differences:	$Chi^2 = 0.48$	3, df = 1	(P = 0.49)	9), $ z = 0$	0%		i avouio exheiiiileiitai	i avours control

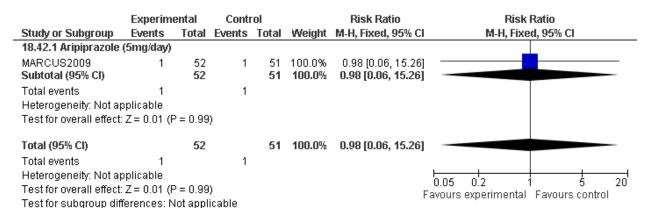
Cough

	Ехрегіте	ental	Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
18.40.1 Aripiprazole (5mg/day)						
MARCUS2009 Subtotal (95% CI)	8	52 52	2	51 51	100.0% 100.0 %	3.92 [0.87, 17.59 3.92 [0.87, 17.59	
Total events	8		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.79	(P = 0.07)						
18.40.2 Risperidone (0.125-0.	175mg/day)					
JOHNSON&JOHNSON2011 Subtotal (95% Cl)	0	30 30	0	35 35		Not estimable Not estimable	· I
Total events Heterogeneity: Not applicable Test for overall effect: Not appli	0 icable		0				
Total (95% CI)		82		86	100.0%	3.92 [0.87, 17.59	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.79 Test for subgroup differences:		able	2				0.05 0.2 1 5 20 Favours experimental Favours control

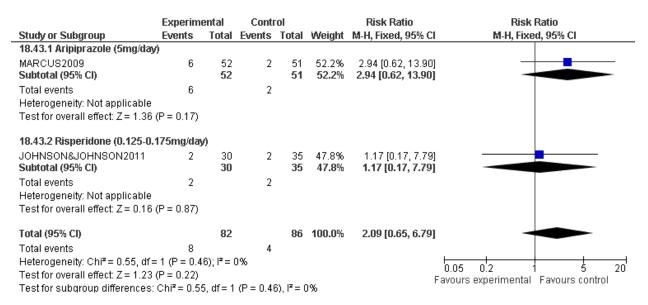
Rhinorrhea

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
18.41.1 Aripiprazole	(5mg/day)						
MARCUS2009	2	52	1	51	100.0%	1.96 [0.18, 20.97	7]
Subtotal (95% CI)		52		51	100.0%	1.96 [0.18, 20.97	7]
Total events	2		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	z = 0.56 (F	9 = 0.58)				
Total (95% CI)		52		51	100.0%	1.96 [0.18, 20.97	7]
Total events	2		1				
Heterogeneity: Not a	pplicable						0.05 0.2 1 5 20
Test for overall effect	t: Z = 0.56 (F	9 = 0.58)				0.05 0.2 1 5 2 Favours experimental Favours control
Test for subaroup di	fferences: N	ot appl	icable				ravours experimental Favours control

Nasal congestion



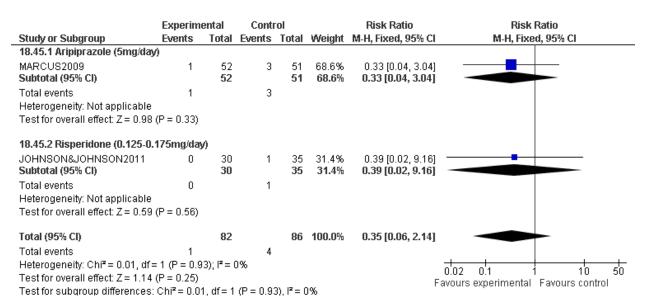
Nasopharyngitis



Nose bleed

	Ехрегіте	ental	Contr	ol		Risk Ratio	Risk I	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixe	d, 95% CI
18.44.1 Aripiprazole (5mg/day))							
MARCUS2009 Subtotal (95% CI)	0	52 52	0	51 51		Not estimable Not estimable		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not appli	cable							
18.44.2 Risperidone (0.125-0.1	175mg/day	0						
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	0	35 35		Not estimable Not estimable		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not appli	cable							
Total (95% CI)		82		86		Not estimable		
Total events	0		0					
Heterogeneity: Not applicable							0.01 0.1 1	10 100
Test for overall effect: Not appli	cable						Favours experimental	
Test for subgroup differences:	Not applica	able					i avouis expellillelital	1 070013 00111101

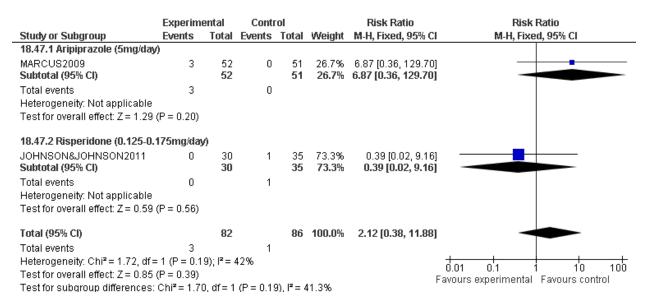
Akathisia



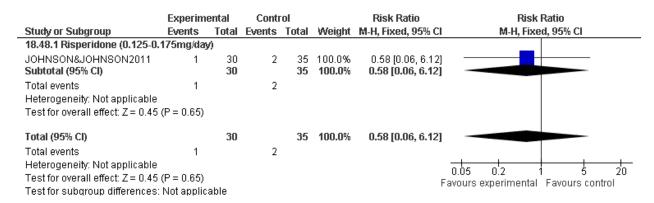
Insomnia

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
18.46.1 Risperidone (0.125-0.	.175mg/day	0					
JOHNSON&JOHNSON2011 Subtotal (95% CI)	0	30 30	2	35 35	100.0% 100.0 %	0.23 [0.01, 4.66 0.23 [0.01, 4.66]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.95			2				
Total (95% CI)		30		35	100.0%	0.23 [0.01, 4.66]	
Total events Heterogeneity: Not applicable	0		2				
Test for overall effect: Z = 0.95 Test for subgroup differences	(P = 0.34)	able					'0.01 0.1 1 1'0 100' Favours experimental Favours control

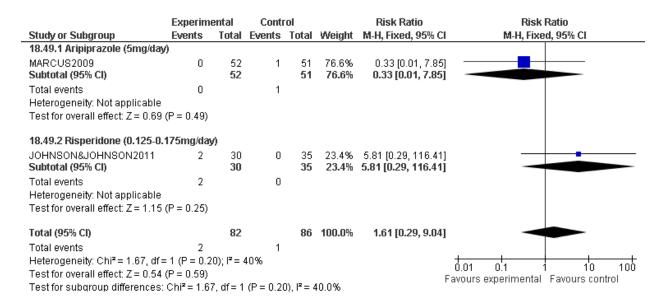
Hypersomnia



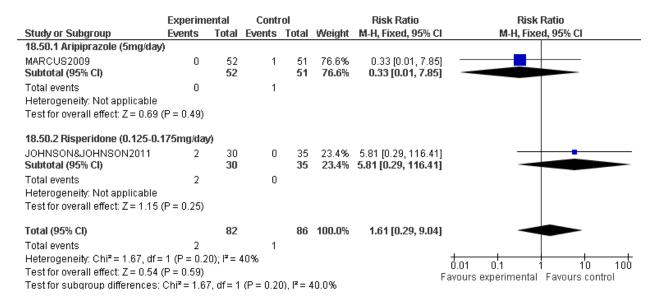
Psychomotor hyperactivity



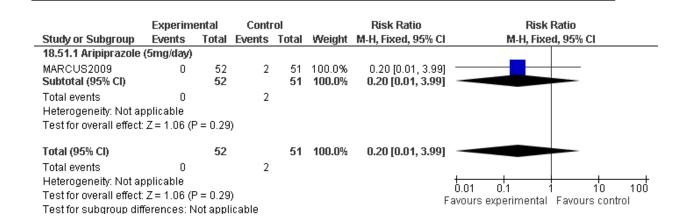
Enuresis



Rash



Clinically relevant prolactin elevation (above upper limit of normal)



Adverse events associated with risperidone versus placebo

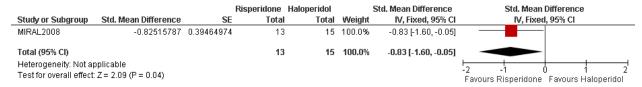
Treatment-emergent extrapyramidal symptoms

	Risp	eridor	ne	Halo	Haloperidol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
MIRAL2008	0.15	0.38	13	1.27	1.75	15	100.0%	-0.83 [-1.61, -0.05]			
Total (95% CI)			13			15	100.0%	-0.83 [-1.61, -0.05]			
Heterogeneity: Not a Test for overall effect).04)						-2 -1 Favours Risperidone) 1 Favours Halop	2 eridol

Prolactin (change score)

			Risperidone	Haloperidol		Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Std. Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	i, 95% CI	
MIRAL2008	-1.01304054	0.40238745	13	15	100.0%	-1.01 [-1.80, -0.22]			
Total (95% CI)			13	15	100.0%	-1.01 [-1.80, -0.22]			
Heterogeneity: Not ap Test for overall effect:	•						-2 -1 Favours Haloperidol	0 1 Favours Risp	2 eridone

Liver problems (change in alanine transaminase [ALT])



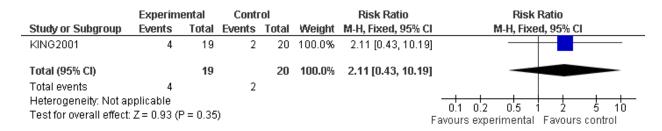
1.33.6 Adverse events associated with antivirals

Adverse events associated with amantadine hydrochloride versus placebo

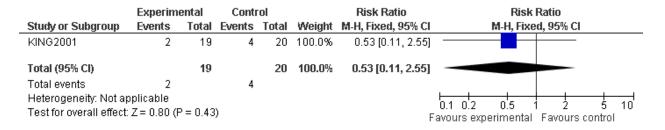
Any adverse event

	Experim	ental	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixed, 95% Cl
KING2001	14	19	14	20	100.0%	1.05 [0.71, 1.56	1 -
Total (95% CI)		19		20	100.0%	1.05 [0.71, 1.56]	ı →
Total events	14		14				
Heterogeneity: Not a	pplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 0.26 (F	P = 0.80)				Favours experimental Favours control

Insomnia



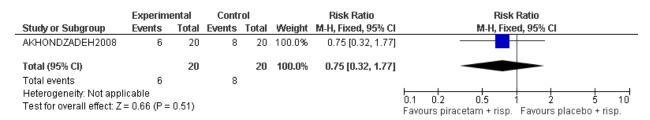
Antisocial behaviour



1.33.7 Adverse events associated with cognitive enhancers

Adverse events associated with piracetam and risperidone versus placebo and risperidone

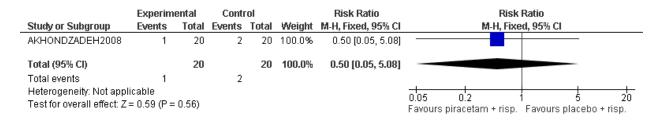
Any treatment-emergent extrapyramidal symptom



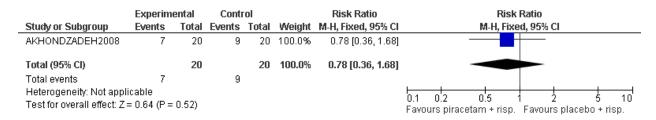
Constipation

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2008	4	20	3	20	100.0%	1.33 [0.34, 5.21]	
Total (95% CI)		20		20	100.0%	1.33 [0.34, 5.21]	
Total events	4		3				
Heterogeneity: Not appl Test for overall effect: Z		0.68)					0.1 0.2 0.5 1 2 5 10 Favours piracetam + risp. Favours placebo + risp.

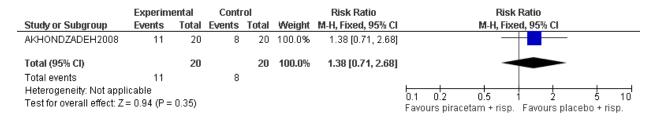
Nervousness



Day time drowsiness



Morning drowsiness



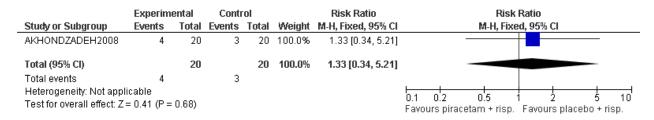
Increased appetite

	Experimental Control			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2008	7	20	6	20	100.0%	1.17 [0.48, 2.86]	
Total (95% CI)		20		20	100.0%	1.17 [0.48, 2.86]	
Total events	7		6				
Heterogeneity: Not appl	icable						0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 0.34 (P = 0.74)							Favours piracetam + risp. Favours placebo + risp.

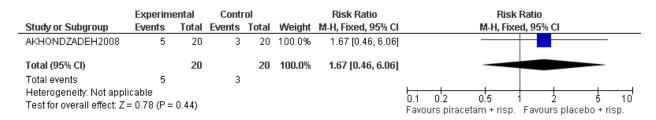
Loss of appetite

	Ехрегіт	ental	Conti	rol	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
AKHONDZADEH2008	1	20	1	20	100.0%	1.00 [0.07, 14.90]	
Total (95% CI)		20		20	100.0%	1.00 [0.07, 14.90]	
Total events	1		1				
Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (P = 1.00)							0.1 0.2 0.5 1 2 5 10 Favours piracetam + risp. Favours placebo + risp.

Dry mouth



Fatigue



1.33.8 Adverse events associated with melatonin

Adverse events associated with melatonin versus placebo

Coughing

	Ехрегіт	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	6	30	13	33	100.0%	0.51 [0.22, 1.17]	
Total (95% CI)		30		33	100.0%	0.51 [0.22, 1.17]	
Total events	6		13				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 1.60 (F	P = 0.11)				Favours Melatonin Favours Placebo

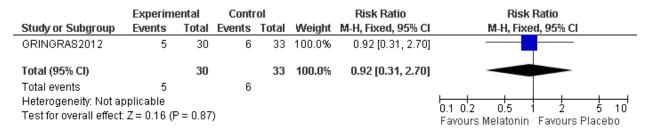
Mood swings

	Experimental Control				Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	7	30	6	33	100.0%	1.28 [0.49, 3.39]	
Total (95% CI)		30		33	100.0%	1.28 [0.49, 3.39]	
Total events	7		6				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.50 (F	P = 0.61)				Favours Melatonin Favours Placebo

Vomiting

	Experimental Control			ol lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	7	30	7	33	100.0%	1.10 [0.44, 2.77]	
Total (95% CI)		30		33	100.0%	1.10 [0.44, 2.77]	
Total events	7		7				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect: $Z = 0.20$ (P = 0.84)							Favours Melatonin Favours Placebo

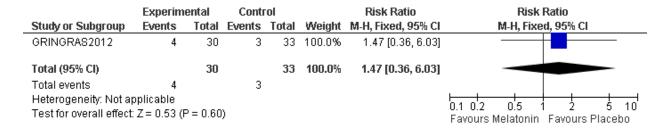
Increased excitability



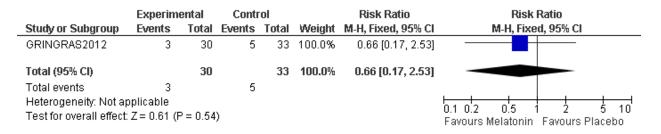
Headache

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	2	30	2	33	100.0%	1.10 [0.17, 7.33]	
Total (95% CI)		30		33	100.0%	1.10 [0.17, 7.33]	
Total events	2		2				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 0.10 (F	P = 0.92)				Favours Melatonin Favours Placebo

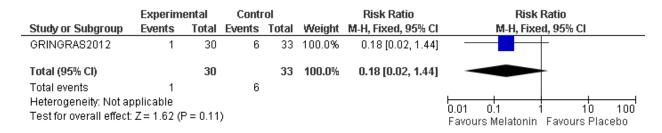
Rash



Somnolence



Fatigue



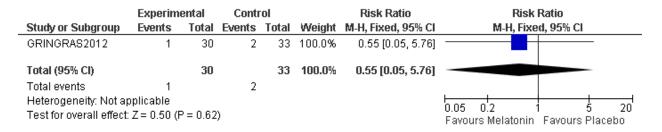
Hypothermia

	Ехрегіт	ental	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	1	30	2	33	100.0%	0.55 [0.05, 5.76]	
Total (95% CI)		30		33	100.0%	0.55 [0.05, 5.76]	
Total events	1		2				
Heterogeneity: Not ap Test for overall effect	• •	P = 0.62)				0.05 0.2 1 5 20 Favours Melatonin Favours Placebo

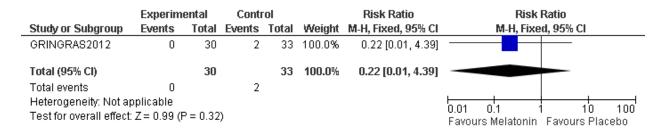
Increased activity

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
GRINGRAS2012	3	30	3	33	100.0%	1.10 [0.24, 5.04]	
Total (95% CI)		30		33	100.0%	1.10 [0.24, 5.04]	
Total events	3		3				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.90)				0.1 0.2 0.5 1 2 5 10 Favours Melatonin Favours Placebo

Nausea



Dizziness



Breathlessness

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	0	30	0	33		Not estimable	
Total (95% CI)		30		33		Not estimable	
Total events	0		0				
Heterogeneity: Not as	oplicable						01.02 05 1 2 5 10
Test for overall effect:	Not applic	able					Favours Melatonin Favours Placebo

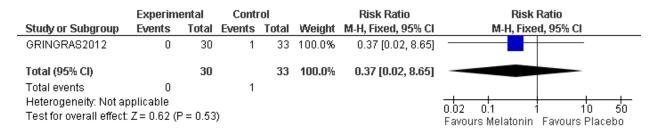
Hung-over feeling

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	1	30	0	33	100.0%	3.29 [0.14, 77.82]	
Total (95% CI)		30		33	100.0%	3.29 [0.14, 77.82]	
Total events	1		0				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 0.74 (F	o = 0.46)				Favours Melatonin Favours Placebo

Tremor

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	0	30	0	33		Not estimable	
Total (95% CI)		30		33		Not estimable	
Total events	0		0				
Heterogeneity: Not ap Test for overall effect:	•	able					0.1 0.2 0.5 1 2 5 10 Favours Melatonin Favours Placebo

Seizures



Other

	Ехрегіт	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GRINGRAS2012	15	30	20	33	100.0%	0.82 [0.53, 1.30]	-
Total (95% CI)		30		33	100.0%	0.82 [0.53, 1.30]	•
Total events	15		20				
Heterogeneity: Not a	pplicable						01 02 05 1 2 5 10
Test for overall effect	Z = 0.84 (F	P = 0.40))				Favours Melatonin Favours Placebo

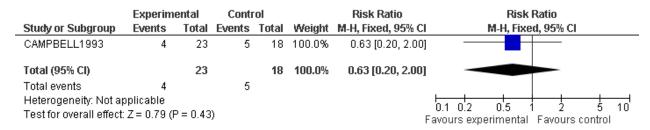
1.33.9 Adverse events associated with opioid antagonists

Adverse events associated with naltrexone versus placebo

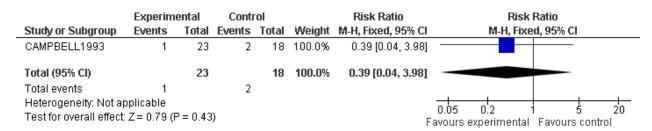
Any side effect

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
CAMPBELL1993	13	23	7	18	100.0%	1.45 [0.74, 2.87]	
Total (95% CI)		23		18	100.0%	1.45 [0.74, 2.87]	*
Total events	13		7				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.08 (F	P = 0.28)				Favours experimental Favours control

Aggressiveness



Self-injurious behaviour



Hyperactivity

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
CAMPBELL1993	2	23	3	18	100.0%	0.52 [0.10, 2.80]	
Total (95% CI)		23		18	100.0%	0.52 [0.10, 2.80]	
Total events	2		3				
Heterogeneity: Not as	oplicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.76 (F	P = 0.45)				Favours experimental Favours control

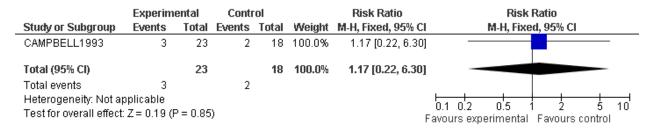
Temper tantrums

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
CAMPBELL1993	2	23	1	18	100.0%	1.57 [0.15, 15.92	1
Total (95% CI)		23		18	100.0%	1.57 [0.15, 15.92	
Total events	2		1				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.38 (F	P = 0.71)				Favours experimental Favours control

Stereotypies

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
CAMPBELL1993	2	23	3	18	100.0%	0.52 [0.10, 2.80	
Total (95% CI)		23		18	100.0%	0.52 [0.10, 2.80]	
Total events	2		3				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.76 (F	P = 0.45)				Favours experimental Favours control

Irritability



Decreased verbal production (transient)

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
CAMPBELL1993	1	23	0	18	100.0%	2.38 [0.10, 55.06]	
Total (95% CI)		23		18	100.0%	2.38 [0.10, 55.06]	
Total events	1		0				
Heterogeneity: Not as	pplicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 0.54 (F	P = 0.59)			F	avours experimental Favours control

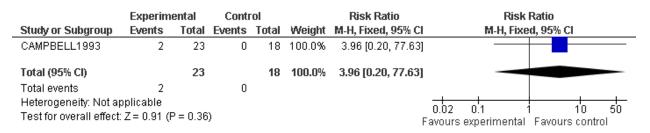
Slight sleepiness

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
CAMPBELL1993	1	23	0	18	100.0%	2.38 [0.10, 55.06]	
Total (95% CI)		23		18	100.0%	2.38 [0.10, 55.06]	
Total events	1		0				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 0.54 (F	° = 0.59)				Favours experimental Favours control

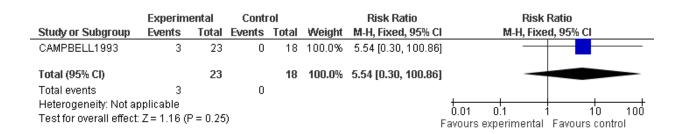
Falling asleep

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
CAMPBELL1993	2	23	0	18	100.0%	3.96 [0.20, 77.63]	
Total (95% CI)		23		18	100.0%	3.96 [0.20, 77.63]	
Total events	2		0				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 0.91 (F	P = 0.36)				Favours experimental Favours control

Decreased appetite



Vomiting



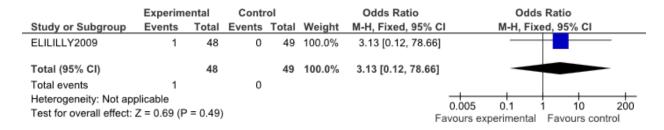
1.33.10 Adverse events associated with SNRIs

Adverse events associated with atomoxetine versus placebo

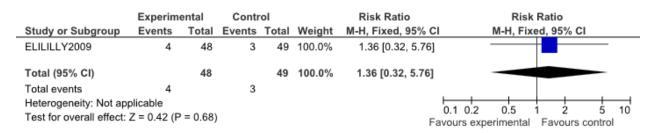
Any adverse event

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
ELILILLY2009	39	48	32	49	100.0%	1.24 [0.97, 1.59]	
Total (95% CI)		48		49	100.0%	1.24 [0.97, 1.59]	*
Total events	39		32				
Heterogeneity: Not ap	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 1.75 (P	9 = 0.08))			Fa	vours experimental Favours control

Discontinuation due to adverse events



Abdominal pain



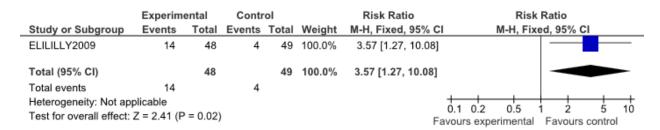
Upper abdominal pain

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
ELILILLY2009	9	48	3	49	100.0%	3.06 [0.88, 10.63]	
Total (95% CI)		48		49	100.0%	3.06 [0.88, 10.63]	
Total events	9		3				
Heterogeneity: Not app	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 1.76 (P	= 0.08)				F	avours experimental Favours control

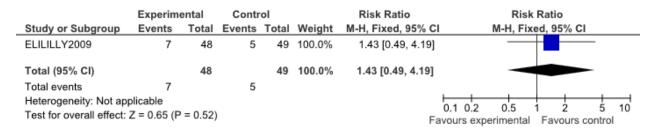
Diarrhoea

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
ELILILLY2009	1	48	3	49	100.0%	0.34 [0.04, 3.16]	
Total (95% CI)		48		49	100.0%	0.34 [0.04, 3.16]	
Total events	1		3				
Heterogeneity: Not app	olicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.95 (P	= 0.34)				Fa	avours experimental Favours control

Nausea



Vomiting



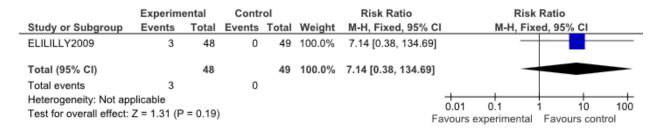
Fatigue

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
ELILILLY2009	11	48	4	49	100.0%	2.81 [0.96, 8.21]	
Total (95% CI)		48		49	100.0%	2.81 [0.96, 8.21]	
Total events	11		4				
Heterogeneity: Not app	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 1.89 (P	= 0.06)				Fa	avours experimental Favours control

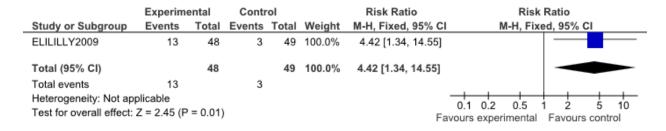
Pyrexia

	Experime	ental	Contr	ol		Risk Ratio	Risk Ra	tio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed,	95% CI
ELILILLY2009	0	48	3	49	100.0%	0.15 [0.01, 2.75]		_
Total (95% CI)		48		49	100.0%	0.15 [0.01, 2.75]		-
Total events	0		3					
Heterogeneity: Not app	olicable						0.01 0.1 1	10 100
Test for overall effect:	Z = 1.29 (P	= 0.20)				Fa		avours control

Influenza



Deceased appetite



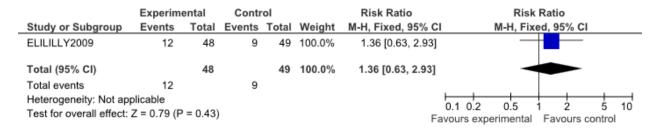
Myalgia

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
ELILILLY2009	3	48	0	49	100.0%	7.14 [0.38, 134.69	
Total (95% CI)		48		49	100.0%	7.14 [0.38, 134.69]	
Total events	3		0				
Heterogeneity: Not app	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 1.31 (P	= 0.19)					Favours experimental Favours control

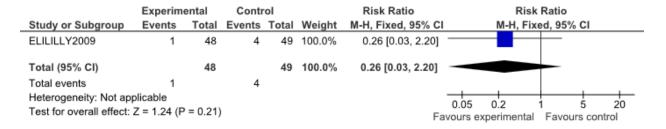
Dizziness

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (I M-H, Fixed, 95% CI
ELILILLY2009	3	48	1	49	100.0%	3.06 [0.33, 28.42]	
Total (95% CI)		48		49	100.0%	3.06 [0.33, 28.42]	
Total events	3		1				
Heterogeneity: Not app	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.98 (P	= 0.32)				F	avours experimental Favours control

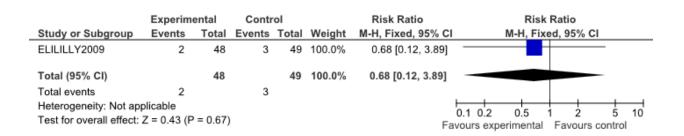
Headache



Psychomotor hyperactivity



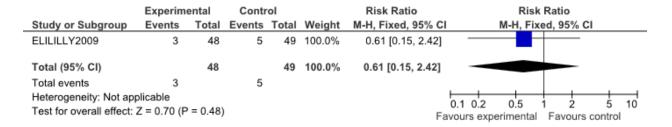
Aggression



Early morning awakening

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
ELILILLY2009	5	48	0	49	100.0%	11.22 [0.64, 197.60	
Total (95% CI)		48		49	100.0%	11.22 [0.64, 197.60]	
Total events	5		0				
Heterogeneity: Not app	plicable						0.005 0.1 1 10 200
Test for overall effect:	Z = 1.65 (P	= 0.10)					Favours experimental Favours control

Initial insomnia

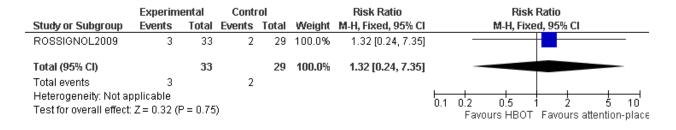


1.34ADVERSE EVENTS ASSOCIATED WITH BIOMEDICAL INTERVENTIONS

1.34.1 Adverse events associated with medical procedures

Adverse events associated with HBOT versus attention-placebo

Any adverse event



Minor-grade ear barotrauma

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
SAMPANTHAVIVAT2012	11	29	3	29	100.0%	3.67 [1.14, 11.79]	
Total (95% CI)		29		29	100.0%	3.67 [1.14, 11.79]	
Total events	11		3				
Heterogeneity: Not applica	able						0.05 0.2 1 5 20
Test for overall effect: $Z = 0$	2.18 (P = 0	.03)					Favours experimental Favours control

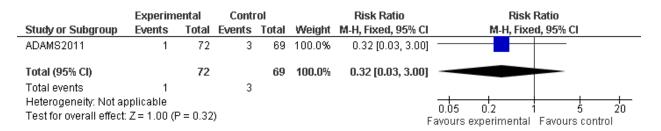
1.34.2 Adverse events associated with nutritional interventions

Adverse events associated with multivitamin/mineral supplement versus placebo

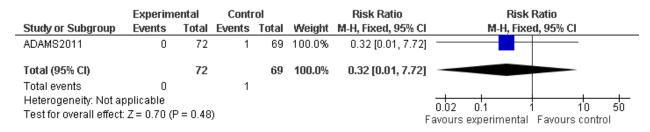
Discontinuation due to adverse events

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
ADAMS2011	3	72	5	69	100.0%	0.57 [0.14, 2.31]	
Total (95% CI)		72		69	100.0%	0.57 [0.14, 2.31]	
Total events	3		5				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.78 (F	P = 0.44)				Favours experimental Favours control

Discontinuation due to diarrhoea



Discontinuation due to increased stimming

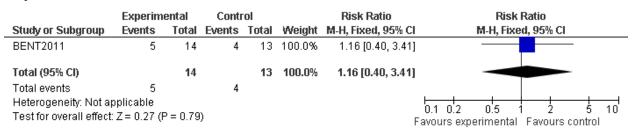


Discontinuation due to behaviour problems

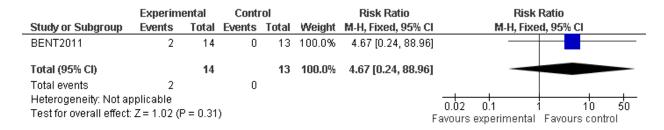
	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
ADAMS2011	2	72	1	69	100.0%	1.92 [0.18, 20.66]	
Total (95% CI)		72		69	100.0%	1.92 [0.18, 20.66]	
Total events	2		1				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.54 (F	P = 0.59)			F	Favours experimental Favours control

Adverse events associated with omega-3 fatty acids versus placebo

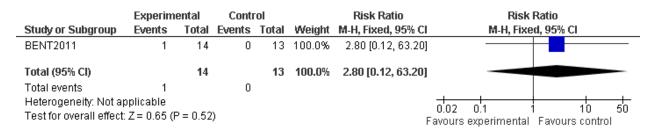
Any adverse event



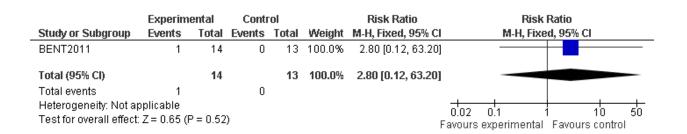
Rash



Upper respiratory infection



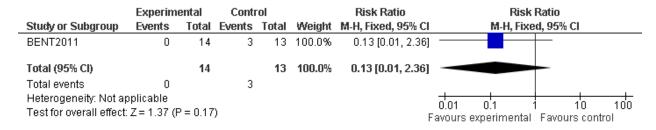
Nose bleeds



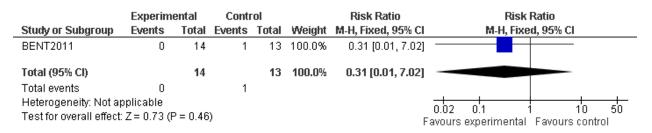
GI symptoms

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
BENT2011	1	14	0	13	100.0%	2.80 [0.12, 63.20]	
Total (95% CI)		14		13	100.0%	2.80 [0.12, 63.20]	
Total events	1		0				
Heterogeneity: Not ap	plicable						0.02 0.1 1 10 50
Test for overall effect:	Z = 0.65 (F	P = 0.52)			F	avours experimental Favours control

Hyperactivity



Self-stimulatory behaviour

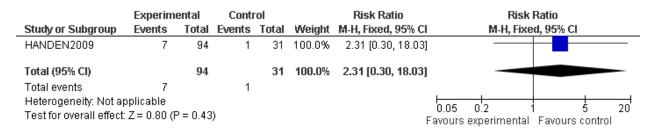


Adverse events associated with immunoglobulin (dosages combined) versus placebo

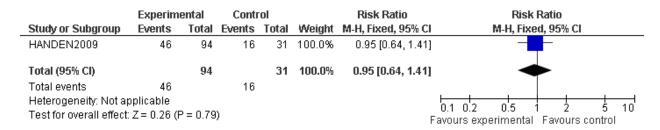
Any side effect

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HANDEN2009	71	94	25	31	100.0%	0.94 [0.76, 1.15	1 =
Total (95% CI)		94		31	100.0%	0.94 [0.76, 1.15	. ♦
Total events	71		25				
Heterogeneity: Not as	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.62 (F	P = 0.54)				Favours experimental Favours control

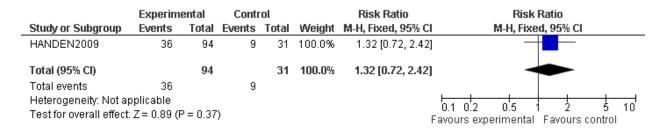
Discontinuation due to adverse events



Infections or infestations



Gastrointestinal disorders



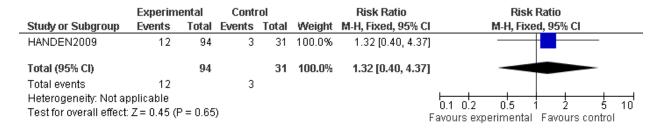
Psychiatric disorders

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
HANDEN2009	17	94	6	31	100.0%	0.93 [0.40, 2.16	1 -
Total (95% CI)		94		31	100.0%	0.93 [0.40, 2.16]	
Total events	17		6				
Heterogeneity: Not as	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.16 (F	P = 0.87)				Favours experimental Favours control

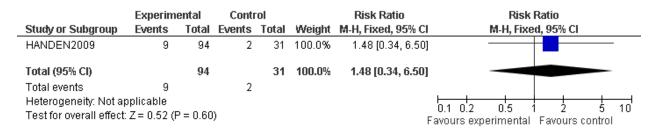
Respiratory, thoracic or mediastinal disorders

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HANDEN2009	15	94	4	31	100.0%	1.24 [0.44, 3.45]	
Total (95% CI)		94		31	100.0%	1.24 [0.44, 3.45]	
Total events	15		4				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.41 (F	P = 0.68)				Favours experimental Favours control

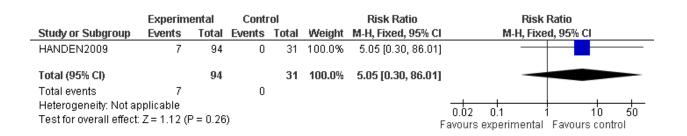
Skin or subcutaneous tissue disorders



General disorders or administration site conditions



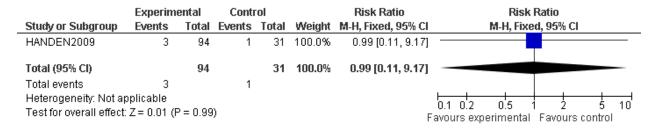
Nervous system disorders



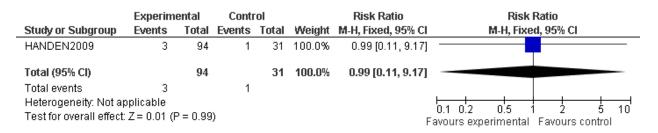
Injury, poisoning or procedural complications

	Ехрегіт	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
HANDEN2009	5	94	1	31	100.0%	1.65 [0.20, 13.58]
Total (95% CI)		94		31	100.0%	1.65 [0.20, 13.58]	
Total events	5		1				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.46 (F	P = 0.64)				Favours experimental Favours control

Investigations



Metabolism or nutrition disorders



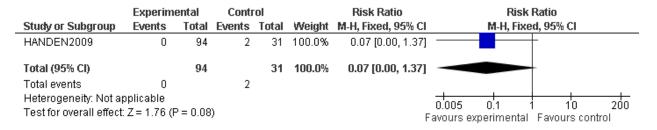
Eye disorders

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HANDEN2009	3	94	0	31	100.0%	2.36 [0.13, 44.42]	
Total (95% CI)		94		31	100.0%	2.36 [0.13, 44.42]	
Total events	3		0				
Heterogeneity: Not as	pplicable						0.02 0.1 1 10 50
Test for overall effect	Z = 0.57 (F	P = 0.57)			F	avours experimental Favours control

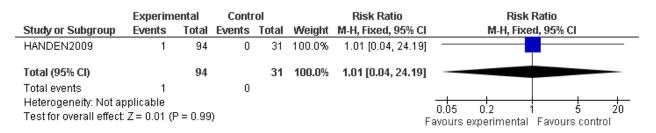
Blood or lymphatic system disorders

	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixe	ed, 95% CI	
HANDEN2009	1	94	1	31	100.0%	0.33 [0.02, 5.12]			
Total (95% CI)		94		31	100.0%	0.33 [0.02, 5.12]			
Total events	1		1						
Heterogeneity: Not as	oplicable						0.02 0.1	1 10	
Test for overall effect:	Z = 0.79 (F	P = 0.43)				Favours experimental	Favours contro	

Renal or urinary disorders



Ear or labyrinth disorders



Immune system disorders

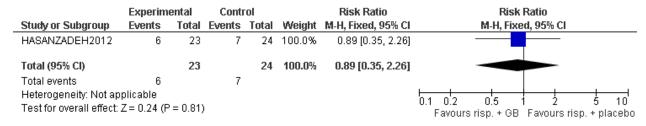
	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HANDEN2009	1	94	0	31	100.0%	1.01 [0.04, 24.19]	
Total (95% CI)		94		31	100.0%	1.01 [0.04, 24.19]	
Total events	1		0				
Heterogeneity: Not as	pplicable						0.05 0.2 1 5 20
Test for overall effect	Z = 0.01 (F	P = 0.99)			F	- 0.05

Vascular disorders

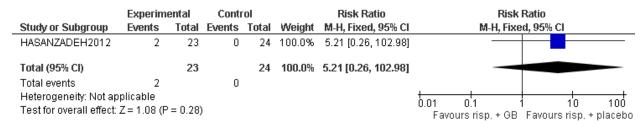
	Ехрегіт	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
HANDEN2009	1	94	0	31	100.0%	1.01 [0.04, 24.19]	
Total (95% CI)		94		31	100.0%	1.01 [0.04, 24.19]	
Total events	1		0				
Heterogeneity: Not ap	pplicable						0.05 0.2 1 5 20
Test for overall effect	Z = 0.01 (F	P = 0.99)				Favours experimental Favours control

Adverse events associated with ginkgo biloba and risperidone versus placebo and risperidone

Day time drowsiness



Morning drowsiness



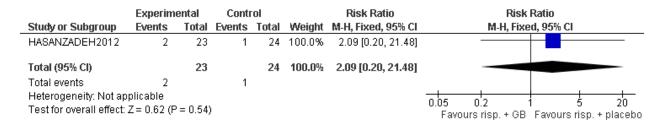
Constipation

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HASANZADEH2012	3	23	3	24	100.0%	1.04 [0.23, 4.65]	
Total (95% CI)		23		24	100.0%	1.04 [0.23, 4.65]	
Total events	3		3				
Heterogeneity: Not ap Test for overall effect:	•	= 0.96))				0.1 0.2 0.5 1 2 5 10 Favours risp. + GB Favours risp. + placebo

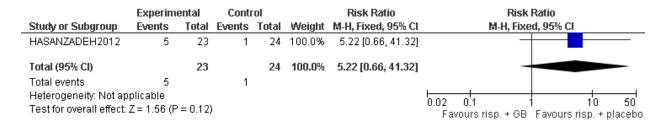
Dizziness

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HASANZADEH2012	1	23	3	24	100.0%	0.35 [0.04, 3.11]	
Total (95% CI)		23		24	100.0%	0.35 [0.04, 3.11]	
Total events	1		3				
Heterogeneity: Not app	plicable						0.05 0.2 1 5 20
Test for overall effect: 2	Z= 0.95 (P	= 0.34))				Favours risp. + GB Favours risp. + placebo

Slow movement



Nervousness



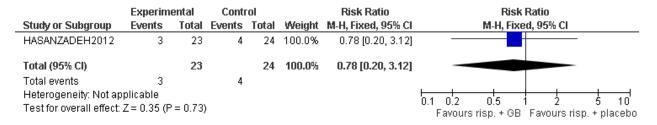
Restlessness

	Experimental		Experimental Control		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
HASANZADEH2012	3	23	5	24	100.0%	0.63 [0.17, 2.33]			
Total (95% CI)		23		24	100.0%	0.63 [0.17, 2.33]			
Total events	3		5						
Heterogeneity: Not applicable Test for overall effect: Z = 0.70 (P = 0.48)							0.1 0.2 0.5 1 2 5 10 Favours risp. + GB Favours risp. + placebo		

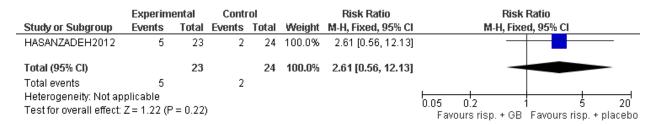
Increased appetite

	Experimental		Control		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
HASANZADEH2012	6	23	10	24	100.0%	0.63 [0.27, 1.44]	
Total (95% CI)		23		24	100.0%	0.63 [0.27, 1.44]	
Total events	6		10				
Heterogeneity: Not applicable							01 02 05 1 2 5 10
Test for overall effect: Z = 1.10 (P = 0.27)							Favours risp. + GB Favours risp. + placebo

Loss of appetite



Fatigue



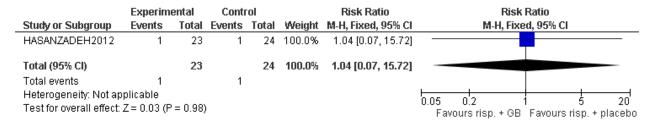
Diarrhoea

	Experimental		Experimental Control		ol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI			
HASANZADEH2012	3	23	3	24	100.0%	1.04 [0.23, 4.65]				
Total (95% CI)		23		24	100.0%	1.04 [0.23, 4.65]				
Total events	3		3							
Heterogeneity: Not applicable Test for overall effect: Z = 0.06 (P = 0.96)							0.1 0.2 0.5 2 5 10 Favours risp. + GB Favours risp. + placebo			

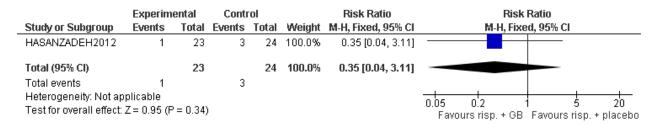
Twitches

	Experimental		Control		Risk Ratio		Risk Ratio
Study or Subgroup	Events Total Events Total		Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
HASANZADEH2012	3	23	0	24	100.0%	7.29 [0.40, 133.82]	
Total (95% CI)		23		24	100.0%	7.29 [0.40, 133.82]	
Total events	3		0				
Heterogeneity: Not applicable Test for overall effect: Z = 1.34 (P = 0.18)							0.01

Dry mouth



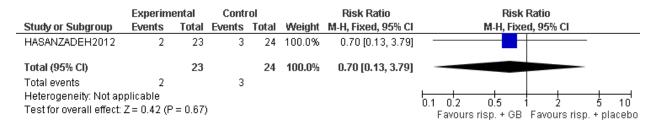
Trouble swallowing



Sore throat/tongue

	Experimental		l Control		Risk Ratio		Risk Ratio
Study or Subgroup	Events	ents Total Events Total			Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
HASANZADEH2012	1	23	5	24	100.0%	0.21 [0.03, 1.65]	
Total (95% CI)		23		24	100.0%	0.21 [0.03, 1.65]	
Total events	1		5				
Heterogeneity: Not applicable Test for overall effect: Z = 1.48 (P = 0.14)							0.05

Abdominal pain



Adverse events associated with gluten-free and casein-free diet versus treatment as usual

	Experimental		Control		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% Cl		
WHITELEY2010	0	38	0	34		Not estimable				
Total (95% CI)		38		34		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	plicable						01 02 05	+ + -	+ ,	 10
Test for overall effect:				F	avours experimental	Favours co		10		